More Than Skin Deep:
Detection of subclinical enthesopathy and early psoriatic arthritis in patients with psoriasis in primary and secondary care and assessment of the response to anti-IL-12/IL-23p40 monoclonal antibody skin-directed therapy using ultrasound and whole-body MRI

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The candidate confirms that the work submitted is her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter two includes work from two joint first-authored publications by Laura Savage and Laura Coates. Laura Savage was equally responsible for writing the protocol, obtaining ethical approval, conducting the study, analysing the results and writing the following two published manuscripts:

L.C. Coates and L. Savage, R. Waxman, A.R. Moverley, S. Worthington and P.S. Helliwell. Comparison of screening questionnaires to identify psoriatic arthritis in a primary-care population: a cross-sectional study. British Journal of Dermatology 2016;175(3):542-8.

L. C. Coates and L. Savage, R. Waxman, D. G. McGonagle, A. R. Moverley and P. S. Helliwell. An educational leaflet improves response to invitation for screening for arthritis in patients with psoriasis in primary care, but only in practices in the most deprived areas. Clinical Rheumatology 2017;36(3):719-23.

Chapters three, four and five include data from a published abstract, following presentation at the American College of Rheumatology Annual Meeting in Washington, D.C. in November 2016. Laura Savage wrote the protocol, obtained ethical approval, conducted the study, analysed the results and wrote the abstract and presentation. Expertise and guidance was provided by the remaining authors:

L. Savage, M. Goodfield, E.M.A. Hensor, P. Emery and D. McGonagle. Ultrasonographic Improvement of Peripheral Subclinical Enthesopathy in Therapy-Naive Patients Treated with Ustekinumab for Chronic Plaque Psoriasis: A 52-Week, Prospective, Open Label, Controlled Cohort Study. Arthritis Rheumatology 2016;68 Suppl 10:1-4550.

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List of Publications and Presentations arising from this Thesis

Published Papers

L. C. Coates* and L. Savage*, R. Waxman, D. G. McGonagle, A. R. Moverley and P. S. Helliwell. An educational leaflet improves response to invitation for screening for arthritis in patients with psoriasis in primary care, but only in practices in the most deprived areas. Clinical Rheumatology 2017;36(3):719-23.

L.C. Coates* and L. Savage*, R. Waxman, A.R. Moverley, S. Worthington and P.S. Helliwell. Comparison of screening questionnaires to identify psoriatic arthritis in a primary-care population: a cross-sectional study. British Journal of Dermatology 2016;175(3):542-8.

Published Abstracts

L. Savage, M. Goodfield, E.M.A. Hensor, P. Emery and D. McGonagle. Ultrasonographic Improvement of Peripheral Subclinical Enthesopathy in Therapy-Naive Patients Treated with Ustekinumab for Chronic Plaque Psoriasis: A 52-Week, Prospective, Open Label, Controlled Cohort Study. Arthritis Rheumatology 2016;68 Suppl 10:1-4550.

National and International Oral Presentations

L. Savage, M.D. Goodfield, E.M.A. Hensor, P. Emery and D. McGonagle. Targeting the Evolution of PsA in the Dermatology Clinic: Ultrasonographic Improvement of Peripheral Subclinical Enthesopathy in Therapy-Naïve Patients Treated with Ustekinumab for Chronic Plaque Psoriasis - A 52-Week, Prospective, Open Label, Controlled Cohort Study. Oral presentation at the 97th British Association of Dermatologists Annual Conference, Liverpool, July 2017.

L. Savage, D. McGonagle. New Perspectives in Shared Care for Psoriatic Disease: From the immunology of the human enthesis to the modification of early PsA in the dermatology clinic setting. Oral presentation at the British Society for Investigative Dermatology Annual Meeting, Manchester, April 2017.

L. Savage, M.D. Goodfield, E.M.A. Hensor, P. Emery and D. McGonagle. Ultrasonographic Improvement of Peripheral Subclinical Enthesopathy in Therapy-Naive Patients Treated with Ustekinumab for Chronic Plaque Psoriasis: A 52-Week, Prospective, Open Label, Controlled Cohort Study. Oral presentation at the American College of Rheumatology Annual Meeting, Washington D.C., USA, November 2016.

Savage L. The Detection and Treatment of Subclinical Enthesitis in Patients with Psoriasis. Oral presentation at the British Society for Rheumatology Autumn Conference, Bath, October 2016.

L. Savage, D. McGonagle. New Perspectives in Psoriasis: The diagnosis and treatment of subclinical enthesitis in the dermatology clinic. Oral Presentation at the IV Brazilian Expert Meeting on Spondyloarthritis, Brasilia, Brazil, August 2016.

L. Savage, M. Goodfield, E.M.A. Hensor, P. Emery and D. McGonagle. Meeting the NICE Guideline: a simple, targeted ultrasound protocol for the detection of early psoriatic arthritis in patients with severe psoriasis. Oral presentation at the 94th British Association of Dermatologists Annual Conference, Glasgow, July 2014.

L. Savage, M. Goodfield, E.M.A. Hensor, P. Emery and D. McGonagle. Ultrasound screening for the detection of early psoriatic arthritis in patients with severe psoriasis. Oral presentation at the 11th European Academy of Dermatology and Venereology Spring Symposium, Belgrade, Serbia, May 2014.

National and International Poster Presentations

L.C. Coates*, L. Savage*, A. Moverley, P. Helliwell. The New Contest Questionnaire: Identifying Psoriatic Arthritis in a Primary Care Population with Psoriasis. Poster presentation at the 96th British Association of Dermatologists Annual Conference, Birmingham, July 2016.

L.C. Coates*, L. Savage*, A. Moverley, P. Helliwell. Detecting Psoriatic Arthritis in Psoriasis: Does an Educational Leaflet Improve Attendance for Screening? Poster presentation at the 96th British Association of Dermatologists Annual Conference, Birmingham, July 2016.

L.C. Coates*, L. Savage*, A. Moverley, P. Helliwell. Can the New Contest Questionnaire Identify Psoriatic Arthritis in a Primary Care Population? Poster presentation at the American College of Rheumatology Annual Congress, San Francisco, USA, November 2015.

L.C. Coates*, L. Savage*, A. Moverley, P. Helliwell. Does an Educational Leaflet Improve Attendance for Screening for Psoriatic Arthritis? Poster presentation at the American College of Rheumatology Annual Congress, San Francisco, USA, November 2015.

L. Savage, A. Jackson, M.D. Goodfield, D. McGonagle. A simple, targeted ultrasound protocol for the detection of subclinical enthesitis in patients with moderate-to-severe psoriasis. Poster presentation at the Group for Research in Psoriasis and Psoriatic Arthritis (GRAPPA) Annual Meeting, New York, USA, July 2014.

(*) denotes joint first authorship

Abstract

Objectives:

Primary care cohort: To determine the rates of undiagnosed psoriatic arthritis (PsA) amongst patients with psoriasis using clinical examination and screening questionnaires, and test the performance a new PsA screening questionnaire alongside the current standard (Psoriasis Epidemiology Screening Tool, PEST).

Secondary care cohort: To develop novel ultrasound and whole body magnetic resonance imaging (WBMRI) protocols to facilitate the comprehensive assessment of subclinical abnormalities within the peripheral and axial skeleton of immunomodulatory therapy-naïve patients with psoriasis referred to secondary care, and to use these protocols to assess the imaging response of abnormalities over 52 weeks of skin-directed treatment with a licensed IL-12/23p40 inhibitor (ustekinumab).

Methods:

Primary care cohort: 932 patients, across five diverse primary care practices, who were coded as having a diagnosis of psoriasis, were invited by their General Practitioner to attend an evening appointment at their surgery for a consultation with a dermatologist and a rheumatologist. Half of patients were sent an educational leaflet regarding PsA with their invitation letter. Attendees were examined and asked to complete a PEST questionnaire and a new PsA screening questionnaire (CONTEST).

Secondary care cohort: 73 immunomodulatory therapy-naive patients, without musculoskeletal disease or symptoms, who were referred to dermatology for treatment of moderate to severe psoriasis were screened using an extensive ultrasound protocol to assess for the presence of subclinical enthesitis. Patients who had at least one inflammatory abnormality, and in whom biologic therapy was not contraindicated, were invited to receive standard-dose skin directed therapy with ustekinumab for 52 weeks. Ultrasound examination of 13 entheses and structures within the adjacent synovio-entheseal complex were performed at weeks 0, 12, 24 and 52. WBMRI was performed at week 0, 24 and 52, to assess the axial skeleton and sites in the peripheral skeleton inaccessible by ultrasound. 23 healthy volunteers had one ultrasound scan and WBMRI using the same protocols, for comparison.

Results:

Primary care cohort: 20.5% of patients invited for screening attended. The provision of an educational leaflet did not have an impact on attendance for screening, except in the most deprived areas. 191 patients were examined, of which 169 had current or previous psoriasis (11.5% misdiagnosis rate). 17 patients were newly diagnosed with PsA (10.1%). The best sensitivity and specificity of the CONTEST questionnaires were 76.5% and 56.5% respectively, without the joint mannequin (cut off ≥3), and 70.6% and 63.3%

respectively, with the joint mannequin (cut off ≥4). The sensitivity and specificity of the PEST questionnaire in this cohort, using the validated cut off ≥3, was 52.9% and 66.0%. Lowering the cut off ≥2, the sensitivity improved to 82.4% with a specificity of 44.9%.

Secondary care cohort: 36 patients (49.3%) had at least inflammatory subclinical abnormality on screening ultrasound. 28 of these 36 were eligible for a biologic therapy and agreed to undergo a more detailed ultrasound scan and WBMRI. 5 patients subsequently chose conventional therapy, and 23 patients consented to treatment with ustekinumab and long-term review. 23 patients reached the primary end point of week 24, and 20 reached week 52. Inflammatory and chronic damage abnormalities were seen with greater frequency in the peripheral rather than axial skeleton, mostly involving the larger entheses of the knee, foot, ankle and elbows. Healthy volunteers exhibited a similar pattern of abnormalities but at a significantly lower frequency (inflammatory lesions 4.5% vs. 31.1%, chronic damage lesions 6.0% vs. 27.0%, both $p<0.00001$). Synovitis was seen in 82.1% of patients, while bursitis and tenosynovitis were uncommon. Following treatment with ustekinumab, ultrasound inflammation scores reduced by 42.2% at the primary end point (week 24, $p<0.001$), and by 51.5% after 52 weeks ($p=0.01$). Chronic damage scores remain unchanged ($p=0.082$ week 24, $p=0.512$ week 52). In the axial skeleton, more patients than volunteers had vertebral unit bone marrow oedema (64.3% vs. 30.4%, $p<0.00001$). Sacroiliac joint inflammation was minimal in both groups. Axial structural changes occurred in 14.3% in patients and were absent in volunteers. No significant change in spine or SIJ osteitis ($p=0.656$ week 24, $p=0.627$ week 52), or structural abnormalities were observed after ustekinumab therapy.

Conclusions:

A proportion of patients with psoriasis have undiagnosed PsA in primary care, even with signs and symptoms of inflammatory arthritis. Screening questionnaires are useful to detect some, but not all patients and further measures are required to capture all cases of PsA. Early identification and treatment is essential to prevent future pain, functional limitation and disability. Treating patients for psoriasis with a therapeutic agent that is effective at reducing the development of PsA is one means of addressing the failings of clinical examination and screening questionnaires, although the evolution from subclinical enthesitis (a common finding in patients with psoriasis) to PsA is not understood. This thesis provides preliminary data to suggest that anti-IL-12/23p40 therapy may reduce the burden of subclinical inflammation at the primary site of lesion development in PsA (the enthesis), and further longitudinal studies are now encouraged to confirm these observations with ustekinumab and other immunomodulatory therapies.

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Abbreviations

ACR	American College of Rheumatology
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis (International Society)
Ax-SpA	Axial Spondyloarthritis
BAD	British Association of Dermatologists
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BMO	Bone Marrow Oedema
BSA	Body Surface Area
CASPAR	Classification Criteria for Psoriatic Arthritis
CD	Cluster of Differentiation
CI	Confidence Interval
CLA	Cutaneous Lymphocyte Antigen
CRF	Case Report Form
CRP	C-Reactive Protein
CTIMP	Clinical Trial of an Investigational Medical Product
DIP(J)	Distal Interphalangeal (Joint)
DMARD	Disease Modifying Anti-Rheumatic Drug
DLQI	Dermatology Life Quality Index
ESR	Erythrocyte Sedimentation Rate
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
GRAPPA	Group for Research in Psoriasis and Psoriatic Arthritis
GS	Grey Scale
GUESS	Glasgow Ultrasound Entheseal Scoring System
HADS	Hospital Anxiety and Depression Score
HAQ	Health Assessment Questionnaire
HLA	Human Leucocyte Antigen

HR	Hazard Ratio
HRQoL	Health-related Quality of Life
FAE	Fumaric Acid Esters
GUESS	Glasgow Ultrasound Enthesitis Scoring System
GS	Grey Scale
ICC	Interrater Correlation Coefficient
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IMP	Investigational Medical Product
LEI	Leeds Enthesitis Index
LRTI	Lower Respiratory Tract Infection
LS-PGA	Lattice System Physicians Global Assessment
MASEI	Madrid Sonographic Entheseal Index
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCP(J)	Metacarpophalangeal (Joint)
MEI	Mander Enthesitis Index
mNAPSI	Modified Nail Psoriasis Severity Index
MRI	Magnetic Resonance Imaging
mSvdH	Modified Sharp van der Heidje
NAPSI	Nail Psoriasis Severity Index
NBUVB	Narrowband UVB
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute of Health Research
NMSC	Non-Melanoma Skin Cancer
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
OMERACT	Outcome Measures in Rheumatology
OR	Odds Ratio

PASI	Psoriasis Area and Severity Index
PD	Power Doppler
PDI	Psoriasis Disability Index
PEASI	Psoriasis Exact Area and Severity Index
PEST	Psoriasis Epidemiology Screening Tool
PGA	Physicians Global Assessment
PIP(J)	Proximal Interphalangeal (Joint)
PLASI	Psoriasis Log-Based Area and Severity Index
PsA	Psoriatic Arthritis
PsAMRIS	Psoriatic Arthritis Magnetic Resonance Imaging Scoring System
PUVA	Psoralen plus UVA
ROC	Receiver Operator Characteristic Curve
SAPASI	Self-Administered Psoriasis Area and Severity Index
SE	Spin Echo
SEC	Synovio-Entheseal Complex
SEI	Sonographic Enthesitis Index
SF-36	Medical Outcomes Study Short Form 36
SI(J)	Sacroiliac (Joint)
SPASI	Simplified Psoriasis Area and Severity Index
SpA	Spondyloarthropathy
SPARCC	Spondyloarthritis Research Consortium of Canada
STI	Soft Tissue Inflammation
T	Tesla
TB	Tuberculosis
TGF	Transforming Growth Factor
Th	T-helper
TNF	Tumour Necrosis Factor
US	Ultrasound
USA	United States of America
UST	Ustekinumab

UV	Ultraviolet
VAS	Visual Analogue Score
VEGF	Vascular Endothelial Growth Factor
VU	Vertebral Unit
WBMRI	Whole Body Magnetic Resonance Imaging

Chapter 1
Review of the Literature

1.1 Psoriasis

1.1.1 Epidemiology

Psoriasis is a common, immune-mediated disorder of the skin, affecting around 1.2 million people in the United Kingdom (Parisi et al., 2013). Rates for psoriasis are equal amongst the sexes (Fry, 1988). It can occur at any age, although two peaks in incidence are recognised: the first, between twenty and thirty years of age and the second, between the ages of fifty and sixty years (Smith et al., 1993). 'Type I' psoriasis begins on or before the age of forty years and accounts for 75% of all cases; 'Type II' psoriasis begins after the age of forty. Patients with type I psoriasis are more likely to have greater disease severity, a positive family history and a carry the human leucocyte antigen (HLA)-Cw06 allele when compared to those with type II disease (Henseler and Christophers, 1985).

At a global level, the epidemiology of psoriasis is diverse and appears to be more common in countries more distant from the equator. The prevalence in children ranges from 0% in Taiwan to 2.1% in Italy, and in adults from 0.91% in the United States to 8.5% in Norway (Parisi et al., 2013). The prevalence of psoriasis is low in certain ethnic groups such as the Japanese (Ogawa et al., 2017), and may be absent in aboriginal Australians (Green, 1984), Samoans and South American Indians (Gudjonsson and Elder, 2007).

1.1.2 Pathogenesis

The pathophysiology of psoriasis is multifaceted and involves a complex interaction between genetic, environmental and immunological factors (Lowes et al., 2014). In recent years, a number of landmark studies have investigated genetic susceptibility in addition to cellular and molecular mechanisms using both human tissue samples and animal models of disease.

Until the early 1980s, psoriasis was considered to be primarily a disease of epidermal keratinocyte proliferation, with the cutaneous inflammatory infiltrate a secondary consequence (Bos et al., 2005). Histologically, psoriatic lesions are characterised by acanthosis (epidermal thickening) arising from rapid keratinocyte proliferation, parakeratosis (nuclear retention within corneocytes in the stratum corneum) and hypogranulosis (reduced or absent granular layer) from aberrant differentiation of keratinocytes with marked dilatation of blood vessels within the papillary dermis (causing

lesional erythema). However, with the increasing recognition of the importance of immune mechanisms in psoriasis, there has been longstanding historical debate about the primacy of these histological changes, as to whether hyperplastic keratinocytes are capable of inducing immune activation or whether they are simply responders to a primary aberrant immune response. Keratinocytes are equipped with innate immune receptors and actively take part in immune responses by producing cytokines and chemokines as well as the antimicrobial peptide LL-37 (Nestle et al., 2009a, Pasparakis et al., 2014).

The effective use of therapies designed to inhibit T-cell activation such as ciclosporin from the late 1970s (Ellis et al., 1986), and more latterly denileukin diftitox (DAB_{389} interleukin (IL)-2 fusion protein) (Gottlieb et al., 1995) and alefacept (a lymphocyte function associated antigen 3/immunoglobulin (Ig)G1 fusion protein targeting CD2+ T cells) (Abrams et al., 2000, Sano et al., 2005) gave specific indication that the immune system could be playing a more integral role in the pathogenesis of psoriasis.The current view is of pathological cross-talk between epithelial keratinocytes and the cutaneous immune system which sustains the aberrant immunological and epidermal responses seen in patients with psoriasis (Di Meglio et al., 2011, Lowes et al., 2013). Evidence from mouse models and translational research now strongly indicates that psoriatic plaques result from both a primary defect in keratinocytes and inappropriate innate and adaptive immune responses, mediated mainly by resident and infiltrating T lymphocytes (Sano et al., 2005, Nestle et al., 2005, Lande et al., 2007, Conrad et al., 2007) in genetically primed individuals.

A greater incidence of psoriasis is observed amongst first-degree and second-degree relatives of patients than among the general population (Farber and Nall, 1974, Karason et al., 2009). Genome wide association studies (GWAS) have confirmed associations with numerous polymorphisms within genes involved in: (i) innate immune regulation such as nuclear factor NFκB signalling (*TRAF31P2*, *TNIP1*, *TYK2*, *TNFAIP3*, *KFKBIA*, *FBXL19*, *REL*, and *CARD14*) (Capon et al., 2012, Nair et al., 2009, Jordan et al., 2012a, Jordan et al., 2012b) (Prinz, 2017) and interferon signalling (*ELM01, TYK2, SOCS1, IFIH1/MDA5, RNF114, IRF4, RIG1/DDX58, IFNLR1/IL28RA, IFNGR2*) (Prinz, 2017); (ii) adaptive immune regulation such as antigen presentation (*ERAP1*), CD8+ T-call maturation, activation and differentiation (*ETS1, RUNX3, TNFRSF9, MBD2, IRF4*) (Prinz, 2017), and Th17 differentiation, IL-23 and IL-17 signalling (*IL-23A, IL-12B, IL-12RB, IL-23R, TYK2, STAT3, STAT5A/B, SOCS1, ETS1, TRAF3IP2, KLF4, IF3*) (Capon et al., 2012, Nair et al., 2009, Nair et al., 2008, Cargill et al., 2007) (Prinz, 2017), (iii) barrier function (late cornified envelope proteins 3B and 3C) (Capon et al., 2012); and (iv) epidermal microbial defence (*DEFB4*) (Hollox et al., 2008). The precise functional effects of these single nucleotide polymorphisms remain to be established, but these

analyses add further support to the definition of psoriasis as an immune cell-mediated disease of defective keratinocytes (Nograles et al., 2010).

PSORS1, a major histocompatibility complex (MHC) class 1 region on chromosome 6p21, is the genetic loci with the largest effect to date (Nestle et al., 2009b), and it is within *PSORS1* that the human leukocyte antigen (HLA)-Cw06 allele is pinpointed as the risk variant that confers the strongest susceptibility to psoriasis (Nair et al., 2006). However, only 60–65% of patients with psoriasis carry the *HLA-Cw06* gene, compared with 15% of individuals without psoriasis (Gudjonsson et al., 2006). Furthermore, a low penetrance of approximately 10% points towards other genetic and environmental factors being involved (Elder et al., 1994).

In those with a genetic predisposition, activation of the innate immune system is triggered through one or more external stimuli (trauma (Koebner phenomenon), infections, drugs, stress and alcohol). Following epidermal damage, 'stressed' keratinocytes release both LL-37 (cathelicidin) antimicrobial peptide and host DNA/RNA, which together activate plasmacytoid dendritic cells to produce large quantities of interferon (IFN)-alpha (Marrakchi et al., 2011, Lande et al., 2007, Ganguly et al., 2009). IFN-alpha induces the maturation of myeloid (dermal) dendritic cells, which in turn produce cytokines including IL-23 and IL-12 (Nestle et al., 2005). IL-23 and IL-12 stimulate the attraction, activation and differentiation of T cells within skin draining lymph nodes, thereby bridging the gap between the innate and adaptive immune systems (Gilliet et al., 2008) (Figure 1.1). Subsequent T-cell expansion and migration into the epidermis (through expression of α1β1 integrin) results in characteristic epidermal remodelling (Conrad et al., 2007).

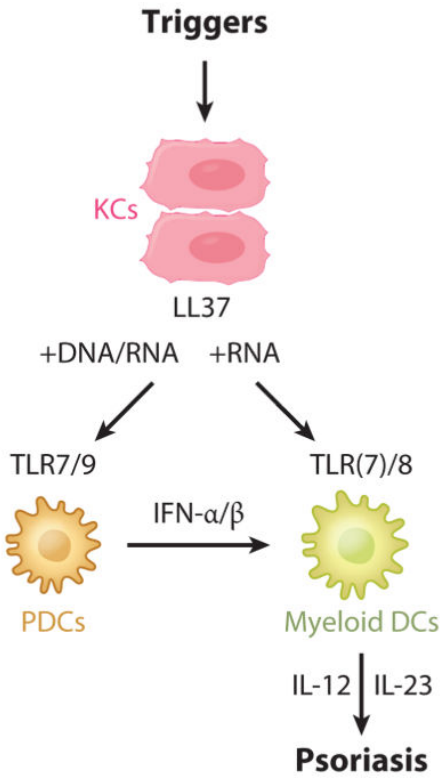

Figure 1.1. Pathway for the initiation of psoriasis. Stressed keratinocytes release LL-37 which bind to nucleic acids to activate plasmacytoid dendritic cells (DCs) to release IFN-α/β. LL37/RNA complexes also activate resident myeloid DCs to produce IL-12 and IL-23.

Differentiated psoriatic T cells are of two distinctly polarised types (Steinman, 2007, Trifari et al., 2009):

- T helper 1 (Th1) cells: Under the influence of IL-12, Th1 cells secrete TNF-α and IFN-gamma (Uyemura et al., 1993), which enhances expression of MHC class I on keratinocytes. In turn, this may promote the presentation of putative autoantigens to intra-epidermal T cells which can lead to further activation of pathogenic autoimmune T cells (Lang et al., 2005).
- T helper 17 (Th17) cells: When influenced by IL-23 (Lee et al., 2004, Chan et al., 2006, Tonel et al., 2010), Th17 cells produce IL-17A, IL-17F, IL-21, IL-22 and TNF-α (Lowes et al., 2008, Kagami et al., 2010, McGeachy et al., 2009). This is supported by experimental IL-23-deficient mouse models, where resistance to autoimmune disease correlates with the absence of IL-17 producing T-cells (Zheng et al., 2007, Nakae et al., 2002).

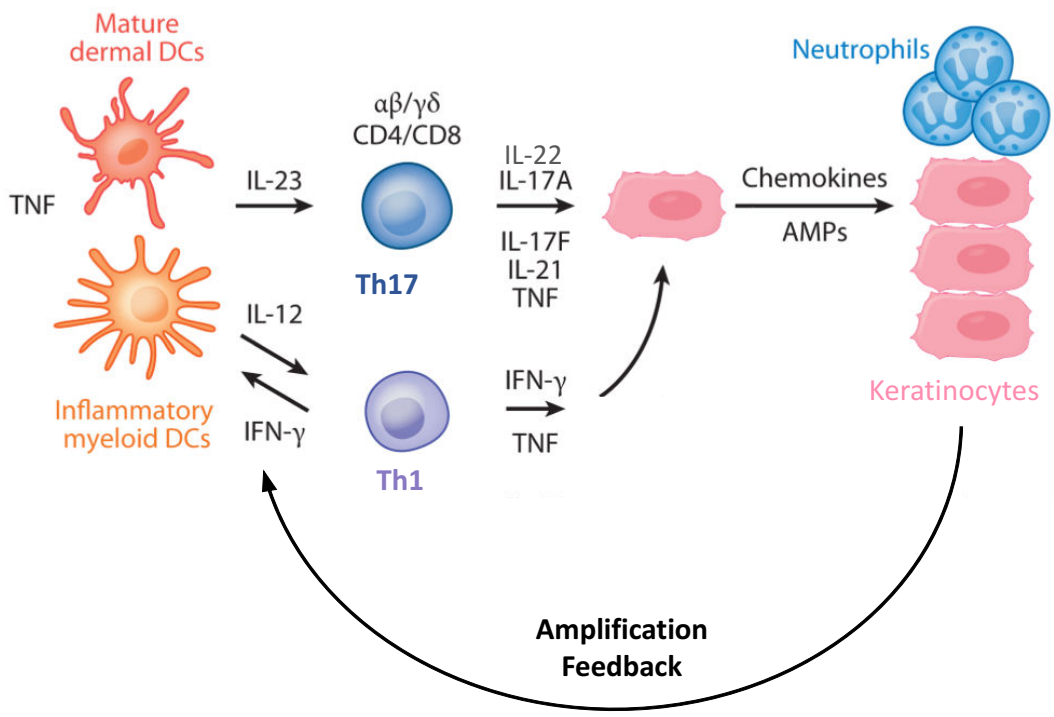

Figure 1.2. The chronic pathogenesis of psoriasis occurs when mature dermal dendritic cells (DCs) and inflammatory myeloid DCs produce cytokines such as IL-23, and IL-12. These cytokines activate Th17 and Th1 cells to contribute to the cytokine milieu and further act on keratinocytes. These then produce chemokines and antimicrobial peptides (AMPs) to augment cutaneous responses.

IL-23 is a member of the IL-12 cytokine family, which constitutes a heterodimer formed by a p40 chain, which is shared with IL-12, and a unique p19 subunit (Figure 1.3). It is produced by dendritic cells, macrophages and other antigen presenting cells and plays a pivotal role in the survival and proliferation of Th17 cells after priming with transforming growth factor (TGF)-β and IL-6 (Cauli A J Rheumatol Supp 2012).

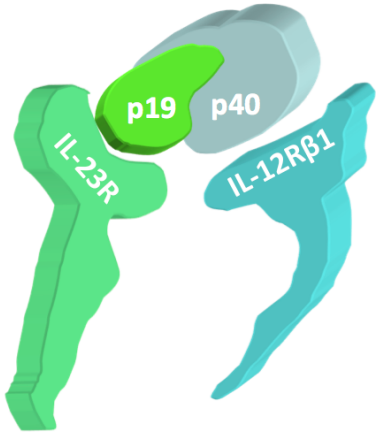

Figure 1.3. IL-23 heterodimer composed of p19 and p40 subunit.

IL-23p19, IL-12p40 (Lee et al., 2004) and IL-23R (Tonel et al., 2010, Wilson et al., 2007) have been detected at high level in psoriatic skin lesions, and intradermal injection of IL-23 in mice is shown to stimulate keratinocyte proliferation and cause epidermal acanthosis (Wilson et al., 2007). In xenotransplant mouse models of psoriasis, injection of a monoclonal antibody specifically neutralising human IL-23 showed IL-23-dependent inhibition of psoriasis development (Tonel et al., 2010).

IL-17 and IL-22 are key mediators downstream of IL-23 that link the adaptive immune response and epithelial dysregulation in psoriasis. Both cooperatively enhance gene expression of antimicrobial peptides by keratinocytes including β-defensin 2, 3 and S100A7/8/9 (Boniface et al., 2005, Liang et al., 2006). Both IL-17 and IL-22 increase production of LL-37 (Liang et al., 2006, Wolk et al., 2004, Peric et al., 2008), leading to sustained production of IFN-α and unregulated activation of myeloid dendritic cells, thus fuelling the continued activation of the immune system through a positive feedback loop (Conrad et al., 2009) (Figure 1.4).

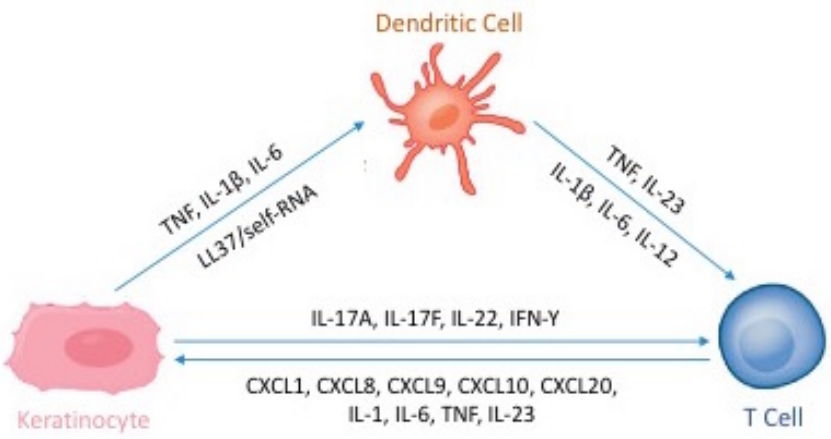

Figure 1.4. The critical interplay between keratinocytes, T cells and dendritic cells is primarily driven by the pro-inflammatory molecules TNF, IL-23 and IL-17 with other mediators such as IFN-α, IFN-γ and IL-22 also contributing to the initiation, amplification and maintenance of the psoriatic plaque.

IL-17 is pro-inflammatory; it induces the expression of chemokines for neutrophils, memory T cells and dendritic cells. IL-22 facilitates keratinocyte hyperproliferation and IL-22 receptor expression on keratinocytes is upregulated by IFN-alpha (Tohyama et al., 2012). IL-22 therefore provides an interface between immune activation and epidermal acanthosis (Tohyama et al., 2012, Eyerich et al., 2009). These observations are supported by experimental mice models - administration of anti-IL-12/IL-23p40 or anti-IL-23p19 monoclonal antibodies to K5.Stat3C mice markedly lowered transcript levels of IL-17 and IL-22, β-defensins and S100A family members in skin lesions, and more so than administration of anti-IL-17A antibody therapy supporting the pivotal role of IL-23 in psoriasis (Nakajima et al., 2011).

In addition to Th17 cells, many innate immune cells respond to IL-23 and are important in both resistance to infection and mediating autoimmune pathology. These cells are characterized by expression of the transcription factor retinoic-acid-receptor-related orphan receptor-γ (RORγt) (Ivanov et al., 2006) and include subsets of γδT cells, natural killer T (NKT) cells, 'natural' Th17 cells and innate lymphoid cells (ILCs) collectively, and are termed 'Type-17' (T17) cells (Cua and Tato, 2010, Annunziato et al., 2009, Zuniga et al., 2013, Kim et al., 2013, Marks et al., 2009). These innate immune cells are located in non-lymphoid tissues where they are poised to respond immediately to tissue injury or pathogenic insults. Accumulations of γδT cells have been found in psoriatic plaques (Cai et al., 2011), as have Vγ9Vδ2 T cells (a novel proinflammatory subset that seems to mediate an immediate tissue response upon koebnerization) (Laggner et al., 2011). Stimulation of Th17 cells and T17 cells with IL-1β and IL-23 induces local tissue inflammation, which is mainly mediated by T17 signature cytokines such as IL-17, IL-22 and granulocyte–macrophage colony-stimulating factor (GM-CSF) (Langrish et al., 2005, Zheng et al., 2007, El-Behi et al., 2011) thus amplifying Th17 responses (Sutton et al., 2009, Cai et al., 2011, Sumaria et al., 2011).

1.1.3 Clinical Presentation

Psoriasis is a papulosquamous dermatosis with a highly variable morphology, distribution, severity and course. Chronic, symmetrical, sharply demarcated, erythematous plaques with adherent silvery-white scale, ranging in size from one to several centimetres are most frequently seen. Removal of scale may reveal many tiny bleeding points (Auspitz sign) and a white blanching ring (Woronoff's ring) may occasionally be observed in the skin surrounding a psoriatic plaque. Lesions are typically distributed on the extensor surfaces of the limbs, the scalp, trunk, lumbosacral area and/or buttocks, although not exclusively. Some patients will develop lesions within the body flexures (axillary, infra-mammary, abdominal pannicular, groin and perineal areas) and/or genitalia, either with classical plaques at other sites or in isolation. Such lesions often lack the classical scale due to a difference in skin keratinisation patterns. Psoriatic plaques may exhibit pathergy at the site of trauma or injury, known as the Koebner Phenomenon.

Several other more uncommon psoriatic phenotypes are recognised; guttate psoriasis presents with multiple 'dew-drop' lesions distributed in a centripetal pattern, 1-10mm in size, often proceeds an acute pharyngeal group B haemolytic streptococcal infection and may be self-limiting; generalised pustular psoriasis (vom Zumbusch) presents with painful and inflamed areas of skin overlaid with sheets of coalescing monomorphic sterile pustules; erythrodermic psoriasis presents as generalised erythema, with or without

exfoliation of the skin in an unwell, haemodynamically unstable individual. Patients with any form of psoriasis may experience symptoms of itching, burning or soreness.

Nail involvement is seen in approximately 12-50% of patients with psoriasis (Mallbris et al., 2005, Armesto et al., 2011) and significantly more if psoriatic arthritis (PsA) is present (Patrizi et al., 2014). Lesions occur due to disease at the nail matrix (causing irregular pitting, leuconychia, red spots in the lunula and crumbling of the nail plate), and at the nail bed (causing onycholysis, subungual hyperkeratosis, oil spot dyschromia and splinter haemorrhages). The fingernails are more commonly affected than the toenails.

1.1.4 Impact on Quality of Life

The chronic and multifaceted nature of psoriasis means that the effects often go deeper, beyond the visual signs and physical symptoms (Kimball et al., 2010). Many patients report a profound impact on their emotional wellbeing and have a reduction in their health-related quality of life similar to, or worse than, patients with other chronic diseases including ischaemic heart disease, diabetes, cancer, arthritis (Finlay and Kelly, 1987, Rapp et al., 1999). Age and gender are unrelated to the impact on quality of life (de Korte et al., 2004). The severity of the emotional impact is also demonstrated not to correlate with the severity of skin lesions (Heydendael et al., 2004); in a German study, almost one quarter of patients with ‘mild’ disease reported that psoriasis had a ‘very large’ or ‘extremely large’ effect on their quality of life (Augustin et al., 2008). Patients often feel stigmatised (Richards et al., 2001, Armstrong et al., 2012) with 82.9% feeling that they need to hide their psoriasis (Weiss et al., 2002). One in five report a sense of rejection due to their condition (Ginsburg and Link, 1993) and this contributes to depression and suicidal ideation in up to 10% of patients (Kurd et al., 2010, Gupta et al., 1993). Up to 85% of those affected by psoriasis feel annoyed with their disease (Sampogna et al., 2012), and 77% describe it as a ‘problem’ or ‘significant problem’ (Dubertret et al., 2006). Willingness to pay assessments reveal that patients are willing to pay large sums of money for a cure; in one study, 71% stated they could pay £1000 or more for a cure, and 38% said they would pay in excess of £10,000. When asked if they would prefer to have ‘a complete cure for their psoriasis’ or be given £1000 in cash but no cure, 98.9% stated that they would prefer to have the cure (Finlay and Coles, 1995). Many patients use negative health behaviours as a means of coping, and up to 32% of patients with moderate to severe psoriasis have been found to have problems with alcohol (McAleer et al., 2011).

1.1.5 Socioeconomic Burden

The long-term management of psoriasis is associated with substantial cumulative expenses to the patient, the healthcare system and to society as a whole. Costs associated with psoriasis are numerous and are classified as direct (treatment and healthcare provision), indirect (loss of work productivity and taxation revenue) and intangible (impairment of quality of life). In 2013, the annual total cost of psoriasis in the United States amounted to approximately $112 billion. Total direct costs ranged from $51.7 billion to $63.2 billion and indirect costs from $23.9 billion to $35.4 billion with the medical co-morbidities associated with psoriasis estimated to contribute $36.4 billion annually (Brezinski et al., 2015). When compared to the general population, the direct cost per psoriasis patient in the USA was $350 more per month ($614 vs. $284) (Fowler et al., 2008).

Within the UK, the mean total direct cost of managing a patient with severe psoriasis with conventional agents (e.g. methotrexate, ciclosporin) was reported in 2010 to be £4207 per year, which compares with published figures from several other European countries (€2169 to €8831 per annum) (Carrascosa et al., 2006, Schoffski et al., 2007, Colombo et al., 2008). With improved treatments comes a higher financial burden to the healthcare system, and the introduction of biologic therapy increased drug acquisition costs to approximately £9500 per patient per annum (Burden, 2010). However, around £1625 can be offset per year due to a substantial reduction in hospital admissions courtesy of the greater efficacy of these agents, and the direct savings from the prevention of psoriatic co-morbidities, although not quantified, are likely to be significant.

In terms of indirect costs, a survey completed by the Swedish Psoriasis Association reported that psoriasis limits employment opportunities and imposes a serious barrier in the job market (IFPA, 2007). Unemployment is three times more likely for people affected by psoriasis than for those unaffected (Schmitt and Ford, 2006) and approximately one third of patients who are not in employment describe being unable to work because of their psoriasis (Finlay and Coles, 1995). For those in work, one third of patients report missing at least one day per month, and one in ten patients miss three or more days due to their psoriatic disease (Schmitt and Ford, 2006). In the USA, it is estimated that Americans with psoriasis collectively lose approximately 56 million hours of work per year. This in turn has an impact on patient finances, and psoriasis is shown to be associated with a reduced household income (Meyer et al., 2010). This is related to disease severity; in a survey by the National Psoriasis Foundation, 21% of patients with severe psoriasis had a low income (less than US$30,000) compared to 13% for patients with mild disease (NPF, 2007).

1.1.6 Assessment of Psoriasis

1.1.6.1 Assessment of Psoriasis Clinical Disease Activity and Severity

The clinical assessment of psoriasis requires recognition of the phenotype (chronic plaque, guttate, inverse, erythrodermic) and the distribution of lesions. The latter is relevant not only because of the prognostic implications of lesions in certain areas for the development of PsA (Wilson et al., 2009, Patrizi et al., 2014) but also because of the higher functional and psychosocial morbidity associated with psoriasis in sites such as the face, hands and genitals as compared to lesions elsewhere (Meeuwis et al., 2011).

In terms of disease *activity*, at the most basic level, the assessment of psoriasis in clinical practice is straightforward. Patient-reported perceptions of severity are combined with the physician's static global assessment (PGA) and the physician is then able to determine how severe the psoriasis is and how well the patient is responding to treatment. However, patients have a heavy emotional investment in their own skin disease with little for comparison, and patient assessed severity and physician assessed severity can often be disparate. Any form of clinical assessment should therefore be complemented by an assessment of psychological, social, financial and functional impact.

The PGA is an average assessment of all psoriatic lesions based on erythema, scale and induration. It does not quantify body surface area (BSA) or evaluate individual lesion locations. Different forms of the PGA exist; the static PGA determines psoriasis severity at a single time point in time, without taking the baseline condition into account, whereas the dynamic PGA relies on the investigator's memory to evaluate the level of improvement of deterioration. The scales used vary widely from four points (Nijsten et al., 2007) to ten points (Heydendael et al., 2003), which has the potential to produce non-standardised assessments. An example of one of the more commonly employed scales is the seven point PGA as described in Table 1.1.

Severity	Description
Clear	No signs of psoriasis (post-inflammatory pigmentation may be present)
Almost Clear	Very minimal psoriasis, between clear and mild
Mild	Slight plaque elevation, scale and/or erythema
Mild-to-moderate	Intermediate between mild and moderate
Moderate	Moderate plaque elevation, scale and/or erythema
Moderate-to-severe	Intermediate between moderate and severe
Severe	Very marked plaque elevation, scale and erythema

Table 1.1: Description of the 7-point Physicians Global Assessment (PGA) for Psoriasis

The PGA should only measure the degree of erythema, scaling and induration. Aside from being subjective, it attracts criticism for not providing an overall measure of psoriasis severity because it does not account for body surface area (BSA) involvement (Robinson et al., 2012, Walsh et al., 2013b). For example, a patient with widespread disease (e.g. BSA 40%) could have the same PGA grade as a patient with very limited disease (e.g. BSA 1%). As a consequence, the PGA is often misused by clinicians with many taking the extent and distribution into account instead of just scoring plaque severity. In addition, the static PGA does not take into account the previous disease state, and whilst the dynamic PGA attempts to overcome this, it can be difficult for a physician to recall prior disease activity for each patient under his/her care, and within one institution, patients may be reviewed by multiple different members of the clinical team. Only moderate inter-rater reliability is found with the PGA (Berth-Jones et al., 2006).

An assessment of the body surface area (BSA) involvement forms part of many other tools for psoriasis activity. The BSA uses the rule of nines, developed for the assessment of burns (Wallace, 1951, Ramsay and Lawrence, 1991). Using this method, the head and neck contribute approximately 10%, the upper limbs 20%, the trunk (chest, abdomen and back) 30% and the lower limbs 40%. It is erroneously suggested that the surface of the patient's own hand (palm and fingers) is approximately equivalent to 1% of the total BSA (Jose et al., 2004); however, this method has been shown to overestimate BSA (Rossiter et al., 1996), with one outstretched palm and five fingers equating to 0.8% in males and 0.7% in females (Long et al., 1992). Several authorities, including the British Association of Dermatologists and The National Psoriasis Foundation in the USA define severe psoriasis as a BSA of 10% or greater (Smith et al., 2009, Mrowietz et al., 2011, Van Voorhees, 2009).

Over 53 clinometric measures for the assessment of psoriasis activity have been described, and aside from the PGA and BSA, the majority combine measures of both

surface area involvement and plaque severity (Spuls et al., 2010). These include the Psoriasis Area and Severity Index (PASI) (Fredriksson and Pettersson, 1978), Self-Administered PASI (SAPASI) (Fleischer et al., 1994), Lattice System-PGA (LS-PGA) (Langley and Ellis, 2004), Simplified PASI (SPASI) (Louden et al., 2004), Psoriasis Log-Based Area and Severity Index (PLASI) and Psoriasis Exact Area and Severity Index (PEASI) (Jacobson and Kimball, 2004).

Of these, the PASI is the most commonly used and best validated instrument and is now widely accepted as the gold standard assessment tool for psoriasis (Feldman and Krueger, 2005, Robinson et al., 2012). In a review of all clinical studies grading the severity of psoriasis over a twenty-nine year period, the construct validity, content validity, internal consistency, inter-observer variation, sensitivity to change and time required to perform the measurement were analysed, and whilst none of the scoring tools met all of the validation criteria, the PASI was the most extensively used and most thoroughly validated (Puzenat et al., 2010).

In this method, the sum of the erythema, induration and scaliness of the lesions (graded 0-4) for each body region (head, upper limbs, trunk, lower limbs) are multiplied by weighted area scores, which take into account the relative BSA for each body area (Appendix 7) to produce a score that ranges from 0 to 72. With practice, the PASI is relatively easy to calculate (Langley and Ellis, 2004), is sensitive to change in chronic plaque psoriasis and has shown substantial intra-rater and inter-rater reliability (defined as >80% agreement) (Berth-Jones et al., 2006, Chandran et al., 2009a).

However, the PASI is not without its limitations. It lacks sensitivity for mild disease with minimal BSA involvement because changes largely depend on plaque severity score (and not surface area) improvement (Jacobson and Kimball, 2004). The PASI score may therefore underestimate the general degree of improvement (Spuls et al., 2010) in patients with, for example, localised disease affecting the genitals, nails, scalp and/or hands (de Korte et al., 2004). Area scores are based on ranges, and areas between 1% and 9% are assigned the same area score of 1 (Jacobson and Kimball, 2004). The PASI is also not a linear index, which makes the score less meaningful in terms of the impact of disease. For example, a small change in the BSA from 9% (area score 1) to 10% (area score 2) results in a doubling of the PASI score if the parameters of plaque activity within that area remain unchanged (Robinson et al., 2012).

The PASI was designed to be used in clinical trials, and its widespread uptake within the research arena means that, in contrast to the incompatibility of measures used up to the 1980s, it is now possible to meaningfully compare outcome data from different studies (Finlay, 2005). In addition, the PASI score is increasingly used by regulatory bodies, such as the National Institute for Health and Care Excellence (NICE) as a means of therapeutic rationing, and as such, its use in the clinical setting is now rapidly increasing.

In the UK, a PASI score of ten or more is forms part of mandatory eligibility criteria for biologic therapy.

Whilst a PASI score of ten or more is generally accepted to reflect a PGA of 'severe', there is no consensus on the interpretability (van de Kerkhof, 1992, Krueger et al., 2000, Gottlieb et al., 2003a, Jacobson and Kimball, 2004, Langley and Ellis, 2004, Berth-Jones et al., 2006). Similarly, there is no consensus on what is a clinically meaningful improvement in response to therapy either in the clinical setting or in research trials. For patients with severe psoriasis, physicians typically consider at least 75% reduction in disease activity (so called a 'PASI 75' response) to be an improvement indicative of treatment success. However, it is clear that patients with far lower decreases in the PASI score can have clinically meaningful improvements in their disease if accompanied by a significant rise in quality of life. There is strong evidence that a 50% response ('PASI 50') can also be clinically significant (Schafer et al., 2010) and that a therapy should not be deemed to have failed if a patient does not reach a PASI 75 response (Carlin et al., 2004). The NICE guidance on the use of biologic therapies in the UK has recognised this, and at predetermined time points (usually 12-16 weeks) will allow continuation of therapy if a patient achieves either; (i) a 75% reduction in PASI from baseline (in isolation) or: (ii) a 50% or greater reduction in baseline PASI and a 5-point or greater improvement in the Dermatology Life Quality Index (DLQI), a quality of life measure (Smith et al., 2009, Shikiar et al., 2006, Khilji, 2002). However, advances in the understanding of the pathogenesis of psoriasis are facilitating an exciting and exponential expansion of molecular targets including IL-23p19, IL-17A and IL-17RA, and a 90% response ('PASI 90') will soon become the new standard in therapeutic efficacy (Puig, 2015, Smith et al., 2017).

1.1.6.2 Assessment of Nail Psoriasis

Nail psoriasis is a common, burdensome feature of psoriasis that can be severe and disfiguring. Nail lesions affect approximately 40% of patients with psoriasis and between 63% and 83% of patients with PsA (Elkayam et al., 2000, Salomon et al., 2003, Augustin et al., 2010, Williamson et al., 2004). One study of 1728 patients with psoriasis found that 93% considered nail psoriasis to be a significant cosmetic handicap, 52% reported pain and 48% felt that it interfered with their occupation (de Jong et al., 1996).

Psoriasis can affect any combination of components of the nail, including the nail plate and surrounding epithelial structures (proximal nail fold, matrix, nail bed and hyponychium). Characteristic features of psoriasis affecting the nail matrix include pitting, nail plate crumbling, leukonychia and red spots in the lunula. Pits are sharply defined depressions in the nail plate, caused by shedding of nail plate cells, much the same as psoriatic scale is shed from the skin. Psoriasis affecting the nail bed produces

oil-drop discolouration, onycholysis, nail bed hyperkeratosis and splinter haemorrhages (Omura, 1985). Treatment of nail psoriasis has been largely unsatisfactory, but the availability of effective therapies for psoriasis and PsA has raised the possibility of treating nail psoriasis in a more effective way.

While not routinely used in clinical practice, quantitative assessments of response in clinical trials have necessitated the development of validated tools for assessing the extent and severity of nail involvement. Several instruments have been developed including Baran's nail psoriasis severity Index (Baran, 2004), Cannavo's Scoring System (Cannavo et al., 2003) and Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) tool (Augustin et al., 2014), although the modified Nail Psoriasis Severity Index (mNAPSI) (Cassell et al., 2007), and its predecessor, the Nail Psoriasis Severity Index (NAPSI) (Rich and Scher, 2003) are the most widely used and validated. The mNAPSI involves rating the presence/absence and severity of features of psoriasis in both the nail matrix and nail bed of each nail, producing a maximum possible score of 14 per nail (140 per patient) (Cassell et al., 2007) (Table 1.2). The mNAPSI has been used as a secondary endpoint in several clinical trials of biologic therapies in psoriasis and is shown to be sensitive to change (Kavanaugh et al., 2012, Ortonne et al., 2013, Reich et al., 2005, Rich et al., 2014, Van den Bosch et al., 2010). However the mNAPSI, like all other nail psoriasis scoring tools, does not provide an objective measure of patient burden or reflect problems such as pain, restrictions on social and working life or the psychological impact of nail changes (Augustin and Ogilvie, 2010).

Features		Right Fingernails					Left Fingernails				
		5	4	3	2	1	1	2	3	4	5
Onycholysis	0 = none	0	0	0	0	0	0	0	0	0	0
	1 = 1-10% of nail surface	1	1	1	1	1	1	1	1	1	1
	2 = 11-30% of nail surface	2	2	2	2	2	2	2	2	2	2
	3 = >30% of nail surface	3	3	3	3	3	3	3	3	3	3
Pitting	0 = none	0	0	0	0	0	0	0	0	0	0
	1 = 1-10 pits	1	1	1	1	1	1	1	1	1	1
	2 = 11-49 pits	2	2	2	2	2	2	2	2	2	2
	3 = >50 pits	3	3	3	3	3	3	3	3	3	3
Nail plate crumbling	0 = none	0	0	0	0	0	0	0	0	0	0
	1 = 1-25% of nail	1	1	1	1	1	1	1	1	1	1
	2 = 26-50% of nail	2	2	2	2	2	2	2	2	2	2
	3 = >50% of nail	3	3	3	3	3	3	3	3	3	3
Features (tick if present)		Right Fingernails					Left Fingernails				
Leukonychia											
Splinter haemorrhage											
Nail bed hyperkeratosis											
Red spots in lunula											
Oil spot dyschromia											
Total per nail (/14)											

Table 1.2. Modified Nail Psoriasis Severity Index (mNAPSI).

1.1.6.3 Assessment of Psoriasis on Health-Related Quality of Life

A major component of the assessment of psoriasis is the measurement of health-related quality of life (HRQoL) in addition to disease activity. Improvement in a patient's life and wellbeing is the principle goal of any therapy; evaluations of HRQoL are very important (Kirby et al., 2001) and should be performed in parallel with measures of visible disease severity. Some patients may have widespread psoriatic lesions but not be affected by them, whist others may have only a few lesions and be greatly bothered by them, especially if they are in very visual sites such as the face, scalp or dorsal hands. Despite this lack of direct correlation between HRQoL values and more objective clinical measures such as the PASI and PGA (Reich and Griffiths, 2008), significant reductions of PASI are likely to correlate with significant improvements of HRQoL. However, the correlation is not linear (Mattei et al., 2014, Revicki et al., 2008).

The effect of psoriasis on HRQoL can be measured using a number of general health, dermatology-specific and psoriasis-specific tools. The most widely cited are listed in Table 1.3.

Category	Assessment Tool
General Health Related	Medical Outcome Survey Short Form 36 (SF-36) (Ware and Sherbourne, 1992)
	EuroQol-5 (EQ-5D) (EuroQol, 1990, Brooks et al., 1991)
Dermatology-Specific	Dermatology Life Quality Index (DLQI) (Finlay and Khan, 1994)
	Skindex (Chren et al., 1996)
Psoriasis-Specific	Psoriasis Disability Index (PDI) (Finlay and Kelly, 1987)
	Psoriasis Index of Quality of Life (PSORIQoL) (McKenna et al., 2003)
	Psoriasis Life Stress Inventory (PLSI) (Gupta and Gupta, 1995)

Table 1.3: Quality of life instruments used in the assessment of patients with psoriasis

The DLQI has been most widely used measure for assessing HRQoL related to psoriasis in clinical trials (Finlay and Khan, 1994). This patient-reported outcome measure was developed for use in all dermatoses, and comprises ten questions that ask the patient to rate how much their skin disease has affected several domains of their life in the past seven days from ‘not at all’ to ‘very much’ (scored 0-3). A maximum score of 30 is achievable (Appendix 3). The questions concern symptoms and feelings, daily activities, work and school, leisure, personal relationships and treatment. Like the PASI, the DLQI is the only quality of life assessment tool that forms part of the eligibility criteria for biologic therapy in the UK, where a score of ten or more is required.

Good internal validity, construct validity, content validity and sensitivity to change are demonstrated for the DLQI (Bronsard et al., 2010, Safikhani et al., 2013, Mazzotti et al., 2003, Shikiar et al., 2003). However, while a Rasch analysis found good internal reliability, poor responsiveness to change was reported in patients with mild disease (Twiss et al., 2012).

The Psoriasis Disability Index (PDI) was the first HRQoL questionnaire designed specifically for use in patients with psoriasis (Finlay and Kelly, 1987). The questionnaire is validated (Finlay et al., 1990) and has shown sensitivity to change (Lewis and Finlay, 2005, Kent and al-Abadie, 1993). However, the PDI is not perfect; it has been shown to have a significant floor effect and specific data relating to the least change in the score that is of importance to patients have not yet been prospectively identified. The PDI also attracts criticism for being more focused on symptoms than quality of life and in more recent clinical trials, it has lacked sensitivity (Nijsten et al., 2005, Fernandez-Penas et

al., 2012). The Psoriasis Index of Quality of Life (PSORIQoL) (McKenna et al., 2003) and the Psoriasis Life Stress Inventory (PSLI) (Gupta and Gupta, 1995) have similarly been developed for use specifically in psoriasis, but there has been little uptake of these tools in clinical trials in over a decade.

The difficulty with novel scoring systems such as the PDI, PSORIQoL and PLSI is that they are of little or no use in the clinical setting if the clinician is not able to interpret the absolute meaning of a score or change in score. This has only been investigated for the DLQI where absolute score banding has been proposed (0-1, 'no effect' on HRQoL; 2-5, 'small effect'; 6-10, 'moderate effect'; 11-20, 'very large effect'; 21-30, 'extremely large effect') (Hongbo et al., 2005). The most critical single concept is that if the DLQI s greater than ten, this represents psoriasis that is having a very large effect on a patient's life, meriting intervention, and this is reflected in the NICE guidance for the use of biologic therapies (Smith et al., 2009).

1.2 Management of Psoriasis

Treatment of psoriasis can be challenging, since a spectrum of clinical presentations, different psoriasis phenotypes, comorbidities and patient factors need to be considered. In the past decade, a large number of effective treatments have been developed and standards regarding management have evolved. These standards include evidence-based guidelines, implementation tools and the use of valid outcome measures such a PASI, mNAPSI and DLQI.

The successful management of psoriasis must be holistic and can include topical and systemic pharmacotherapeutic agents, physical treatments (e.g. phototherapy), psychological support and lifestyle modification. The approach to treatment should follow a step-wise approach and correlate with the severity of psoriasis (Figure 1.5).

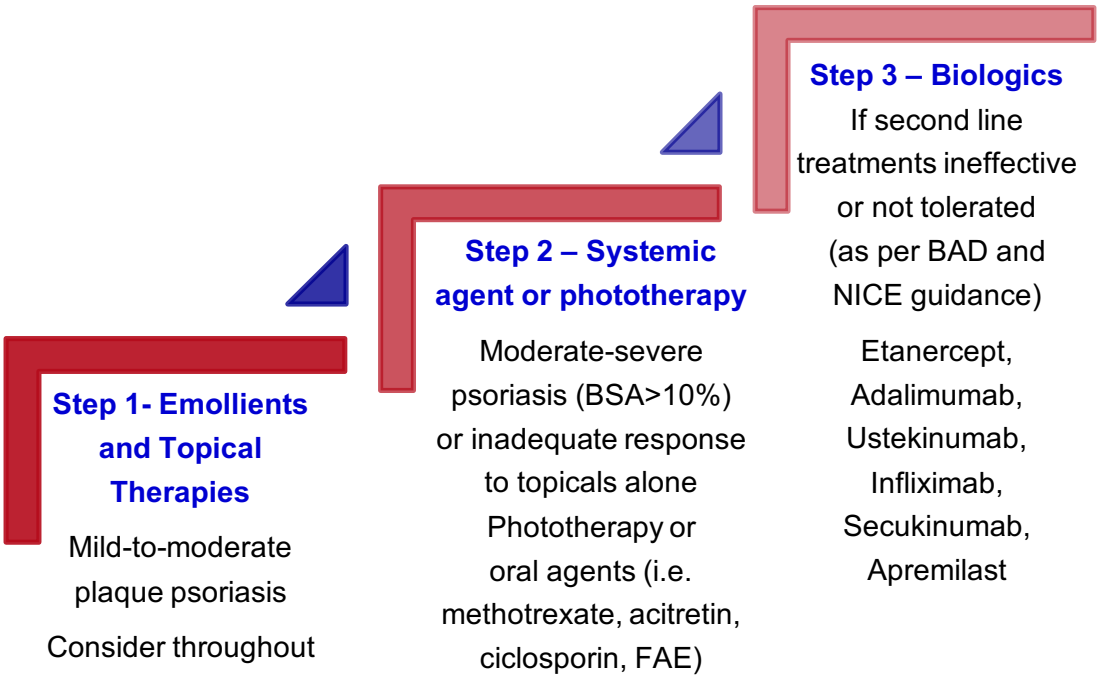

Figure 1.5. The stepwise approach to managing psoriasis. FAE; Fumaric acid esters.

For patients with moderate to severe psoriasis, the landscape has evolved significantly and patients can now aim for clear or almost clear skin. Until 2003, phototherapy and conventional systemic agents were the mainstay (and top line) of treatment for moderate or severe psoriasis that could not be adequately controlled with topical therapies, and they remain an integral part of all psoriasis management guidelines as they are effective therapy for some patients. However, for others, inadequate response or significant side effects (e.g. gastrointestinal upset, organ toxicity or skin cancer) necessitate discontinuation and the search for an alternative. Following the first approval of alefacept and efalizumab by the FDA in 2003, major advances in the understanding of the pathogenesis of psoriasis have facilitated the development of highly selective biological agents targeting TNF-α, IL-23 and IL-17, which have revolutionised modern psoriatic disease management.

1.2.1.1 Biologic Therapies

The recognition that the beneficial effect of ciclosporin in psoriasis is attributable to the drug's impact on T lymphocytes provided a breakthrough in terms of understanding the pathogenesis of psoriasis and identified T cells as an important target for psoriasis therapy (Griffiths and Voorhees, 1990). The role of the lymphocyte was confirmed when Krueger and colleagues successfully treated psoriasis using a lymphocyte-selective fusion protein consisting of IL-2 and fragments of diphtheria toxin. This selectively blocks activated lymphocytes but has no effect on keratinocytes. Eight out of ten patients treated

with two doses had a moderate or marked reduction in their psoriasis, confirming the role of the lymphocyte (Gottlieb et al., 1995).

Beyond the cellular components, the concept of a cytokine network in genetically predisposed patients leading to abnormal keratinocyte proliferation in response to infectious or traumatic skin exposures began to emerge. The importance of Th1 cytokines and IFN-γ in the activation of lymphocytes and T-cell trafficking (Huang et al., 2001) lead to the development of the first two FDA-approved biologic agents, alefacept and efalizumab (both now withdrawn), which blocked T-cell activation (Krueger et al., 2002, Lebwohl et al., 2003).

The role of TNF-α was not recognised until anecdotal clinical efficacy had been observed in non-psoriatic diseases, where it was noted that TNF-α antagonists rapidly reduced IL-1 and IL-8, followed by reductions in inflammatory gene expression including IFN-γ. The reduction in T-lymphocyte activation and decreased production of cytokines, chemokines, lymphocytes, neutrophils, dendritic cells and keratinocytes stopped the feedback cycle of immune activation leading to keratinocyte proliferation and chronic inflammation. By 2004, the FDA approved the first TNF inhibitor, etanercept (a human TNF receptor p75 Fc fusion protein), followed by infliximab (a chimeric human-mouse IgG monoclonal antibody, 2006) and adalimumab (a recombinant human IgG1 monoclonal antibody, 2008). These agents are still at the fore of biologic therapy for moderate to severe psoriasis and provide PASI 75 responses (by week 10-12) of 30%, 53% and 80% respectively (Gordon et al., 2006, Gottlieb et al., 2003b, Reich et al., 2005, Menter et al., 2008). However, due to the development in some of anti-drug antibodies, which can be exacerbated by poor drug compliance, efficacy can be lost and alternative agents required to obtain or maintain such PASI responses. TNF inhibitors are also associated with worsening of cardiac failure and demyelination.

Further advances in understanding of the complex cytokine network in psoriasis focused attention on the p40 subunit, found on both IL-12 and IL-23, which lead to the development of two new anti-p40 monoclonal antibodies, ustekinumab (Lebwohl et al., 2012) and briakinumab (Reich et al., 2011) (both recombinant human IgG1 kappa monoclonal antibodies). Impressive PASI 75 responses were observed (67-76% for ustekinumab), and the former was FDA approved for psoriasis in 2009. Briakinumab was equally effective but approval was not pursued after a small increase in major adverse cardiac events during phase III clinical trials (Langley et al., 2013). Data from the British Association of Dermatologists Biologics Intervention Register (BADBIR) (Warren et al., 2015), the Danish DERMBIO registry (Gniadecki et al., 2015) and PSOriasis Longitudinal Assessment and Registry (PSOLAR) have all shown that ustekinumab has a significantly longer drug survival than the anti-TNF-α agents, reflecting greater effectiveness, safety and tolerability.

It has since become apparent that it is inhibition of IL-23 that is the main reason for the efficacy of ustekinumab in psoriasis, and the IL-23/IL-17 axis has since come to the fore as the key target in psoriasis for the pharmaceutical industry. IL-23 is produced by antigen presenting cells and induces and maintains differentiation of Th17 cells, a primary cellular source of IL-17, which mediates the epidermal hyperplasia, keratinocyte immune activation and tissue inflammation inherent in psoriasis. Selectivity for the other subunit of IL-23 (p19) could offer advantages in efficacy over IL-23p40 blockade with respect to distal blockade of IL-17A, or its receptor. Two biologic agents, guselkumab (CNTO1959, Janssen Biotech, Inc.) and Tildrakizumab (MK-3222, Sun Pharmaceuticals) have received FDA approval for psoriasis in 2017, and phase II and III trials are currently underway with several other new anti-IL-23p19 biologic drugs including Brazikumab (AMG-139, Amgen), Risankizumab (BI 655066, Boehringer-Ingelheim), Mirikizumab (LY3074828, Eli Lilly). In a head to head comparator study of guselkumab versus adalimumab (VOYAGE-1), significantly higher proportions of patients receiving the former achieved PASI 90 by week 16 (73.3% vs. 65.9% for guselkumab and adalimumab, respectively) (Blauvelt et al., 2017) suggesting a therapeutic shift away from TNF-inhibition is highly likely in the near future. The first IL-23p19 is due to come to market in the UK in early 2018.

At least four antibodies directly targeting IL-17A, IL-17A/F or its receptor have also been studied clinically and have shown dramatic PASI responses in as little as 12 weeks (PASI 90 59.2-70.9%). Secukinumab (Langley et al., 2014) and Ixekizumab (Leonardi et al., 2012) both target IL-17A and have received approval by NICE in 2017, and a third, Brodalumab (Papp et al., 2012), an antibody to the IL-17 receptor, is expected to receive approval imminently. Bimekizumab, which neutralises both IL-17A and IL-17F, has completed phase IIb studies with impressive results and has now progressed to a full phase III programme (Papp et al., 2018). Class-related adverse effects have been observed with IL-17A blockade including mucocutaneous candidiasis and triggering or worsening of inflammatory bowel disease, which are absent for other drugs targeting cytokines further upstream in the IL-23/Th17 pathway.

1.2.2 The ‘Psoriatic Disease’ Complex

Psoriasis should no longer be considered as a distinct disease entity affecting only the skin (Lotti et al., 2010). It is believed that up to 73% of patients with psoriasis will have at least one comorbidity (Puig-Sanz, 2007), and psoriasis should therefore be considered as part of a multisystem psoriatic disease spectrum. This spectrum includes psoriatic arthritis, inflammatory bowel disease, non-alcoholic fatty liver disease, uveitis, metabolic syndrome (obesity, dyslipidaemia, diabetes mellitus, hypertension), cardiovascular disease and psychiatric disorders (Nijsten and Wakkee, 2009). Systemic inflammation is

the common denominator for all of these immune-mediated co-morbidities, although uncertainty still remains about the factor(s) that either initiate or perpetuate this immune reaction and the complex interplay with genetic factors that cause the wide phenotypic variation of patients with psoriatic disease. It is not yet known if the presence or severity of these comorbid conditions can be attenuated with the early introduction of immunomodulatory treatment, and this is the current focus of much research interest.

1.3 Psoriatic Arthritis

The association between psoriasis and arthritis was first recognised by Baron Jean Luis Aliberti in 1818, and later in the nineteenth century, several French physicians described the association between arthritis and psoriasis, including Charles Bourdillon, whose 1988 doctoral thesis was entitled 'Psoriasis et Arthropathies' (Gladman and Chandran, 2009). However, many considered the presence of arthritis associated with psoriasis to be a variant of rheumatoid arthritis, and it was not until 1956 that Professor Verna Wright first described PsA as a specific entity (Wright, 1956). Rheumatoid factor, a test discovered in 1948, was found to be positive in 85% of patients with RA and fewer than 15% of patients with PsA, which cemented the distinction of PsA as a distinct arthropathy (Alexander, 1967).

1.3.1 Epidemiology

PsA is now recognised as an immune-mediated inflammatory disease that predominately affects the musculoskeletal structures as well as the skin, nails and mucosa. PsA is considered to be part of the spectrum of seronegative spondyloarthropathies, which are unified by their involvement of the axial skeleton and entheses and association with human leukocytes antigen (HLA) B27. The prevalence of PsA in the general population of Europe, based on studies from the Netherlands, England, France, Greece, Norway, Iceland and Denmark, is estimated to be between 0.05% and 0.195%, in the US, estimates range from 0.101% to 0.25% and in Australia, one study revealed a prevalence of 0.47%. Variations are probably due to ethnic differences, heterogeneity in study methods and criteria for defining PsA between populations. The introduction of the ClASsification criteria for Psoriatic Arthritis (CASPAR) has helped to standardise epidemiological assessments for PsA (Figure 1.6) (Taylor et al., 2006). Studies outside of Europe and the US are few, but the reported prevalence in Japan is strikingly low at 0.00001% (Gladman and Chandran, 2009).

Inflammatory articular disease that may involve joint, entheseal or axial manifestations

AND

Current psoriasis + 1 of the following	Personal or family history of psoriasis + 2 of the following	No psoriasis + 3 of the following

Dactylitis	Psoriatic nail dystrophy	Negative Rheumatoid Factor	Radiological evidence of juxta-articular new bone formation

Figure 1.6. The ClASsification criteria for Psoriatic ARthritis (CASPAR).

Amongst patients with psoriasis, clinic-based studies have reported PsA prevalence as 6 to 48%, again depending on the population measured, diagnostic codes and criteria for defining PsA. For example, Alenius et al reported the prevalence at 48%, but included a broad reaching definition including peripheral arthritis, axial arthritis, enthesitis and undifferentiated spondyloarthritis (Alenius et al., 2002). An international study involving clinics from the UK, France, Germany and Spain showed the prevalence increased with time since diagnosis of psoriasis, reaching 20.5% after 30 years (Mease et al., 2013). In Japan, among a sample of 28,628 cases of psoriasis in 148 dermatology centres, only 1% had PsA, confirming the very low prevalence of PsA in Japan (Kawada et al., 2003). Table 1.4 shows the differences in PsA prevalence from studies of patients with psoriasis in the western world.

Author (year)	Centre	Psoriasis Patients (n=)	PsA (%)
Leczinsky (1948)	Sweden	534	7
Vilanova (1951)	Barcelona, Spain	214	25
Little (1975)	Toronto, Canada	100	32
Scarpa (1984)	Napoli, Italy	180	34
Stern (1985)	Boston, US	1285	20
Zaneli (1992)	Winston-Salem	459	17
Barisic-Drusko (1994)	Osijek region, Croatia	553	10
Salvarani (1995)	Regio Emilia, Italy	205	36
Shbeeb (2000)	Mayo Clinic, US	1056	6.25
Brockbank (2001)	Toronto, Canada	126	31
Alenius (2002)	Sweden	276	48
NPF (2002)	US	4.4 m	23
Zachariae (2003)	Denmark	5795	30
Reich (2008)	Germany	1511	20.6
Ogdie (2012)	UK	4064	8.6
Haroon (2013)	Dublin, Ireland	100	29
Walsh (2013)	Utah, US	189	30
Mease (2013)	International	1000	30

Table 1.4. Summary of published studies of the prevalence of psoriatic arthritis (PsA) in the western world.

The incidence of PsA among patients with psoriasis in Europe and the US in the general population ranges between 3 and 7.2 cases per 100,000 population (Shbeeb et al., 2000, Wilson et al., 2009, Alamanos et al., 2003), although a higher incidence of 23.1 to 27.3 per 100,000 population is reported in Scandinavia (Egeberg et al., 2017, Kaipiainen-Seppanen, 1996). In a recent prospective cohort study from Canada that involved psoriasis patients without PsA at entry, 51 of 464 patients developed PsA over eight years of follow up. The annual incidence rate was 2.7 cases per 100 psoriasis patients (Eder et al., 2016). This is an increase from 2011, where a previous observational study by the same group showed an annual incidence rate of 1.87 cases of PsA per 100 psoriasis patients (Eder et al., 2011a).

1.3.2 Pathogenesis

Investigating the pathology of PsA is complex given the heterogeneity of clinical manifestations. As understood in psoriasis, PsA appears to be associated with abnormal activation of both the innate and adaptive immune system in genetically primed individuals. The heritability of PsA is much greater than that of psoriasis (recurrence risk

ratio estimated at 27 for PsA, and between 4 and 11 for psoriasis) (Gladman et al., 2003, Bhalerao and Bowcock, 1998). In those with a first to fourth degree relative with PsA, a study from Iceland confirmed significantly increased risk ratios for the development of PsA (39, 12, 3.6 and 2.3, respectively, $p<0.0001$) (Karason et al., 2009). Numerous genetic susceptibility loci have been identified for PsA including HLA-B27, B7, DR4, B38 and DR7, in addition to those shared with psoriasis (HLA-B13, B17, B57 and B39) (Ho et al., 2008, Al-Heresh et al., 2002, Chandran et al., 2009b). Assocaition with HLA-Cw06 remains contentious, with recent cross-phenotype association mapping of the MHC in one study finding no association of PsA to HLA-C*06:02 after controlling for the age of psoriasis onset. The most significant association was to amino acid at position 97 of HLA-B, where the presence of asparagine or serine residue increased PsA risk (Bowes et al., 2017). Asparagine at position 97 of HLA-B defines the HLA-B27 alleles. GWAS studies have also identified a number of gene polymorphisms including TNF-α promoter, IL-23A, IL-23R and IL-12B, and associations within the NFκB pathway (TNF-a induced protein 3 (TNFAIP3), and TNFAIP3 interacting protein, TNIP1 (Rahman et al., 2006, Cargill et al., 2007, Liu et al., 2008, Nair et al., 2009).

The presence of susceptibility genes in an individual defines the T-cell repertoire that is developed on the individual's self-peptides and self-MHC, and is poised for auto-reactivity until triggered. Several environmental factors appear to trigger PsA, with multiple studies showing an association with acute trauma, either physical (akin to a 'deep koebner' response) (Thorarensen et al., 2017, Eder et al., 2016, Ogdie and Gelfand, 2010, Punzi et al., 1997, Scarpa et al., 1992), or psychological distress (e.g. emotional stress) (Pattison et al., 2008). Like psoriasis, infection may also be a significant trigger for PsA. Clear associations between human immunodeficiency virus (HIV) infection and both psoriasis and psoriatic arthritis have been reported (Njobvu and McGill, 2000), and an increased prevalence of hepatitis C infection has been observed in patients with PsA compared to patients with psoriasis, RA or the general population (Taglione et al., 1999). Group A streptococcal infections are associated with the development of guttate psoriasis, and ribosomal RNA of this bacterium have been detected in the peripheral blood and synovial fluid of patients with PsA (Wang et al., 1999).

Once triggered, the immune process results in the two main features of PsA; the inflammatory infiltrate of T lymphocytes and accessory cells into the entheses and synovium, and the response of these tissues to the products and consequences of the inflammatory infiltrate. Within the synovium, significant angiogenesis is observed due to the upregulation of promoters of angiogenesis, much like in a psoriatic plaque, which facilitates an increase in infiltrating immune cells (Gao et al., 2013, Kruithof et al., 2005). Synovial tissue in PsA is characterised by expression of proinflammatory cytokines including TNF-α, IFN-γ, IL-1, IL-6, IL-8 and IL-10 IL-12, IL-15, IL-18 and IL-23 (van Kuijk

et al., 2006), with relationships observed between cytokine levels and clinical arthritis severity (Szodoray et al., 2007). Destructive matrix metalloproteinases have been associated with synovitis and subsequent bone erosion in PsA, which occurs through increased osteoclast activity (Bond et al., 2007). Osteoclasts are derived from TNF-α-activated peripheral blood mononuclear cells, which migrate to inflamed synovium and subchondral bone. Here they are exposed to unopposed receptor activator of NFκB ligand (RANKL) and TNF-α, leading to osteoclastogenesis and the formation of bone erosions (Ritchlin et al., 2003). Increased osteoclast precursors have been identified in the peripheral blood of patients with PsA, which decease with administration of TNF inhibitors, which may account for some of their clinical activity (Anandarajah et al., 2008).

Heterogeneity has been observed in patients with PsA, with some showing predominantly synovial disease on MRI (as seen in RA), while others show neighbouring inflammation in thickened collateral ligaments and periarticular soft tissue, exhibiting a predominantly entheseal driven disease (Jevtic et al., 1995). Subsequently, enthesitis was demonstrated to be a common clinically inconspicuous finding in inflamed synovial joints (McGonagle et al., 1998b) and can occur in the absence of synovitis (Frediani et al., 2001). Enthesitis is now generally accepted as the primary inflammatory lesion in PsA, with secondary dissipation of inflammation to the synovium and extracapsular structures. Further detail regarding enthesitis can be found in Chapter 1.3.

1.3.3 Diagnosis, Classification and Subtypes

The diagnosis of PsA is principally clinical, based on history and examination findings, with support from several imaging modalities. Psoriasis tends to precede the development of PsA in 70% of cases, occur simultaneously in 10-15% and develop before skin manifestations in 10-15% (Cohen et al., 1999, Leung et al., 2007). Typically, in those with precedent psoriasis, PsA symptoms emerge within the first seven to fifteen years after psoriasis onset (Tillett et al., 2017a). Patients describe joint stiffness and pain, fatigue and decreased physical function, and in those with axial disease, back pain and/or buttock pain. Stiffness generally is worse after rising, and improves throughout the morning. In the majority, the onset is insidious, but it can be acute in up to one third of patients.

The CASPAR criteria (Figure 1.6) are now widely adopted to help classify patients with inflammatory arthritis as PsA if they meet the criteria (Taylor et al., 2006), and have been shown to be more sensitive than other classification criteria, even in early PsA (Coates et al., 2012). The sensitivity and specificity have been reported in three separate cohorts as 98.2-100% and 98.8-99.7%, respectively (Leung et al., 2010, Chandran et al., 2008, Tillett et al., 2012a).

Five subtypes of PsA have been recognised, although they are seen as a spectrum rather than distinct phenotypes (Moll and Wright, 1973):

- Distal interphalangeal joint predominant arthritis
- Asymmetrical polyarthritis
- Symmetrical polyarthritis (similar to rheumatoid arthritis but without a positive rheumatoid factor)
- Arthritis mutilans
- Axial disease-predominant

Oligoarthritis is observed most frequently in early PsA, with phenotypic progression to polyarthritis described with time (Gladman et al., 1987, Helliwell et al., 1991, Jones and McHugh, 1994, Marsal et al., 1999, Khan et al., 2003). Approximately one third of patients will also exhibit dactylitis, a uniform swelling of a finger or toe digit or digits (Gladman et al., 2013), and/or enthesitis, which may present with tenderness and/or swelling over tendon insertion sites (Sakkas et al., 2013).

1.3.4 Impact on Quality of Life

PsA places a substantial burden on patients, causing pain and diminishing their capacity to carry out daily activities which has an impact on quality of life. Many patients also have visible skin involvement, resulting in self-consciousness, embarrassment and anxiety, further adding to poor psychosocial function (Mease, 2009). Measures of health-related quality of life are lower in patients with PsA than in healthy people and those with other inflammatory arthritides (Borman et al., 2007, Husted et al., 2001), and also than in patients with psoriasis alone (Rosen et al., 2012). In the Nottingham Health Profile, PsA patients reported greater role limitations caused by emotional problems as well as more bodily pain, reduced energy and sleep and social isolation (Borman et al., 2007). Depression is also often present; in an observational Canadian study, patients who had had PsA for longer than two years were two to five times higher than those of age-matched controls who had no history of PsA or psoriasis.

Patients with PsA commonly report fatigue and sleep disturbances, which can contribute to reduced quality of life. Approximately 50% complain of moderate-to severe fatigue, and 29% complain of severe fatigue (Husted et al., 2009), with the presence of PsA being a strong predictor of sleep disturbance (odds ration 3.27, $p<0.001$) (Callis Duffin et al., 2009). A pilot test of willingness to pay for cure, most participants were willing to pay a median of $10,00 for physical comfort, sleep and work, and $5,000 for emotional health, with patients earning higher incomes willing to pay even more (Hu et al., 2010).

1.3.5 Socioeconomic Burden

Approximately 40-60% of patients with PsA may develop erosive and deforming joint disease, leading to progressive disability and pain (Liu et al., 2014). PsA is also associated with several comorbidities including anxiety and depression, reduced quality of life, obesity, hypertension, type II diabetes and cardiovascular disease (Husni and Mease, 2010). The proportion of work disabled patients with PsA has been reported to be approximately 40% yet few studies to date have focused on the inequities of PsA from a social and economic perspective (Kristensen et al., 2013, Tillett et al., 2012b). In a recent nationwide population-based cohort study from Denmark based on prospectively recorded register data, patients with PsA were found to have significantly more comorbidities including cardiovascular disease, respiratory illnesses and infectious diseases compared with the general population. Patients had higher total healthcare costs and lower income, and incurred on average, a net increased cost to society of €10,641 per patient-year than the general population. The relative risk (compared to the general population) for being on a disability pension five years prior to the diagnosis of PsA was 1.36 (95 C.I. 1.24-1.49), rising to 1.60 (1.49-1.72) at diagnosis and to 2.69 (2.40-3.02) 10 years after diagnosis, where 21.8% of patients with PsA received a disability pension (Kristensen et al., 2017). Given the clinical burden of PsA, it is not surprising that patients are significant users of health care resources. In a German study, patients made 20.3 visits to a general practitioner every year, and 3.9 visits to a rheumatologist, and 12.7% had required at least one hospitalisation in the previous year (Zink et al., 2006).

Disease activity and the need to maintain physical function are the major drivers of cost associated with PsA. Mean total healthcare costs in the UK for PsA are reported to range from £11 to £20,782 (mean (± s.d.) £1446 ±£1756), with more than one third attributed to prescription costs and secondary care attendances (Poole et al., 2010). In another study from Germany, mean annual direct costs per patient were €3156, and the mean annual indirect cost ranged from €2414 to €7919 per patient, depending on the method used to calculate costs (Huscher et al., 2006). Since these studies were performed, the expansion of biologic drug prescribing is likely to have significantly added to these costs – on analysing the cost in patients with PsA who were treated for six months with or without a biologic agent, a greater than 5-fold increase was observed in direct costs, estimated at around $7768 per patent year (Olivieri et al., 2008). However, in studies of patients with only severe PsA, markedly elevated per patient year costs are observed in terms of direct ($8,808), indirect ($48,834) and total ($57,642) costs, providing further motive to provide effective therapeutic intervention early to reduce disability and maintain function (Huscher et al., 2006). In a recent study of 229 working age patients with PsA, a 30% improvement in work presentism (p<0.001) and a 40% improvement in work productivity (p<0.001) was observed among patients treated with a TNF inhibitor for six

months, thus to some degree offsetting the high direct pharmaceutical costs for these drugs (Tillett et al., 2017b).

1.3.6 Management of Psoriatic Arthritis

Much like the management of psoriasis, the approach to the management of PsA also follows a 'step up' approach to therapy. Data in the literature on treatment strategies for PsA are scarce, and therefore a step-wise approach is appropriate to balance safety with efficacy. Recommendations for the management of PsA have been published by two international organisations: the European League Against Rheumatism (EULAR) and the Group for Research in Psoriasis and Psoriatic Arthritis (GRAPPA) (Gossec et al., 2016, Coates et al., 2016).

The first step in both guidelines involves the treatment of symptoms of PsA through the use of non-steroidal anti-inflammatory drugs (NSAIDs) and where applicable, local glucocorticoid injections. NSAIDS are efficacious for the relief of musculoskeletal symptoms, particularly in patients with mild joint disease, although the risks and contraindications need to be considered (Ash et al., 2012a). Local glucocorticoid injections alleviate pain and inflammation in joints, tendon sheaths and entheses (Eder et al., 2010). If ineffective, the next step is to escalate to use of the conventional synthetic disease modifying anti-rheumatic drugs (DMARDS) including methotrexate, sulphasalazine, leflunomide and ciclosporin, with the exception of patients with symptomatic enthesitis or axial disease, in whom, these drugs are ineffective. These individuals, as well as those with peripheral disease in whom conventional DMARDS are not adequate at controlling symptoms or progression, should receive biologic agents (Coates et al., 2016, Gossec et al., 2016). The clinical response to therapy and the needs of the patient should be reviewed periodically in accordance with a treat-to-target approach, aiming to achieve minimal disease activity (MDA) as set out in seven criteria (Figure 1.7) (Coates et al., 2010, Coates and Helliwell, 2016).

Patients must fulfil five of the following seven criteria:
• Swollen joint count ≤1 • Tender joint count ≤1 • PASI ≤1 or BSA ≤3% • Patient pain (visual analogue score, VAS) ≤15 • Patient global disease activity (VAS) ≤20 • Health Assessment Questionnaire (HAQ) ≤0.5 • Tender entheseal points ≤1

Figure 1.7. Minimal Disease Activity (MDA) Criteria for PsA (Coates et al., 2010).

The approval for and availability of biologic therapies for PsA is rapidly expanding, although little or no data exist to inform treatment order or strategy. TNF inhibitors, including adalimumab, etanercept, infliximab, golimumab and certolizumab, have demonstrated efficacy in all aspects of PsA treatment (Antoni et al., 2005, Kavanaugh et al., 2009, Mease et al., 2014a, Mease et al., 2005, Mease et al., 2004), including the inhibition of structural joint damage and are given preference as the first-line biologic therapy in the EULAR guidelines, but not the GRAPPA recommendations. In the latter, non-anti-TNF biologics can be used first line if the clinician deems it to be appropriate. TNF inhibitors were the only available biologic agent licensed for the treatment of PsA until 2015, and it is the longer duration of experience and greater quantity of long-term efficacy and safety data that lead to them being chosen as first line biologic therapy in the EULAR guidelines. However, given the impressive results from trials of IL-23 inhibition and IL-17A inhibition in psoriasis, dermatologists and rheumatologists working in collaboration may wish to consider ustekinumab or secukinumab as first line monotherapy for patients with both PsA and moderate to severe skin disease (Kimball et al., 2012, Menter et al., 2016).

ACR20, 50 and 70 rates, amounting to a 20%, 50% or 70% improvement in the American College of Rheumatology (ACR) response criteria (Figure 1.8), are shown below for the different biologic agents after 24 weeks of therapy (Table 1.5) (Antoni et al., 2005, Kavanaugh et al., 2009, Kavanaugh et al., 2014a, McInnes et al., 2013, McInnes et al., 2015, Mease et al., 2014a, Mease et al., 2005, Mease et al., 2004). Aside from TNF inhibitors, the FDA have approved ustekinumab (IL-12/IL-23p40 inhibitor), secukinumab (IL-17A inhibitor), ixekizumab (IL-17A inhibitor), brodalumab (IL-17RA antibody), guselkumab (IL-23p19 inhibitor), tildrakizumab (IL-23p19 inhibitor) and apremilast (phosphodisetersae-4 (PDE-4) inhibitor), and there are many more biologic therapies and oral small molecules nearing the end of phase III clinical trials in PsA.

>20/50/70% improvement required in both of the following measures of disease activity:
Tender joint count
Swollen joint count
>20/50/70% improvement required in at least three of the following measures of disease activity:
Patient assessment of pain
Patient global assessment of disease activity
Physician global assessment of disease activity
Patient assessment of physical function
Markers of inflammation

Figure 1.8. American College of Rheumatology (ACR) Criteria for psoriatic arthritis (Felson et al., 1993).

	Etanercept*	Adalimumab*	Infliximab*	Golimumab	Certolizumab	Ustekinumab*	Secukinumab*	Apremilast*
ACR20	59 (15)	57 (15)	54 (16)	52 (12)	64 (24)	42 (23)	51 (15)	59 (22)
ACR50	38 (5)	39 (6)	41 (4)	30 (6)	44 (13)	25 (9)	35 (7)	32 (7)
ACR70	11 (1)	23 (1)	27 (2)	19 (2)	28 (4)	12 (2)	21 (1)	17 (1)

Table 1.5. American College of Rheumatology (ACR) 20/50/70 responses (week 24) from registry trials for biologic and small molecule therapies approved by the FDA for the treatment of psoriatic arthritis. Percentage placebo responses are shown in brackets. *denotes EMA and FDA approval for psoriasis.

The majority of biologic drugs approved for use in PsA also have a license to treat psoriasis, with the exception of golimumab and certolizumab. Collaborative working between dermatology and rheumatology is therefore imperative to identify the most suitable monotherapy for patients with both psoriasis and PsA (Soleymani et al., 2017, Okhovat et al., 2017). It is not yet known if skin-directed treatment for psoriasis with a biologic therapy that has demonstrated independent efficacy in PsA is able to modify the development of future joint disease.

1.4 Enthesitis

The term ‘enthesis’ is rooted in the ancient Greek word ‘ἔνθεσις’ or ‘énthesis’, meaning ‘putting in’ or ‘insertion’. This refers to the role of the enthesis as the site of attachment of tendons, ligaments, joint capsule fibres or fascia into bone (Francois et al., 1995). Entheses are numerous in the appendicular and axial skeleton and can be classed as fibrous or fibrocartilaginous according to the tissue present at the skeletal attachment site (Francois et al., 2001). At fibrous entheses, the collagenous tendon or ligament attaches directly to bone and typical examples include the metaphyses and diaphysis of long bones. At fibrocartilaginous entheses, cortical bone is extremely thin or absent, and tendons and ligaments must therefore connect directly to an underlying bony trabecular network and/or bone marrow spaces (Benjamin and McGonagle, 2007). Most entheses are fibrocartilaginous and these are the ones that are affected in SpA (Benjamin and McGonagle, 2001).

Fibrous entheses anchor through a network of splayed fibres, tethering to the underlying bone like the roots of a tree to provide secure union (Harner et al., 1999). The entheses are sites of repeated compression and/or shear during locomotion and mechanical

loading, and it is proposed that their splayed and interlocking interface is an evolutionary means of attempting dissipating this biomechanical stress to adjacent structures. However, the consequence of repeated stress is the accumulation of microtrauma at the bony interface, as predicted from estimates of insertion-site deformation that occurs during tensile loading of tendon and ligaments (Woo, 1998). Repeated microtrauma leads immune activation in an attempt to promote repair, and if this becomes excessive, may lead to a clinically significant inflammatory pathology such as SpA (Benjamin et al., 2007).

Inflammation at the entheses is termed ‘enthesitis’. If inflammation is sustained, it leads to thickening and calcification of the tendon at insertion sites and cystic and erosive changes in the bone at insertion sites, followed by periosteal changes, the formation of bony spurs (enthesophytes), sub-periosteal new bone and syndesmophytes. Insertional disorders in general are referred to as ‘enthesopathies’ and in addition to the widely accepted association with SpA, may also be related to degenerative, traumatic, metabolic and endocrinological conditions (Resnick and Niwayama, 1983).

Despite the widespread acceptance of an enthesis being a junction between the tendon or ligament and bone, anatomical studies have shown that the enthesis is not restricted to just the focal attachment to bone. The enthesis is associated with other adjacent structures that are functionally related, giving rise to the concept of the ‘enthesis organ’ (Benjamin and McGonagle, 2001, McGonagle et al., 2003). For example, at the Achilles tendon, the enthesis organ not only includes the junction point (true enthesis), but also the periosteal and sesamoid fibrocartilages, the retrocalcaneal bursa, the tip of Kager’s fat pad and the adjacent calcaneal bone. The enthesis is in close proximity to synovium with a synovial membrane covering the tip of the fat pad (Rufai et al., 1995, McGonagle et al., 2003, McGonagle, 2005). The enthesis itself is avascular, thus enthesis organ cartilages rely on adjacent synovium for nourishment and lubrication in a manner identical to articular cartilage in synovial joints. These structures, termed the ‘synovio-entheseal complex’ (SEC), are anatomically, functionally and physiologically related and can perform as one entity to protect the enthesis during locomotion (McGonagle et al., 2007). All of these structures may therefore be involved in entheseal inflammation. This concept of the SEC is supported by the pathological changes seen in patients with SpA, with diffuse changes in the connective tissue and underlying bone in the immediate vicinity of the insertion (McGonagle et al., 1999). The SEC is reported to exist at 82% of all entheses (Benjamin and McGonagle, 2007, McGonagle et al., 2007).

The term ‘functional enthesis’ was coined by Benjamin and McGonagle to refer to sites where tendons and ligaments wrap around bony pulleys. Such locations share strong anatomical, biomechanical and histological similarities to entheses, however while there is *contact* between hard and soft tissues, there is no anchorage as seen at the traditional enthesis. Similar to compressive forces acting at the fibrocartilaginous enthesis insertion,

the wraparound nature of these tendons leads to a comparable functional demand for fibrocartilage, and this may explain why these regions can also be affected in SpA (Benjamin and McGonagle, 2001). Knowledge of these anatomical concepts is important as inflammation in enthesitis may be diffuse and not confined to the insertional site exclusively. When investigated with imaging such as ultrasound or MRI, abnormalities may be seen at sites that are not recognised as true insertions but nevertheless represent the same pathological process.

1.4.1 Histopathological Features of Enthesitis

It is technically and ethically difficult to obtain suitable tissue from patients with enthesitis, and thus most work relating to the pathology of enthesitis stems from cadaveric work investigating 'normal' entheses. Such studies have shown that the entheses of elderly persons sustain a substantial amount of microdamage at the attachment site and at adjacent fibrocartilage and synovium through decades of mechanical stress (Benjamin et al., 2007). In patients with SpA, it is proposed that there is a perturbation in tissue repair or remodelling responses at sites of high mechanical stress leading to a much earlier, more pronounced and sustained inflammatory response in genetically primed individuals (McGonagle et al., 2007).

In patients with SpA, the data for acute enthesitis is limited, but histologically inflammatory changes are seen including macrophage infiltration (McGonagle et al., 2002a). Chronic enthesitis is characterised histologically by bony erosions, inflammatory infiltrates (comprising mainly of T lymphocytes) in the bone adjacent to the enthesis and oedema in the bone marrow close to fibrocartilage (Maksymowych, 2000, Bollow et al., 2000). Within the aged enthesis, there are degenerative changes including clusters of hypertrophied fibrocartilage cells and matrix fissuring. In later disease, capsular ossification, myxoid bone marrow changes, chondroid metaplasia and the formation of synchondroses occur.

1.4.2 Pathogenic Relevance of Enthesitis to Psoriatic Arthritis

The pathogenesis of PsA is not fully understood, and the cascade of events is subject to debate. One model suggests that an adaptive T-cell response to a common skin and synovial membrane antigen drives the inflammatory manifestations that occur in PsA (Fitzgerald and Winchester, 2009). However, McGonagle and colleagues proposed that enthesitis is the primary and unifying event in all types of SpA, and that all other manifestations are secondary. The SEC, due to mechanical stress, is prone to microdamage (fissuring) and this triggers an innate immune response within the adjacent vascular synovium (Benjamin and McGonagle, 2001). An animal model of spontaneous

PsA (aging DBA/1 mice) supports this concept of enthesitis triggering the innate immune response (Lories et al., 2004). However, TNF-inhibitor treatment of this animal model reduced inflammation but did not affect ankylosis, suggesting the process of entheseal ankylosis may be independent of TNF-α.

A different animal model (type II collagen antibody-induced arthritis in B10.RIII mice) demonstrated that enthesitis develops first, in the initial complete absence of synovitis, and is induced by IL-23 alone. Blocking IL-23 during the induction of arthritis reduced both the clinical disease and the levels of entheseal inflammation in the mice. Over-expression of IL-23 alone in naïve B10.R111 mice was sufficient to induce enthesitis, psoriasis and sacroilitis (Sherlock et al., 2012).

This mouse model represented a breakthrough in the understanding of how IL-23 can promote SpA disease pathogenesis, as previous attempts at producing IL-23 transgenic mouse models have been fatal. Sherlock and colleagues developed a new mouse model containing a DNA minicircle injection of IL-23. Through IL-23 dose titration, they demonstrated that IL-23 promotes a pathology resembling SpA by acting on a previously unidentified, very specific subset of ($IL\text{-}23R^{+}ROR\text{-}\gamma t^{+}CD3^{+}CD4^{-}CD8^{-}Sca1^{+}$) T cells that reside in the enthesis. This resident entheseal population of innate-like T cells express the IL-23 receptor and CD3, but not CD4 and CD8. Further characterisation revealed they express the transcription factor RAR-related orphan receptor γt (RORγt) and produce IL-17 and IL-22 in response to stimulation with IL-23. Mice subsequently treated with antibodies that specifically block IL-17 and IL-22 had reduced clinical disease. Further adding to the similarity between pathways in skin psoriasis and this mouse model of early psoriatic-like SpA, overexpression of IL-22 in these mice promoted bone remodelling and foot pad oedema, explained by IL-22 induced STAT3 phosphorylation in osteoblasts in vitro (Sherlock et al., 2012).

Reinhardt et al confirmed these observations in B10.R111 mice, identifying abundant activated $ROR\gamma t^{+}IL\text{-}23R^{+}$ enthesis-resident lymphocytes in uninflamed entheseal tissue, the majority of which were activated $V\gamma 6^{+}CD27^{-}$ γ/δ T cells capable of producing IL-17A. When exposed to mechanical stress, γ/δ T cells increased in number at the Achilles tendon enthesis, further supporting the role of γ/δ T cells as key players in the pathogenesis of IL-23-induced local inflammation (Reinhardt et al., 2016).

Collectively, these data, in combination with IL-23 signalling pathway loci in genome-wide association studies in psoriasis and PsA, provide promising evidence for the key role of IL-23 in spondyloarthopathy-based, entheseal-driven pathology as a possible forerunner of clinical PsA. However, further studies are necessary to validate these findings and replicate them in human tissues to add clinical significance.

1.4.3 Clinical manifestations of Enthesitis

A small number of patients with PsA may have enthesitis alone and/or dactylitis for months to years before developing peripheral or axial arthritis (Salvarani et al., 1997). Enthesitis is more frequent in the lower than upper limbs, with the Achilles tendon and plantar aponeurosis entheses being the most frequently affected entheses. Enthesitis may be asymptomatic or cause pain, depending on the site involved, and pain may vary from mild to disabling. Pain is most often reported at the heel, with pain experienced on weight bearing, after a period of prolonged rest, and which improves gradually with movement. Clinically, there may be tenderness on pressure over the enthesis, and occasionally soft tissue swelling (McGonagle, 2015). The latter is mostly visible in Achilles enthesitis, the humeral lateral epicondyle and the patellar tendon. The frequency of clinically detectable enthesitis ranges from 13% to 60%, depending on the type of SpA and the entheses involved (Table 1.6) (Braun and Sieper, 1996, Burgos-Vargas and Vazquez-Mellado, 1995, Boyer et al., 1999, Collantes et al., 2000, Leirisalo-Repo, 2000).

Spondyloarthopathy	Frequency of Enthesitis (%)
Ankylosing Spondylitis	25-28
Reactive Arthritis	13-58
Psoriatic Arthritis	20
IBD-associated Spondyloarthropathy	7-53
Undifferentiated Spondyloarthropathy	27

Table 1.6: Reported frequency of clinically recognisable enthesitis in the various spondyloarthropathies

Clinically recognisable sites include the large tendons and ligaments adjacent to joints and superficial spinal insertions. However, many sites of enthesitis, including most of those in the spine and in large joints, are clinically inaccessible. This accounts for the discrepancy in detection between enthesis identified on clinical examination and that detected by imaging such as ultrasound and MRI (Balint et al., 2002, Song et al., 2011a, Weckbach et al., 2011, Frediani et al., 2002, Lehtinen et al., 1994).

1.4.4 Clinical Assessment of Enthesitis

On clinical examination, enthesitis is detected clinically as tenderness by applying firm pressure (approximately 4kg/cm^2, or enough to blanch the fingernail) with the pulp of the thumb over the enthesis (Mease, 2011). To improve discrimination between true tenderness and hyperalgesia (increased sensitivity to pain stimuli), a standard palpation

of control sites should be introduced at the beginning of each assessment. For example, pressure applied to the anterior-superior aspect of the middle of the medial third of the clavicle provides the patient with a reference point for the sensation arising from pressure alone (Mander et al., 1987).

Several clinical methods have been developed to measure enthesitis. The majority of these scoring systems were developed primarily for patients with AS, but have since been applied to patients with PsA. Table 1.7 lists the most commonly cited scores and the entheseal sites assessed in each.

Site	MASES	MEI	SPARCC	SPARCC (8)6/16	Major	Gladman	LEI
Nuchal crest		+					
Manubriosternal joint		+					
1st costochondral	+	+					
2^{nd}-6^{th} costochondral		+					
7th costochondral	+	+					
Supraspinatus insertion			+	(+)		+	
Lateral epicondyle humerus		+	+		+		+
Medical epicondyle humerus		+	+		+		
Greater tuberosity humerus		+					
5^{th} lumbar spinous process (one point)	+	+					
Cervical, thoracic and lumbar spinous processes (one point)		+					
Posterior-superior iliac spine	+	+					
Anterior-superior iliac spine	+	+					
Iliac crest	+	+			+		
Sacroiliac joint		+					
Ischial tuberosity		+					
Greater trochanter		+	+	+	+		
Medial femoral condyle		+					+
Lateral femoral condyle		+					
Medial tibial condyle		+					
Lateral tibial condyle		+					
Adductor tubercle		+					
Fibula head		+					

Site	MASES	MEI	SPARCC	SPARCC (8)6/16	Major	Gladman	LEI
Inferior pole patella			+				
Tibial tubercle		+	+			+	
Proximal Achilles	+	+	+	+	+	+	+
Plantar Fascia		+	+	+	+	+	

Table 1.7: Enthesitis Indices used in SpA. All assess the enthesis bilaterally unless stated. (MEI: Mander Enthesitis Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC: Spondyloarthritis Research Consortium of Canada; LEI: Leeds Enthesitis Index)

The Mander Enthesitis Index (MEI) was the first reported clinical measure of enthesitis, in 1987, in the context of AS. In a development pilot of six patients, sites that were not tender at any time point were excluded, leaving 66 sites (Figure 1.9). The patient's response is recorded in a 4-point tenderness scale (0: no pain to 3: severe tenderness causing withdrawal). Further validation studies demonstrated correlation between the MEI and pain and stiffness VAS scores, and it appears sensitive to change in patients treated with a NSAID. Inter-observer variability was not tested. (Mander et al., 1987). However, the MEI has attracted criticism for being too time consuming, for having the potential to cause the patient distress, for the scale being subjective and for including many sites that are tender in fibromyalgia.

The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) reduced the number of entheseal sites tested to 13 as part of a simplification process of the MEI (Table 1.7, Figure 1.9). The sites with greatest frequency of tenderness were recorded, and then excluded if they were difficult to localise or adjacent to other sites already included. A dichotomous 0/1 response to tenderness without grading was found to perform with the greatest consistency (Heuft-Dorenbosch et al., 2003). The MASES was tested as part of the INSPIRE study, which involved the assessment of 19 patients with AS and PsA by ten experienced rheumatologists. There was moderate inter-assessor agreement (ICC 0.56), with superior performance in patients with AS compared to PsA (Gladman et al., 2007a). Subsequently, a PsA-modified MASES has been designed which includes 15 sites (plantar fascia included) (Kavanaugh et al., 2012). The MASES has also been shown to correlate with ultrasound sonographic scores (both total and acute enthesitis) (Hamdi et al., 2011). One limitation of the MASES is that it has a floor effect due to the reduced number of entheses tested and therefore may not detect low level enthesitis occurring at other insertion sites.

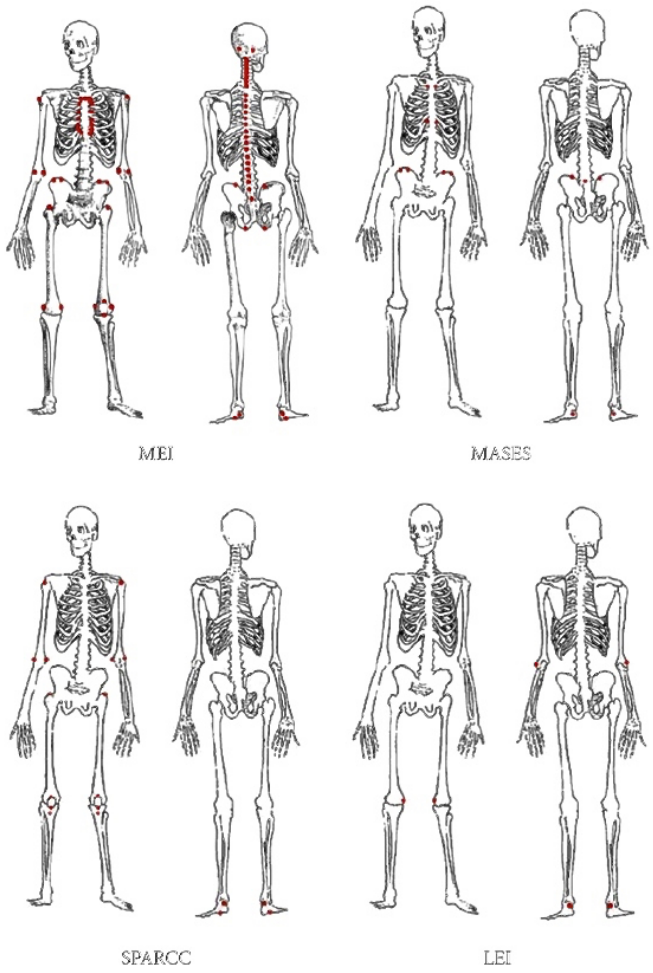

Figure 1.9. Schematic representation of entheseal sites assessed by the four principle entheseal indices. (MEI: Mander Enthesitis Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC: Spondyloarthritis Research Consortium of Canada; LEI: Leeds Enthesitis Index). Reproduced with permission from Dr. Laura Coates (Coates and Helliwell, 2010).

Around the same time as the MASES, the Major Enthesitis Index was developed in a cohort of patients with AS and targeted 12 entheseal sites (Table 1.7) (Braun et al., 2002). In the INSPIRE cohort, it did not perform as well as the MASES, and it has not been validated, widely used, nor studied since (Gladman et al., 2007a).

The Gladman Index was developed in ten SpA patients using entheseal sites included in the MASES. Fair to moderate reliability was found between ten assessors, with greatest agreement at the tibial tuberosity of the knee and plantar fascia (Gladman et al., 2004). A large effect size has been seen with treatment (Healy and Helliwell, 2008).

The Leeds Enthesitis Index (LEI) is the only clinical measure developed specifically for patients with PsA. Following the methodology for the MASES, a dichotomous score was used to assess tenderness, followed by a process of data reduction. The most commonly involved enthesis was identified and noted, with exclusion of this enthesis in subsequent

rounds. This step-wise reduction was performed until 80% of all patients with a positive score were identified. This resulted in an index with six sites, which has been well received for its brevity and simplicity (Healy and Helliwell, 2008). The LEI was then compared with other entheseal indices including the MEI and MASES in an open-label longitudinal study. The LEI showed the largest effect size and the closest correlation with other disease activity measures. It also had the smallest floor effect size when compared to the MEI, meaning that it can identify the majority of patients with enthesitis by testing just six sites (Healy and Helliwell, 2008). In the INSPIRE cohort, there was excellent inter-rater agreement (ICC 0.81) between rheumatologists (Gladman et al., 2007a). However, in a validation study using ultrasound, there was a poor relationship between clinical and imaging findings at sites included in the LEI, with 20% of sites exhibiting tenderness but no ultrasound changes and 26% having sonographic evidence of enthesitis but no tenderness elicited on clinical examination (Ibrahim, 2010).

Establishing criterion validity for clinical outcome measures has been difficult due to a lack of a gold standard. The ideal gold standard would be histological evidence of tissue abnormality, but as discussed, biopsy of tendons is invasive and unsafe. Given the increasing sensitivity of MRI and ultrasound in detecting enthesitis, it seems imaging is the best gold standard available at present. With this in mind, the Spondyloarthritis Research Consortium of Canada (SPARCC) adopted a novel approach and created an enthesitis index for patients with SpA utilising MRI and ultrasound data to decide which sites should be included (Maksymowych et al., 2009b). 16 sites were identified as being commonly involved in imaging studies and could be accessed for clinical assessment (McQueen et al., 2007b). Good inter-observer reliability and a substantial correlation between the enthesitis score and other disease activity measures was found in the development cohort, and further validation took place in two Canadian cohorts of AS patients. However, the reduction in SPARCC score in patients treated with a TNF inhibitor was not significant after 12 weeks of therapy (Maksymowych et al., 2009b). In the INSPIRE study, there was excellent agreement between assessors (ICC 0.81) but notably the SPARCC performed better in patients with AS rather than PsA (Gladman et al., 2007a). Correlation has also been shown between the SPARCC index and total sonographic enthesitis score (Hamdi et al., 2011). Reduced versions of the SPARCC index targeting the more frequently involved sites (SPARCC 8/16) and only sites that discriminate between treatment and placebo (SPARCC 6/16) have shown larger effect sizes and standardised response means (Maksymowych et al., 2009b).

The use of clinical tools for enthesitis has become commonplace in clinical trials of PsA but there is debate about which particular measure is optimal. As discussed, validation is difficult due to the lack of gold standard to prove or dispute the true presence of enthesitis. Imaging techniques can show changes within tendons and tendon sheaths at the enthesis, but correlation with clinically appreciable tenderness or swelling is less

convincing (D'Agostino et al., 2003). In addition to soft tissue changes, MRI can identify the involvement of adjacent bone, but no studies have addressed whether this can be identified clinically.

Clinical measures of enthesitis are also limited in terms of their specificity. Many entheseal points are near joints and are accepted fibromyalgia points, thus there is a possibility that misdiagnosis may occur. This was investigated by Marchesoni and colleagues in a multicentre cross-sectional study of 266 patients with PsA and 120 patients with fibromyalgia. Univariate analysis showed that patients with fibromyalgia had higher mean tender point and MASES [enthesitis] scores. It was the number of affected sites (≥8) rather than location that was the discriminating factor, in addition to the number of fibromyalgia symptoms such as headache, fatigue and anxiety (≥6) (Marchesoni et al., 2012). The key to the reliability of clinical measures of enthesitis is in training of assessors to correctly localise the sites and to use any findings within the context of a patient's symptoms.

1.4.5 Subclinical Enthesitis in Psoriasis

Subclinical musculoskeletal inflammation, especially osteitis and periostitis, have been recognised since the 1970s in patients with psoriasis but no arthritis. Subsequently, further understanding of the anatomical basis of enthesitis (and the secondary dissipation of inflammation and consequent damage to structures within the surrounding synovio-entheseal complex) provides explanation for this osteitis. Asymptomatic entheseal inflammation is shown to be common in patients with psoriasis, with ultrasound studies showing rates from 39.0% to 59.3% depending on the number of entheses assessed and the definition of enthesopathy used (Acquacalda et al., 2015, Ash et al., 2012b, De Simone et al., 2003, Naredo et al., 2011, Ozcakar et al., 2005). Patients with nail psoriasis have been found to have a greater burden of subclinical enthesitis than those without nail disease, due to the attachment of the extensor tendon to the terminal phalynx enclosing the nail root, which anchors the nail laterally (Ash et al., 2012b, Aydin et al., 2012).

Subclinical inflammation has been demonstrated in psoriasis patients using numerous imaging modalities at many peripheral anatomical sites including the large tendon insertions of the knee, ankle, the elbow and digits, and using MRI, in the axial skeleton within the spine, sacroiliac joints, shoulders, hips and chest wall entheses. Table 1.8 lists the many studies using ultrasound and MRI to demonstrate subclinical enthesopathy in patients with psoriasis.

Within these studies and others in spondyloarthropathy, many 'healthy' volunteers have been imaged and variable proportions are also noted to have similar subclinical entheseal changes, albeit at a much smaller magnitude than is seen in psoriasis patients

(Ash et al., 2012b, Gisondi et al., 2008, Gutierrez et al., 2011, Naredo et al., 2011, Ozcakar et al., 2005, Bandinelli et al., 2013, De Simone et al., 2003). While erosions and calcifications tend not to occur in healthy volunteers, thickening of entheses around weight bearing joints are reported in up to 8.4% of sites assessed in addition to the presence of enthesophytes (Gutierrez et al., 2011). Age, BMI and waist circumference have been shown to correlate with the GUESS score, a sonographic scoring system for the lower limb entheses, in both patients with psoriasis and healthy volunteers (Gisondi et al., 2008). Entheseal abnormalities are attributed to age related degeneration due to repeated biomechanical sheer stress on weight bearing joints (Benjamin et al., 2007, McGonagle et al., 2002b), but unlike in genetically primed patients with psoriasis, inflammation is controlled and structural deformities therefore occur with much lower frequency.

The long-term significance of subclinical enthesitis in patients with psoriasis is not yet known, and only one small preliminary cohort study provides data on the predictive value of asymptomatic entheseal inflammation. Tinazzi and colleagues performed ultrasound of the lower limbs of 30 patients with psoriasis, and of 28 who returned for re-evaluation at a mean of 3.5 years, 23% had developed symptomatic inflammatory arthritis that satisfied the CASPAR criteria for PsA. Two patients had polyarticular disease, and 5 had oligoarticular PsA. These patients had not received systemic immunosuppression (Tinazzi et al., 2011).

1.4.5.1 Management of Subclinical Enthesitis

The potential evolution of subclinical enthesopathy to frank PsA raises the question as to whether skin-directed therapy for psoriasis could prevent the development of PsA. Only one small study to date has assessed the response of subclinical enthesitis to therapy. 22 patients with psoriasis were treated with methotrexate, with or without infliximab (n=1), adalimumab (n=1) or ustekinumab (n=3) for six months. 13 patients that returned for a second ultrasound scan, which assessed 5 entheses bilaterally, and the number of entheses with morphological abnormalities decreased from 30% to 17.7% (p=0.021) (Acquacalda et al., 2015). These data provide an interesting foundation for further longitudinal analyses to determine if the early introduction of immunomodulatory therapy in patients with psoriasis could impact on the evolution of subclinical enthesitis.

Year	Author	Psoriasis n=	Controls n=	Modality	Site(s)	PASI	Findings
2003	De Simone	59	50 Healthy	US	AT	3.7-34.7	59.3% patients had tendonitis with or without bursitis.
2005	Ozcakar	30	20 Healthy	US	AT	NA	56% of patients had enthesopathy. Mean AT thickness significantly greater in psoriasis patients.
2005	De Filippis	24	14 PsA	US	FFT and FET	NA	33% psoriasis patients had enthesopathy, and 25% had joint effusion.
2008	Gisondi	30	30 Healthy	US	PPT, DPT, QT, AT, PF	Median 7.54	24.7% entheses were thickened, compared with 9.0% in controls. Mean GUESS score 7.9 vs 2.9. More enthesophytes in psoriasis patients.
2008	Erdem	26	10 Healthy	MRI	Foot	NA	92% of patients had enthesopathy or BMO. Retrocalcaneal bursitis in 50% retroachilles bursitis in 4%. One bone erosion seen, no enthesophytes. No abnormalities in controls.
2010	Gutierrez	45	45 Healthy	US	PPT, DPT, QT, AT, PF	NA	32.9% entheses with enthesopathy vs. 8.4% controls, 0.9% with PD vs. 0%. Mean GUESS score significantly higher than in controls.
2010	Farouk	30	30 PsA	US	AT, PF	Mean 23.0	33.3% patients with enthesopathy. Calcifications seen only in patients with PsA.
2010	Emad	6	20 Healthy	MRI	Knees	NA	5/6 had enthesitis at the patellar tendon insertion, 1/6 at the medial patellofemoral ligament. 1/6 had bone marrow oedema. No entheseal changes, BMO or bone erosions seen in controls.
2011	Naredo	162	60 Healthy	US	PPT, DPT, AT, PF, FFT	Mean 6.7	11.6% entheses with enthesopathy vs 5.3% controls. 7.4% entheses had PD vs. 0% controls. 3.2% joints had synovitis vs 1.3% controls.
2012	Ash	46	21 Healthy	US	PPT, DPT, QT, AT, PF	Mean 6.3	39% entheses with enthesopathy, 1% with PD. Total and inflammation scores significantly greater than in control group.

Year	Author	Psoriasis n=	Controls n=	Modality	Site(s)	PASI	Findings
2012	Emad	48	20 Healthy	MRI	Knees	Mean 1.99	20.8% patients with BMO, 60.4% STI, 28% erosions. BMO seen in 10% of controls but no enthesitis.
2015	Acquacalda	12	22 PsA	US	DBT, PPT, QT, AT, PF	Mean 15.8	46.4% entheses with enthesopathy in psoriasis group, 0% with PD
2015	Hamdy	50	20 Healthy	MRI	LSS, SIJs	Mean 6.9	44% patients with spine BMO, 10% SIJ BMO. 16% controls with spine BMO, 6% SIJ BMO.
2016	Acquitter	37	Nil	US	CET, CFT, PPT, DPT, QT, AT, PF	NA	20.8% entheses with enthesopathy, 0.77% with PD
2016	Faustini	55	30 Healthy	MRI	FFT	Mean 6.2	11% patients with BMO, 38% synovitis, 4% tenosynovitis, 29% erosions. 10% controls with BMO, 7% synovitis and 0% tenosynovitis.
2017	Moshrif	50	Nil	US	PPT, DPT, QT, AT, PF	PASI >15	36% of patients had enthesopathy, % PD not stated.

Table 1.8. Imaging assessments of subclinical enthesopathy in asymptomatic patients with psoriasis. (AT: Achilles tendon; BMO: Bone marrow oedema; CET: Common extensor tendon; CFT: Common flexor tendon; DBT: Distal brachial triceps tendon; DPT: Distal patellar tendon; FET: Finger extensor tendons; FFT: Finger flexor tendons; LSS: Lumbosacral spine; NA: Not applicable; PD: Power Doppler; PF: Plantar fascia; PPT: Proximal patellar tendon; QT: Quadriceps tendon; SIJ: Sacroiliac joints; STI: Soft Tissue Inflammation).

1.5 Screening for Psoriatic Arthritis in Patients with Psoriasis

In six out of every seven patients with psoriatic disease, skin lesions precede the development PsA (Chang et al., 2011, Gottlieb et al., 2006), with an average time to occurrence of between seven and twelve years (Qureshi et al., 2005). Dermatologists and primary care physicians managing patients with psoriasis are therefore at an ideal juncture for the early PsA detection. However, knowledge and recognition of PsA within such clinical settings remains suboptimal, with an epidemiological study showing that up to 29% of patients with psoriasis seen by dermatologists have undiagnosed PsA (Haroon et al., 2013). Even when patients are diagnosed with PsA, many are undertreated; published results from the population based 'Multi-national Assessment of Psoriasis and Psoriatic Arthritis' (MAPP) survey revealed that 59% of PsA patients were receiving no treatment or only topical therapy for their skin disease (Lebwohl et al., 2014). Whilst this survey is limited by the requirement for accurate recall and interpretation of questions by the 3426 patients involved, it is still evident that a significant proportion of patients are not receiving adequate therapy to prevent the progression of joint damage that may ensue. Without early intervention, patients may develop functional limitation, pain and disability (Husted et al., 2007, Gladman et al., 2005). Methods of identification of patients at greatest risk of developing PsA may therefore provide dermatologists and primary care physicians with the ability to screen such patients for early signs or symptoms of PsA during their skin follow up and collaborate closely with their colleagues in rheumatology to refer early and ultimately improve patient outcomes.

The impetus for the recognition of early PsA and its effective treatment stems from research into rheumatoid arthritis (RA) (Kane et al., 2003, Svensson et al., 2002, Chandran et al., 2007) where early disease recognition and prompt therapy initiation minimizes joint damage, maintains patients in work and reduces long-term complications (Emery, 2002, Cush, 2007, van der Heide et al., 1996). While some patients with RA recover spontaneously, most do not; indeed, most sustain erosive damage from significant joint inflammation within the first two years of onset (van der Heijde, 1995, Mottonen, 1988). The early phase of RA is predominated by inflammation and represents a window of opportunity for intervention – it has been hypothesised that immune mechanisms involved in the pathogenesis may be more responsive to treatment during this phase (Ahmed, 1999). Data from early arthritis clinics show that rheumatological assessment in less than twelve weeks is associated with less joint destruction and a higher chance of achieving drug-free remission compared with a longer delay in assessment (van der Linden et al., 2010). Increasing the proportion of patients treated with effective disease modifying drugs within three months of disease onset, from a current figure of 10% to 20%, could result in productivity gains for the UK economy of £31 million over five years (2009).

Collectively, such findings have led to the development of 'treat-to-target' guidelines in RA, and the concept of achieving tight control of RA early in the disease course is now standard practice, with significant numbers of patients achieving low levels of disease activity or clinical remission (Ruderman et al., 2012).

This shift towards early diagnosis and aggressive early arthritis treatment has gradually extended to PsA following confirmation that significant inflammation and damage is occurring at an early stage in the disease process. One study has shown that patients with PsA had similar radiological damage to patients with RA, suggesting that the disease may be just as destructive radiologically (Rahman et al., 2001).

Several studies have now specifically addressed the prognosis of early PsA (Harrison et al., 1997, Kane et al., 2003, Lindqvist et al., 2008). Harrison et al evaluated 51 patients with early inflammatory polyarthritis and psoriasis in a primary care setting, and found that 22% had irreversible joint erosions by one year (Harrison et al., 1997). Kane and colleagues prospectively examined a cohort of 129 patients presenting to an early inflammatory arthritis clinic; at presentation, 40% had oligoarticular and 60% had polyarticular PsA. At baseline, 27% already had radiographic evidence of bony erosion(s), increasing to 47% at 2 year follow up (Kane et al., 2003). Similar evidence of early disease progression was shown in a Swedish cohort of 183 patients with identical frequencies of articular PsA at presentation. 20% had signs of radiographic damage at baseline, increasing to 32% after 2 years (Lindqvist et al., 2008).

More recently, a large retrospective cross-sectional cohort analysed the outcomes of PsA patients in relation to lag time from symptom onset to first encounter with a rheumatologist. Haroon and colleagues identified that the probability of achieving of drug-free remission has a significant negative association with a diagnostic delay of greater than one year, and a significant positive association with an early rheumatologist encounter within six months of diagnosis. Using univariate model analysis, where this six month 'window of opportunity' to intervene was missed, patients encountered increased radiographic damage (bony erosions: OR 4.58 (95% CI 2.5-8.2) $p<0.001$; osteolysis OR 3.6 (95% CI 1.3-9.5) $p=0.01$) and joint deformity (OR 2.28 (95% CI 1.35-3.85) $p=0.002$), higher functional disability (as measured by HAQ scores) (OR 2.17 (95% CI 1.30-3.61) $p=0.003$) and an increased risk of developing sacroilitis (OR 2.28 (95% CI 1.17-4.44) $p=0.01$) (Haroon et al., 2014a). These results suggest that to further improve outcomes in PsA patients, an important challenge is to get patients with arthritis to see a rheumatologist as early as possible after symptom onset. The early identification of PsA among patients with psoriasis assumes considerable importance and this strengthens the need for screening within the dermatology setting, supported by close collaborative working between dermatologists and rheumatologists. However, the best methods for identifying early PsA amongst non-rheumatologists remain unclear.

Aside from joint damage, the impetus for early treatment is also driven by the recognition of increased mortality in patients with PsA. Patients with PsA are at an increased risk for death with a standardised mortality ratio of between 1.36 and 1.62 depending on the age of the population studied and duration of disease (Wong et al., 1997, Ali et al., 2007, Mok et al., 2011). The causes of death are similar to those within the general population, with cardiovascular causes being the most common (Wong et al., 1997, Alamanos et al., 2003, Ali et al., 2007). PsA is known to be associated with increased subclinical atherosclerosis (Eder et al., 2008) and an altered atherogenic lipid profile (Jones et al., 2000), and many of the immunological factors involved in both atherosclerosis and PsA (e.g. TNF-α and IL-1β) are proinflammatory to the vascular endothelium and synovial tissue. In PsA, both metabolic syndrome and insulin resistance are also highly prevalent and these are shown to be independently associated with the severity of underlying PsA (Haroon et al., 2014b). This is supported by the findings in a cohort of patients followed prospectively for almost two decades, where the risk for premature mortality in PsA was related to previously active and severe joint disease in addition to the presence of erosive disease and a high erythrocyte sedimentation rate (ESR) at presentation (Gladman et al., 1998).

1.5.1 Predictors of Psoriatic Arthritis Risk

While there are similarities between RA and PsA in terms of early progression, PsA lacks a reliable serum biomarker such as the anti-citrullinated protein antibody for RA. Efforts have been made to identify clinical factors that may help to predict the development of PsA in patients with psoriasis, however, there is currently no reliable means of determining in an individual psoriasis patient who will develop PsA, nor the pattern, severity and time course of the arthritis.

The risk of developing PsA has been reported to increase with the duration and severity of psoriasis, although conflicting data have been published. Yang et al found that an older age at psoriasis onset was significantly associated with the development of PsA, with 23.3% of patients with type II psoriasis (onset >40 years) developing PsA compared to 15.6% of patients with type I disease (p=0.035) (Yang et al., 2011). However, in contrast, Reich and colleagues found that patients with PsA had developed psoriasis at a younger age (28.4+/-14.8 vs. 34.9+/-18.2 years, p<0.0001) (Reich et al., 2009). Christophers et al included a logistic regression model with age of psoriasis onset as a continuous variable to control length of time with psoriasis, and found that age at psoriasis diagnosis was not associated with an increased risk of developing PsA (OR=1.00 for each additional year of age, 95% CI 0.987-1.014, p=0.983) (Christophers et al., 2010). A number of other cross-sectional studies have not found any significant association between the age of psoriasis onset and PsA risk (Tey et al., 2010, Love et

al., 2012a, Gladman and Chandran, 2011, Jamshidi et al., 2008, Salvarani et al., 1995, Stern, 1985).

Three studies have reported psoriasis severity as a risk factor for PsA, with severity defined in different ways – three or more sites of psoriasis compared to one site (HR 2.24, 95% C.I. 1.23-4.08), worst-ever body surface area (HR 1.01 for each unit increase in BSA), and >75% BSA of psoriasis at its worst compared to ≤25% (Soltani-Arabshahi et al., 2010, Tey et al., 2010, Wilson et al., 2009). All three case-control studies used retrospective data relating to worst-ever BSA rather than a baseline or time-updated variable for BSA. While these studies suggest that psoriasis severity may be associated with the development of PsA, further adequately powered studies providing information on the temporal association between psoriasis severity and the development of PsA are needed to confirm this relationship.

Six cross-sectional studies (Table 1.9) have compared the duration of psoriasis between patients with PsA and without; four studies found no significant difference (Gladman and Chandran, 2011, Palmou et al., 2011, Soy et al., 2008, Salvarani et al., 1995), and two reported an association between a longer duration and an increased risk of developing PsA (Yang et al., 2011, Christophers et al., 2010). Christophers and colleagues showed that the prevalence of PsA increased progressively with disease duration, reaching 20.5% in patients with psoriasis for 30 years duration, while the incidence remained relatively constant during this period (74 per 1000 person years) (Christophers et al., 2010).

Author (Year)	**Patients with psoriasis (n=)**	**Patients with PsA (n=)**	**Duration of psoriasis - WITH PsA (years)**	**Duration of psoriasis - WITHOUT PsA (years)**	**Significance**
Yang (2011)	1816	112	14.1+/-11.7	7.8+/-8.9	p<0.001
Gladman (2011)	438	1066	15.2+/-12.3	16.1+/-14.1	NS
Palmou (2011)	52	121	23.8+/-19.5	19.6+/-15.2	NS
Christophers (2010)	1434	126	17.3+/-11.3	11.0+/-11.3	p<0.0005
Soy (2008)	40	49	19+/-23	17+/-11	NS
Salvarani (1995)	130	75	17.7+/-14.4	14.2+/-13.8	NS

Table 1.9. Studies comparing the duration of psoriasis in patients with and without PsA (NS: Not Significant)

1.5.1.1 Cutaneous Predictors of PsA

Three studies, including one cohort and two-cross sectional studies, have compared the clinical type of psoriasis between patients with and without PsA (Wilson et al., 2009, Yang et al., 2011, Jamshidi et al., 2008). No particular psoriatic phenotype was more often associated with PsA, although palmoplantar psoriasis was not investigated.

Conflicting data has been published regarding an association between specific anatomical locations of psoriasis and an increased risk of PsA. In multivariate models, Eder et al identified a relative risk of 2.5 (p=0.002) for the onset of PsA in patients with psoriatic nail pitting in a cohort of 464 patients followed up for 8 years (Eder et al., 2016). In a larger prospective cohort study of 1593 psoriasis patients with extended follow up (mean (+/-S.D.) 13.1 (+/-8.8) years), a higher risk of developing PsA was found in patients with scalp lesions and intergluteal/perianal disease (HR 3.89 (95% CI 2.18-6.94 and HR 2.35 (95% CI 1.32-4.19) respectively) (Wilson et al., 2009). Scalp disease was also identified as a risk factor in two cross-sectional studies (Yang et al., 2011, Zanolli and Wikle, 1992), with an increased prevalence of PsA in patients with scalp psoriasis compared to those without (90.2% vs. 76.4%, p=0.001 and 87% vs. 72%, p=0.0237 respectively). Zanolli et al also identified an association between PsA and psoriasis at other locations, with PsA occurring more frequently in patients with psoriasis on the buttocks and back (68% vs. 45%, p=0.0016 and 68% vs. 49%, p=0.0086 respectively) (Zanolli and Wikle, 1992). However, these associations have not been supported in several other large scale cross-sectional studies (Love et al., 2012a, Stern, 1985, Christophers et al., 2010), making it difficult to draw meaningful conclusions on the relationship between anatomical location of psoriasis and PsA risk.

1.5.1.2 Nail Disease and PsA

Unlike other body sites where data is conflicting, psoriasis of the nail has repeatedly been shown to hold a strong positive association with PsA. Wilson et al reported a higher risk of PsA in patients with nail dystrophy compared to those without, with a hazard ratio (HR) of 2.93 (95% CI 1.68-5.12) (Wilson et al., 2009). Twelve of thirteen cross-sectional studies assessing the association between nail psoriasis and PsA risk have also shown an increased risk of PsA in patients with nail disease (Love et al., 2012a, Gladman and Chandran, 2011, Yang et al., 2011, Soltani-Arabshahi et al., 2010, Reich et al., 2009, Jamshidi et al., 2008, Salvarani et al., 1995, Stern, 1985, Soy et al., 2008, Zanolli and Wikle, 1992, Eder et al., 2011b, Maejima et al., 2010, Scarpa et al., 1984), and a recent combined meta-analysis of these studies gave an OR of 2.92 (95% CI 2.34-3.64) with a significant level of heterogeneity (p=0.00051) (Rouzaud et al., 2014).

The type of nail changes also appears to be important, with nail bed disease having the strongest link to PsA risk. In a small study, Maejima and colleagues found an association

with an OR of 4.68 (95% CI 1.29-16.98) for onycholysis and 6.41 (95% CI 1.13-64.91) for nail bed hyperkeratosis (Maejima et al., 2010), while Love et al performed multivariate analysis and found an OR of 2.05 (95% CI 1.43-2.93) for onycholysis (Love et al., 2012a). No association was identified for other nail changes including pitting and subungual hyperkeratosis, although this is in contrast to the findings by Eder et al, that found the presence of nail pitting to be predictive of the development of PsA (RR 2.5, p=0.002) (Eder et al., 2016). Love et al found that overall fingernail involvement was higher in those with PsA than those without (mNAPSI score 4.8 +/- 5.3 vs. 2.3 +/- 3.7 respectively, $p<0.05$). In patients with psoriasis but without known PsA, those with nail disease have also been found to have a greater magnitude of underlying systemic subclinical enthesopathy than those without nail disease, and nail severity (mNAPSI score) correlated with both inflammatory entheseal changes ($r(2)=0.45$, $p=0.005$) and chronic bone damage changes such as erosions ($r(2)=0.35$, $p=0.04$) (Love et al., 2012a).

1.5.1.3 Nail disease and Distal Interphalangeal (DIP) Joint Arthritis

An association between nail psoriasis and arthritis specifically at the distal interphalangeal (DIP) joint has long been reported (Green, 1968, Jones et al., 1994, Cohen et al., 1999, Kane et al., 2003, Williamson et al., 2004, Scarpa et al., 2004, Stern, 1985). The rationale for this has been extensively investigated by McGonagle and colleagues, who have shown that the nail is functionally integrated into the enthesis network around the DIP joint. (McGonagle et al., 2009a, Tan et al., 2007, Tan et al., 2006b). The nail is directly anchored to the underlying bony structures by interdigitating fibres from the extensor tendon which envelope the nail root and from the joint collateral ligament entheses that merge with the lateral borders of the nail (Tan et al., 2013). It is postulated that in genetically primed individuals, frequent microdamage and repair at these attachment sites provokes activation of regional innate immunity and persistent inflammation, which may then dissipate to the adjacent tissues and cause arthritis of the DIP joint (McGonagle, 2009). This has been confirmed by histopathological studies and also through use of high resolution MRI scanning. The latter confirmed that the dorsal capsular enthesis was the epicentre of the inflammatory reaction in patients with DIP joint PsA, with inflammation extending to involve the soft tissues adjacent to the nail. Such changes were not seen in patients with OA, who do not exhibit nail disease (Tan et al., 2007).

Using ultrasound, Aydin and colleagues found good agreement between the presence and severity of clinically evident nail changes and sonographic nail findings (kappa value 0.52, $p<0.0001$). Entheseal thickening of the extensor tendon on ultrasound occurred with greater frequency in patients with psoriatic nail disease compared to those without nail disease in patients with and without known PsA (38% vs. 16%, $p=0.03$ and 47% vs. 19%, $p=0.008$, respectively) (Aydin et al., 2012).

At the present time, there is strong evidence to support the presence of nail psoriasis as predictive for the development of both subclinical and symptomatic PsA, whereas cutaneous disease at other anatomical sites remains inconclusive and inadequate as a basis for targeted screening for PsA in dermatology clinics.

1.5.1.4 Obesity and PsA

Obesity has been identified as a risk factor for psoriasis, and three studies now support an increased risk of PsA amongst obese patients with psoriasis, two of which have shown a dose effect of BMI on the development of PsA (Li et al., 2012a, Love et al., 2012b, Soltani-Arabshahi et al., 2010). Possible explanations include increased mechanical loading on joints (akin to a deep koebner response), increased systemic inflammation induced by adipose tissue and a link with dyslipidaemia, as shown in osteoarthritis (Thijssen et al., 2015). A further study has shown the hyperlipidaemia, independent of obesity, was associated with the development of PsA (Wu et al., 2014). Improvement in disease activity and medication response with weight loss also support the concept of high BMI as a driver of inflammation in psoriatic disease.

1.5.1.5 Smoking and PsA

Smoking has been shown to be associated with the development of psoriasis and rheumatoid arthritis (Setty et al., 2007, Sugiyama et al., 2010), presumably due to smoking-induced oxidative stress that may stimulate chronic inflammation. However, nicotinic receptor activation inhibits intracellular proinflammatory pathways that are thought to be involved in the development of inflammatory arthritis, akin to the 'protective' role of smoking hypothesised in the development of ulcerative colitis (Eder et al., 2012). These contradictory observations may account for the opposing results reported from studies examining the relationship between smoking and PsA. Eder and colleagues found an inverse association between smoking and the development of PsA, although when stratified by HLA-Cw06, the inverse association only held amongst those without the gene (Eder et al., 2012). Pattison et al. also observed an inverse association, although not statistically significant in a univariate model (OR 0.68, 95% C.I. 0.39-1.17) (Pattison et al., 2008). In contrast, Li and colleagues identified a positive association, particularly for those who smoked in excess of 15 cigarettes per day, although this study only examined women with psoriasis (Li et al., 2012b). Additional studies are therefore required to better understand the role of smoking on the development of PsA.

1.5.1.6 Alcohol and PsA

Excessive alcohol intake may be a risk factor for psoriasis, but studies examining this have produced mixed results. Studies investigating the link between alcohol and PsA

have assessed various time points, including at the onset of PsA, and found no association (Tey et al., 2010). In one study, women consuming the most alcohol, had a substantially elevated risk of PsA compared to those who were tee-total at baseline (HR 4.45, 95% C.I. 2.07-9.59). However, this association was not significant among patients with psoriasis, only the entire study population (Wu et al., 2015). However, a significant positive association was observed in excessive drinkers with psoriasis compared to those who consumed moderate amounts of alcohol (HR 2.79, 95% C.I. 1.24-6.26).

1.5.2 Screening Questionnaires for PsA

In an attempt to improve the diagnostic capabilities of primary care physicians and treating dermatologists, a number of screening questionnaires have been developed for use in patients with psoriasis. While the gold standard for every psoriasis patient would involve an assessment by a rheumatologist combined with imaging, the burden of psoriasis in both primary and secondary care renders this unfeasible. Screening tools are therefore useful to sub-select a population of patients who have a higher probability of PsA for further assessment. The most recent consensus guidelines from both the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) for managing psoriasis recommend the use of questionnaires for this purpose (Burden et al., 2010, NICE, 2012).

All of the screening questionnaires that have been developed to date are patient-completed, although their method of development and purpose are slightly different. One of the first to be published (in abstract form) was the Psoriasis and Arthritis Questionnaire (PAQ), which was developed in Canada as a twelve-item questionnaire in 1997. This predicted PsA with a sensitivity of 0.85 and a specificity of 0.88 for a score of seven or higher. In 2002, the PAQ was re-studied and modified in a Swedish cohort of 202 community and hospital patients, where a receiver operator characteristic (ROC) curve analysis determined a best cut off of 4 out of 8, providing a sensitivity of 0.60 and a specificity of 0.62 (Alenius et al., 2002).

In 2007, the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire was developed in Boston, USA. Designed by both dermatologists and rheumatologists using a Delphi method, it consists of 15 questions, separated into two subscales: symptoms (7 questions) and functional impact (8 questions). Each item is scored on a scale from 1 (strongly disagree) to 5 (strongly agree), giving a maximum possible function score of 40 and symptom score of 35. Validation took place in 69 patients in a tertiary care setting, against a physician-made diagnosis of psoriasis and psoriatic arthritis, assessed by a dermatologist and rheumatologist respectively. Within this cohort, PsA was diagnosed in 25% and OA in 35%. Patients with PsA had higher scores than those with psoriasis and OA, and patients with more severe PsA had higher scores than those with milder

disease. PASE scores ranged from 28 to 63, and a cut off of 47 proved optimal for differentiating patients with PsA (sensitivity 83%, specificity of 73%) (Husni et al., 2007). Further validation was carried out in a further 194 patients with psoriasis and/or PsA. In this cohort, the optimal cut off was 44, providing a sensitivity and specificity of 76%. Reasonable sensitivity to change in disease state has been shown, and acceptable reliability was confirmed with an interclass correlation coefficient of 0.90 for the total PASE score (Dominguez et al., 2009).

The Toronto Psoriasis and Arthritis Screen (ToPAS) was developed and validated by Gladman et al in 2008. It was designed by an expert panel of dermatologists and rheumatologists as a screening tool for PsA, regardless of whether the patient has cutaneous psoriasis. The twelve-item questionnaire differs from other questionnaires in that it includes photographs of plaque psoriasis, 'lifting of the nail' (onycholysis) and pitting in addition to assessing any previous history of (rather than just current) symptoms. Following initial development, it was validated on patients with PsA, patients in a general rheumatology clinic (with those with PsA excluded), patients in a tertiary psoriasis clinic, patients in a general dermatology clinic and patients in a 'family medicine' (general practice) clinic. Logistic regression and ROC curve analysis were used to assess questionnaire responsiveness and in all settings, it was found to be highly sensitive and specific, with a sensitivity and specificity of 89-93% and 86-100% respectively. While the additional validation in a number of different settings is valuable, the ToPAS does not make any assessment of functional impact, instead being designed primarily for case identification (Gladman et al., 2009).

The Psoriasis Epidemiology Screening Tool (PEST) was developed in Leeds by rheumatologists with patients from the primary and secondary care settings. Patients coded by their General Practitioner as having psoriasis were invited to complete the questionnaire by post, and a sample were selected for assessment within the rheumatology clinic. A second group of patients with known PsA were also asked to complete the questionnaire. 168 questionnaires were returned, of which 89 patients were subsequently examined. The questionnaire was based upon the PAQ with some additional questions, and unlike previous questionnaires, a mannequin was also included to allow patients to easily identify the joints that were causing them symptoms. A logistic regression analysis was used to identify the five best performing questions, and in the initial cohort a cut off of three or more positive responses provided a sensitivity of 92% and specificity of 78% (Ibrahim et al., 2009).

In 2009, a further self-administered screening questionnaire, the Psoriasis and Arthritis Screening Questionnaire (PASQ), was developed in patients with both early and established psoriatic arthritis. Like the PEST, it is based on the PAQ, and includes ten questions on arthritis and nail signs/symptoms (each scored 0 or 1, to a maximum of ten points) and a homunculus with 68 joints on which patients identify painful and swollen

sites (either current or historic) (Khraishi, 2010). The diagram is scored 0, 1, 3 or 5 with points weighted according to the different presentations of PsA as described by Moll and Wright (Moll and Wright, 1973) (Table 1.10). A maximum PASQ score of 15 is achievable.

Points	Areas marked on the homunculus
0	Nothing OR non-joint areas
1	Many symmetric joints (MCP, MTP, wrists, not DIP)
3	One large joint only OR spine only
5	DIPs OR less than five joints OR one large joint (knee, hip or shoulder) plus the spine

Table 1.10. Scoring scheme for the homunculus component of the PASQ. (MCP: metacarpophalangeal; MTP: metatarsal-phalangeal; DIP: distal interphalangeal)

The PASQ was initially developed in a cohort of psoriasis and PsA patients seen at a combined dermatology and rheumatology centre in St John's, Newfoundland, who had a mean duration of psoriasis of 20.18 +/- 13.5 years. 58 patients with PsA (that met the CASPAR criteria) and 29 patients with psoriasis and no evidence of PsA were included. The latter were assessed by a nurse experienced in rheumatological examination, and the findings confirmed by a rheumatologist. With a cut off of seven, a sensitivity of 92% and a specificity of 78% were achieved. A further study selected patients from a prospective cohort of patients with suspected early PsA (with and without psoriasis) who were referred for assessment by their general practitioner or dermatologist. The objectives were to assess an identical electronic version of the questionnaire (ePASQ), which was designed to be self-scoring and require no physician assessment and to validate it against the original paper version. ROC curve analysis with a composite ePASQ score of 7 provided a sensitivity of 97.6% and a specificity of 75%, and analysis of the paper PASQ with a composite score of 7 provided a sensitivity and specificity of 92.86% and 75% respectively (Khraishi et al., 2011). The ePASQ has yet to be validated in patients with psoriasis and no known diagnosis or symptoms of joint disease, and neither the paper nor electronic form has been assessed in patients with other rheumatological conditions.

More recently, a screening tool for use in patients with suspected early PsA has been developed by Tinazzi and colleagues within the psoriasis clinic in Verona, Italy. The Early ARthritis for Psoriatic Patients (EARP) questionnaire initially consisted of 14 questions, and after psychometric analysis in a cohort of 228 patients, a simplified questionnaire of ten questions was found to have good inter-rater reliability (Cronbach's α=0.83). An

optimal cut off of 3/10 provided a specificity of 91.6% and sensitivity of 90.7%. Patients with known PsA, RA, OA and gout were excluded. It has not been validated in any other cohorts and its uptake has been limited (Tinazzi et al., 2012).

Each of the screening tools that have been developed have performed well in their development cohorts, and some have been further validated in outside the dermatology clinic, such as in the primary care setting or in general rheumatology clinic. They are all self-administered and relatively simple to complete and score. However, the optimal screening questionnaire for the detection of PsA risk is unknown. Five studies have attempted to address this dilemma by comparing several of the tools head-to-head; three compare the PASE, PEST and ToPAS (Coates et al., 2013, Haroon et al., 2013, Walsh et al., 2013a) one compares the PASQ, PEST and ToPAS (Mease et al., 2014b) and one compares the PASE, PEST and EARP. Table 1.11 outlines the comparative sensitivity and specificity of each of the questionnaires and the cohorts in which they were tested. The number of psoriasis patients diagnosed by a rheumatologist as having PsA is displayed in brackets.

Author (Year)	Psoriasis Cohort (n=)	PEST		ToPAS		PASE		PASQ		EARP	
		Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Coates (2013)	657 (47 with PsA)	76.6	37.2	76.6	29.7	74.5	38.5				
Haroon (2013)	100 (29 with PsA) + 100 PsA	27.5	98	41	90	24	94				
Walsh (2013)	213 (137 with PsA)	85	45	75	55	68	50				
Mease (2014)	949 (285 with PsA)	84	75	77	72			67	64		
Karreman (2017)	473 (53 with PsA)	68	71			66	57			87	34

Table 1.11: Comparative sensitivity and specificity of different psoriatic arthritis screening questionnaires from head-to-head studies.

Interpreting the findings of these head-to-head trials is problematic owing to substantial variation in patient characteristics, including age, duration of psoriasis, severity of psoriasis, presence and duration of PsA and therapies used, in addition to recruitment methodology. The very low sensitivities found by Haroon and colleagues compared to the other investigators may be explained by differences in study population and psoriasis

duration, but also high levels of immunosuppressant use (91%), which may be effectively treating any symptoms of underlying PsA in the patients with psoriasis. While it is difficult to make comparisons however, it is evident that the performance of the screening tools is not as optimal as in their development cohorts and that further work is needed to produce a screening tool that is reproducible within its intended clinical setting. In order to address this, the 'best performing' questions from the PEST, PASE and ToPAS have been analysed by the investigators of the CONTEST head-to-head study (Coates et al., 2013) and a new questionnaire ('CONTEST') has been developed that incorporates these elements (Coates et al., 2014).

Of four candidate questionnaires combining existing discriminatory items to identify PsA in people with psoriasis, three were found to be significant on ROC curve analysis. These three were then tested retrospectively in similar PsA screening datasets in Ireland and the US, and of these, two questionnaires appeared to perform slightly better than the PEST questionnaire – the simple CONTEST questionnaire which included the most discriminate items from each of the existing questionnaires and the same questionnaire with the addition of a joint mannequin (similar to that seen on the PEST questionnaire) (Coates et al., 2014) (Appendix 2). Using a cut-off of 4, the CONTEST without the joint mannequin had a sensitivity of 86.0% and a specificity of 35.4%, and with the mannequin, using a cut-off of 5, 86.0% and 36.9%, respectively. In the same cohort, the PEST questionnaire (using the validated cut-off of 3) had a sensitivity of 76.6% and a specificity of 32.0%. Unlike the PEST, these CONTEST questionnaires have only been tested in a secondary care dermatology population and remain to be tested in their ability to detect PsA in a primary-care population.

1.6 Imaging in Enthesitis

The 'gold standard' for the diagnosis of enthesitis is histological examination, this is neither ethical nor practical in the clinical or research setting. The limitations of clinical assessment for entheseal pathology have been previously discussed. Imaging is therefore the best option in terms of acceptability, reliability and reproducibility. Radiographs, while cheap and readily accessible, can only identify changes arising from chronic inflammation that lead to irreversible damage. They provide no information about the soft tissues, tendons, entheses or early bone pathology. These limitations can be overcome with the use of ultrasound and MRI. Both modalities have advantages and disadvantages in enthesitis, and the choice is often largely determined by time availability, equipment, economic resources and availability of skilled operators (Table 1.12).

	Advantages	Disadvantages
US	Comfortable for the patient Dynamic assessment Multiple sites can be assessed Easy to use at follow up	Time consuming Limited by the acoustic window Lack of comparison with histology
MRI	Ability to detect bone marrow oedema Able to demonstrate deep as well as superficial enthesis	Patient discomfort Cost Lack of comparison with histology

Table 1.12: Advantages and disadvantages of US and MRI for detecting enthesitis

1.6.1 Ultrasound

Ultrasound is easy to use, negates the need for radiation, is low in cost, widely available and acceptable to patients. The improved resolution of modern scanners allows for the detection of small structures or subtle abnormalities. For these reasons, peripheral joint ultrasound is an attractive imaging modality for the detection of disease of the entheses. Modern ultrasound also has the capacity to visualize the entheseal fibrocartilage, a structure of approximately 0.5mm in thickness, which may become eroded as part of disease of the entheseal organ.

Typical ultrasound abnormalities of enthesopathy include tendon thickening, tendon hypoechogenicity, calcifications, enthesophyte formation, erosions, bony irregularities or loss of the normal fibrillar tendon structure (Gutierrez et al., 2010, Balint et al., 2002, Falsetti et al., 2002). In addition, power Doppler can be applied to signal increased vascularity occurring at sites of inflammation, further improving the detection of active enthesitis (Iagnocco et al., 2012, D'Agostino et al., 2011).

1.6.1.1 Ultrasound Definition of Entheseal Disease

In 2005, the OMERACT group published a consensus definition for the ultrasound detection of enthesopathy that includes abnormalities reflective of both active inflammation and structural damage: ‘abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions or irregularity’ (Wakefield et al., 2005). This was recently supported by an international Delphi exercise, which found good (>80%) inter-rater agreement for a number of core defining features for ultrasound-detected enthesitis: hypoechogenicity, increased tendon thickness at the bony insertion, calcification(s),

enthesophyte(s), erosion(s) and power Doppler activity (Terslev et al., 2014). Bone irregularities are shown to be a less reproducible finding (Filippucci et al., 2009).

Enthesitis is rarely identified in isolation, with varying degrees of tendon and/or synovial inflammation, joint effusion and soft tissue oedema being seen, dependent upon the stage of PsA. Ultrasound is superior to radiographic imaging; in one study of early PsA patients (symptom duration < 1year), no radiographic abnormalities were seen, but ultrasound confirmed an effusion in the target joint in every patient (Bonifati et al., 2012). In addition, ultrasound has been shown to have good specificity in PsA, with greater sensitivity in detecting erosions than x-rays (Wiell et al., 2007).

1.6.1.2 Limitations of Ultrasound in Enthesitis

A key problem of the ultrasound assessment of enthesitis is determining the distinction between normal and disease. With increasing age, healthy controls often have thickened entheses as a consequence of mechanical frequent use, particularly in the lower limbs. Ultrasound is operator dependent, and experience in scanning is a prerequisite for the assessment of subtle features such as enthesopathy. Appropriate healthy controls must be recruited to trials so as not to over-estimate minor changes that are in fact within the normal range for the age of the patient.

1.6.1.3 Sensitivity to Change of Ultrasound in Enthesitis

The sensitivity to change of ultrasound in entheseal disease has only been investigated in four prospective studies (Genc et al., 2007, Naredo et al., 2010, Aydin et al., 2010, Mouterde et al., 2014). There were no significant changes in entheseal abnormalities found after sulphasalazine therapy, but this may be due to a lack of treatment efficacy (Genc et al., 2007). In contrast, enthesitis scores reduced dramatically in two independent studies following TNF inhibition, even after a short treatment term (Naredo et al., 2010, Aydin et al., 2010). In a recent trial of patients taking non-steroidal anti-inflammatory agents, ultrasound scores were seen to rise from baseline after one week of stopping the therapy, and subsequently fall again within one week of restarting (Mouterde et al., 2014). These data suggest that ultrasound is sensitive enough to visualize changes in a timely manner and should be considered as a useful adjunct in the assessment of efficacy of novel therapeutic agents for SpA.

1.6.1.4 Ultrasound Evaluation Vs. Clinical Examination for Enthesitis

The majority of studies have found that clinical examination underestimates the prevalence of enthesitis in PsA, suggesting that subclinical disease is common (Balint et al., 2002, Frediani et al., 2002, Lehtinen et al., 1994). Even dedicated entheseal indices

(e.g. Leeds Entheseal Index, LEI) designed to detect enthesitis clinically have been shown to correlate poorly with ultrasonography (Ibrahim et al., 2011).

Balint et al found clinical enthesitis in 22% of lower limb sites examined in patients with spondyloarthritis (SpA), compared to 56% by ultrasound. Clinical examination had a sensitivity and specificity of just 23% and 80% respectively, indicating that further modalities are needed for adequate assessment of enthesitis (Balint et al., 2002). Data from different studies of the quadriceps tendon and knee tendons also showed an underestimation of entheseal disease by clinical examination when compared to ultrasonography (Frediani et al., 2002). However, it should be noted that clinical assessment of the knee in 14 patients suggested enthesitis, although ultrasound was normal. One reason for this may be that the authors excluded enthesophytes from their criteria for enthesopathy, deeming them common and non-specific (Li et al., 2010), whilst other authors routinely accept enthesophytes as a diagnostic feature on ultrasound (Aydin et al., 2010, Gutierrez et al., 2010).

1.6.1.5 Ultrasound in Subclinical Enthesitis

The most plausible reason for the discrepancy between the clinical and ultrasound assessments of enthesitis is the presence of asymptomatic or 'subclinical' enthesitis. Estimates of subclinical enthesitis vary considerably, ranging from 4-59.3% (De Filippis et al., 2005, Farouk et al., 2010, Gisondi et al., 2008, Gutierrez et al., 2011, Naredo et al., 2011, Ash et al., 2012b, Ozcakar et al., 2005, Acquacalda et al., 2015, Acquitter et al., 2016, De Simone et al., 2003, Moshrif et al., 2017, Freeston et al., 2012). A cross-sectional study by D'Agostino et al (D'Agostino et al., 2003) found that 38% of entheses in patients with SpA had evidence of subclinical disease using grey-scale (GS) and power Doppler (PD) ultrasound, compared with 11% of controls (D'Agostino et al., 2003).

Naredo et al (Naredo et al., 2011) performed a similar study comparing 162 psoriasis patients without arthritis to 60 age matched controls with other skin diseases. Ultrasonographic enthesitis was detected in 11.6% of entheses in the psoriasis group compared to 5.3% of the entheses of the controls ($p<0.0005$). Entheseal PD signal was detected in 7.4% psoriatic patients, whereas no controls showed this finding (Naredo et al., 2011). In a different study of 30 chronic psoriasis patients without clinical features of PsA, mean ultrasound scores (GUESS) of enthesitis were significantly higher ($p=0.0001$) than in healthy age and sex matched controls, and scores correlated with obesity and age. In particular, the thickness of all tendons examined was significant higher in cases than in controls, as well as the number of enthesophytes in all sites examined (Gisondi et al., 2008). More recently, Acquacalda and colleagues found subclinical enthesopathy in 46.4% of entheses scanned in the upper and lower limbs of a cohort of 12 psoriasis patients (Acquacalda et al., 2015). Moshrif et al identified lower limb enthesitis in 36% of

asymptomatic psoriasis patients with severe psoriasis (mean PASI>15.0) (Moshrif et al., 2017). In the only ultrasound study of psoriasis patients without diagnosed PsA in primary care, 45% of 111 patients had at least one inflammatory entheseal lesion, although most had clinically tender entheses using MASES and/or LEI, and some had musculoskeletal complaints (van der Ven et al., 2016). Further studies are described in Table 1.8.

In contrast, Freeston et al found only 4% of non-tender entheses had GS and/or PD ultrasound evidence of subclinical disease in a cohort of patients with early PsA (Freeston et al., 2012). However, in this study, the authors permitted a GS score of 1 to be classified as normal, as this *can* occur in healthy individuals as a consequence of mechanical stress. GS changes were common in their control group (n=10), although only 1% had a positive low-grade PD signal (Freeston et al., 2012); this suggests that PD may be a requisite tool for the determination of pathological entheseal disease.

Data from Aydin and colleagues further supports the use of PD in subclinical enthesitis (Aydin et al., 2013a). In their study, psoriasis patients (with or without arthritis) were more likely to express an 'inflammatory' or vascular phenotype than healthy controls, as detected by PD ultrasound. The highest inflammation-related enthesopathy scores were found in patients with PsA, even when symptomatic entheses were excluded. Doppler positivity in at least one entheseal site was observed more frequently in PsA (36.2%) versus psoriasis alone (9.5%) (Aydin et al., 2013a). In other studies of asymptomatic patients with psoriasis, PD is reported, albeit at a much lower frequency than in patients with established PsA, in 0.7-1% of entheses (Acquitter et al., 2016, Ash et al., 2012b, Gutierrez et al., 2011).

1.6.1.6 Power Doppler Ultrasound in Enthesitis

The value of PD ultrasound in the diagnosis of early stage SpA has also been evaluated in a French cohort (D'Agostino et al., 2011). D'Agostino and colleagues found that the presence of at least one vascularized enthesis seen with PD ultrasound gave a sensitivity of 76.5% and a specificity of 81.3% for the diagnosis of SpA. In agreement with the majority of other studies in this domain, the Achilles and lateral epicondyle tendons were more frequently involved in SpA than non-SpA patients (D'Agostino et al., 2011).

Of the several scoring systems described for the quantification of ultrasound abnormalities in SpA, the addition of PD signal has been received favourably both in terms of improved sensitivity and specificity of classifying inflammatory arthritis (D'Agostino et al., 2011, D'Agostino et al., 2003, Iagnocco et al., 2012), but also in terms of responsiveness to treatment (Hammer and Kvien, 2011, Kurosaka et al., 2010, Naredo et al., 2008).

1.6.1.7 Ultrasound in the Distinction Between Psoriatic Enthesopathy and Other Inflammatory Arthritides

The majority of data relating to the use of ultrasound in inflammatory musculoskeletal disease has been obtained through the investigation of RA. Several early studies confirmed not only the ability of PD to identify vascular abnormalities known to be associated with inflammation in RA, but also the relationship between these features and both later damage and response to treatment (Hammer and Kvien, 2011, Kurosaka et al., 2010, Naredo et al., 2008).

Distinguishing between inflammatory arthritides, especially RA and PsA, on the basis of entheseal ultrasound can be difficult and several studies have been unable to differentiate at a patient level (Iagnocco et al., 2012). Enthesopathy tends to be more severe in PsA when compared to RA, but this is insufficient for diagnosis. Frediani et al investigated the ultrasound findings of the quadriceps tendon in patients with RA and PsA, and found patients with the latter were more likely to have evidence of enthesitis (45% RA vs. 7.5% PsA) (Frediani et al., 2001). Patients with RA were more likely to have a joint effusion (95% vs. 60%), and isolated enthesitis without effusion was only seen in patients with PsA. RA patients exhibited more inflammatory changes including tendon thickening, hypoechogenicity and oedema, whilst features of new bone formation were almost exclusively present in those with PsA (Frediani et al., 2001).

Investigation of the distal upper limb has helped to provide further distinction. In a cohort of 25 PsA patients, three had enthesophytes and four had distal phalynx enthesopathy, compared to 0/25 patients with RA (Fournie et al., 2006). At the metacarpophalangeal joint level, an Italian group found the presence of inflammation around the extensor tendon region potentially differentiated PsA and RA patients, with an incidence of 65.8% vs. 0% respectively (Gutierrez et al., 2011). When compared to OA, inflammatory features were more frequent in the heel entheses of patients with PsA and RA, with Achilles enthesitis seen in 8% with PsA and 0% with OA or control subjects. However, it is worth noting that in this last cohort, plantar fasciitis was not significantly more common in PsA than RA, and the frequency of enthesophytes at the heel was similar in OA and PsA (Falsetti et al., 2003).

In addition to the presence of new bone formation, the presence and shape of bone erosions associated with enthesitis may aid diagnosis. McGonagle and colleagues used ultrasound to assess the topography of erosions and new bone formation in Achilles tendon enthesitis (McGonagle et al., 2008). Erosions were found to occur only in the more fibrocartilaginous areas – at the proximal part of the insertion site or the superior tuberosity, with none observed in the distal enthesis. In terms of the shape of erosions, Finzel et al (Finzel et al., 2011) identified profound differences between the periarticular bone changes in PsA and RA. Whilst patients had a similar number of erosions, they

tended to be less severe, more evenly distributed and overall smaller in size and depth in PsA. Erosions in PsA were mostly Ω-shaped and tubule shaped, whereas U-shaped lesions were more typical for RA (Finzel et al., 2011). These data were however derived from studies using high resolution μCT scanning, and it remains to be determined if such distinction can be made using ultrasound.

1.6.1.8 Ultrasound in the distinction between Psoriatic Enthesopathy and Fibromyalgia

Clinically, the distinction between PsA and fibromyalgia can be very difficult, especially in patients with concomitant psoriasis. Both manifest with tender points, especially on palpation during clinical examination. An Italian study aimed to assess the utility of ultrasound in this domain, and found that although entheseal changes were significantly more common in patients with PsA, patients with fibromyalgia also frequently had imaging abnormalities; 80% had enthesopathy, 23% had inflammatory lesions and 23% had altered entheseal PD signal. The Achilles and quadriceps tendons were most frequently abnormal. Patients with fibromyalgia were more likely to have clinically tender but sonographically normal entheses (37% vs. 8% PsA). An ultrasound finding of at least three abnormal entheses predicted a diagnosis of PsA with a sensitivity of 72% and a specificity of 76% in this cohort (Marchesoni et al., 2012).

1.6.1.9 Ultrasound Scoring Systems for Enthesitis

In an attempt to confirm the presence and severity of enthesopathy, several groups have attempted the development of ultrasound scoring systems. One of the earliest and most widely cited is the Glasgow Ultrasound Enthesitis Scoring System (GUESS), designed by Balint and colleagues in 2002. The initial study demonstrated substantial to excellent interobserver agreement (Balint et al., 2002), although criticism is levied at the inclusion of only the lower limbs, and absence of any PD assessment. In 2003, D'Agostino et al aimed to improve on these exclusions by introducing a composite grading system (grade 0-3b) which included both GS and PD assessments of the common extensor and flexor origins at the elbow, the gluteus insertion at the greater trochanter and pubis enthesis as well as those of the knee and distal lower limb in patients with SpA (D'Agostino et al., 2003). The group refined their assessment in 2009 to focus only on those entheses most frequently involved (common extensor origin of the elbow, quadriceps tendon insertion, superior patella tendon insertion, Achilles tendon and plantar fascia) and to use a more simplified scoring system for vascularization and morphological and structural abnormalities. Helpfully, both the grading system by Balint and that by D'Agostino contain maximum measurements for 'normal' entheseal thickness, enabling reproducibility in future studies, unlike other published scoring systems.

The Madrid Sonographic Entheseal Index (MASEI) was developed in 2009 in a cohort of patients with SpA (de Miguel et al., 2009). Again, an enthesis in the upper limb was included in order to determine the strength of influence of mechanical factors prone to affect the lower limb entheses. GS and PD abnormalities were scored at six sites, with a maximum potential score of 136. de Miguel et al reported that with a cut-off point of 20 more, MASEI correctly classified patients as having SpA with a sensitivity of 53% and a specificity of 83.3% among a group of patients with variable probabilities of having some form of SpA (de Miguel et al., 2009).

In psoriatic disease specifically, an independent group in Toronto assessed the usefulness of the MASEI in classifying patients as having PsA (Eder et al., 2014). It is known that entheseal lesions are commonly found in patients with psoriasis but who do not have clinical signs of enthesitis or synovitis (Naredo et al., 2011, Gutierrez et al., 2011, Gisondi et al., 2008). The significance of such abnormalities is unclear, and other factors such as age and high body mass index (BMI) may be contributory. 50 PsA, 66 psoriasis and 60 healthy controls were scanned and the MASEI scoring system used to quantify the extent of entheseal abnormalities in each of these groups. Total, damage and inflammatory MASEI scores were, as expected, significantly higher in patients with PsA; however, the sensitivity of the MASEI to correctly classify patients as having PsA was only 30%, suggesting ultrasound alone is insufficient for diagnosis (Eder et al., 2014). Specificity ranged from 89% to 95% (for comparison with psoriasis patients and healthy controls respectively), confirming a role for GS and PD ultrasound assessment in patients where there is clinical suspicion. It was apparent however, that this is dependent upon other factors, and most specifically BMI - in this study, no significant differences were seen in MASEI scores across the three groups where BMI was in excess of 30 (Eder et al., 2014).

The ultrasound score proposed by Naredo et al in 2010 includes GS and PD assessment at seven sites, with two in the upper limb and five in the lower. In addition to demonstrating excellent intraobserver reliability, it has also exhibited responsiveness to change to treatment. Morphological abnormalities, PD signal and bursitis scores all improved with effective anti-inflammatory therapy in the form of TNF inhibition (six months), whilst calcific deposits and cortical abnormalities remained unchanged or increased, confirming the irreversibility of structural damage (Naredo et al., 2010).

Other ultrasound scoring systems have been used to assess for enthesopathy and treatment responsiveness in cohorts not including patients with PsA. A scoring system previously described by Filippucci et al was used to assess only Achilles enthesitis in forty-three patients with ankylosing spondylitis (AS) (Filippucci et al., 2009). After two months of TNF inhibition, significant improvements in GS and total inflammatory scores were seen, although reductions in PD score specifically did not reach statistical

significance. Features of chronicity and damage were not assessed as they were expected not to change.

The Sonographic Enthesis Index (SEI) was also developed in patients with AS. A good interobserver reliability was found in the initial study, although this did not include PD assessment (Alcalde et al., 2007). The SEI was modified in 2011 by Hamdi et al, again in patients with AS (Hamdi et al., 2011). The Doppler score correlated well with disease activity measures, and the total score correlated well with clinical enthesitis indices; however, the validity of the SEI and modified SEI have not been assessed in patients with PsA, where peripheral disease tends to be more prominent and where there may be associated skin disease associated with entheseal abnormalities.

Further large-scale validation studies are required to determine which of these published scoring systems is the most sensitive and specific scoring system for use in the detection and treatment of psoriatic disease. To date, no scoring systems have been published that encompass all components of the OMERACT definition of enthesopathy, nor that include the full synovio-entheseal complex.

1.6.2 Magnetic Resonance Imaging in Enthesitis

Magnetic resonance imaging (MRI) is of primary benefit in the spondyloarthropathies (including PsA) for the evaluation of the axial skeleton, principally the sacroiliac (SI) joints and spine. However, it can be used as a sensitive imaging modality for any structures critical in the evolution of inflammatory arthritis, providing detail of the bone and surrounding tissues in three planes. The majority of studies of MRI in PsA have used conventional 1.5-Tesla (T) magnets with a surface coil, although 3T magnets are now becoming more widely available in the research setting.

PsA (and SpA in general) are characterised by diverse and anatomically widespread disease manifestations and conventional MRI can be inadequate, allowing visualisation of a small anatomical area at one examination, limiting its ability to provide an overall assessment of disease status. However, with the advent of whole-body MRI (WB-MRI), assessment is now possible from ‘head-to-toe’ of all peripheral and axial joints in only one examination and in a relative short period of time. Using multi-coil systems and a moving table platform, scanning of adjacent anatomical regions is possible without repositioning the patient or imaging coils. Fusion of the images allows visualisation of lesions in the axial skeleton, anterior chest wall, shoulder and hip girdles, peripheral joints and entheses may be visualised within the same image. In axial SpA, reports show that reliability of detection is comparable with that of conventional MRI (Weber, 2008b, Weber, 2008a). The possible features of SpA that can be assessed with MRI are listed in Table 1.13 (Ostergaard et al., 2009, Mager et al., 2009, Maksymowych and Lambert, 2007).

Anatomical Location	Lesion	Feature
Sacroiliac Joints	Juxta-articular osteitis (active)	High signal of periarticular bone marrow on STIR images and low signal intensity on T1w images. Can be seen further away from the joint where fatty replacement of bone marrow is extensive.
	Synovitis (active)	Seen in the joint space, usually only after contrast enhancement.
	Capsulitis (active)	Anterior and posterior high signal intensity, usually only after contrast enhancement.
	Enthesitis (active)	Usually affects the interosseous ligaments as they course through the retroarticular space (small synovial joint compartment of the SI joints), seen as high intensity signal on STIR images.
	Subchondral Sclerosis (chronic)	First arises in the iliac bone as a thin band of low signal intensity on all sequences and increases as sclerosis progresses.
	Erosions (chronic)	Destructive discontinuations of the cortical layer with low signal intensity on T1w images and high signal intensity on STIR images. Discrete when early – can become confluent to give a ‘string of pearls’ appearance.
	Transarticular bridging (chronic)	Reflects SI joint ankylosis and represents new bone formation. Characterised by low signal intensity on all sequences. Progressive ankylosis leads to progressive joint space narrowing due to fatty replacement of the bone marrow, characterised by increased T1 signal intensity.

Anatomical Location	Lesion	Feature
Spine	Enthesitis (active)	Involves the interspinous ligaments and is seen as an increase in signal intensity in STIR images and fat saturated, contrast-enhanced T1w sequences.
	Bony irregularities (active and chronic)	Acute romanus lesions (irregularities of the anterior and posterior edges of the vertebral endplates) are characterised by low signal intensity on T1w images and increased signal intensity on STIR images. Chronic romanus lesions show T1 hyperintensity due to fatty replacement of the bone marrow. Advanced lesions may give rise to anterior syndesmophytes.
Peripheral Joints	Enthesitis (active)	Seen as a non-uniform increase in signal intensity in STIR images and fat saturated, contrast-enhanced T1w sequences at tendon insertion sites with swelling or oedema of surrounding soft tissues.
	Synovitis (active)	High signal intensity in the synovial compartment on T1w sequences, with a thickness greater than the width of normal synovium. Contrast enhancement is usually needed.
	Tenosynovitis (active)	Increased water content adjacent to a tendon in an area with a tendon sheath, seen as hyperintensity on T2w fat-saturated and STIR images, and low signal intensity on T1w images. Contrast enhancement is needed for T1w image sequences.
	Periarticular inflammation (active)	Increased water content at extra-articular sites including the periosteum and entheses but not the tendon sheaths, seen as high signal intensity on T2w fat saturated and STIR images. Contrast enhancement is needs for T1w image sequences.
	Bone marrow oedema (active)	A lesion within trabecular bone with high signal intensity on T2w fat-saturated and STIR image sequences and low signal intensity on T1w images. Often has ill-defined margins and may occur alone or surrounding bony abnormalities.
	Bony irregularities (chronic)	Enthesophytes and erosions are seen using T1w sequences, with a loss of normal low signal intensity of the cortical bone and a loss of normal high signal intensity of bone marrow fat.

Table 1.13: Potential manifestations of PsA identifiable on MRI

The characteristic features of enthesopathy identifiable by MRI include bone marrow oedema, soft tissue oedema, tendon thickening, intra- and extra-osseous erosions and enthesophytes, and additional findings such as fluid around tendons or adjacent to bursa may also be visualized (Eshed et al., 2007).

In terms of optimal MRI sequences and acquisitions, spatial resolution and signal-to-noise ratios need to be considered. T1 weighted (T1w) spin-echo (SE) sequences are effective at depicting bone, fat, muscles, ligaments and tendons (Eshed et al., 2007). T1w SE sequences with fat suppression after contrast administration are advised for depicting bursitis, tendonitis and bony lesions such as osteitis, although experience in AS has suggested that axial T1w sequences lack sensitivity for the detection of syndesmophytes (Braun et al., 2003), which may apply to the bony lesions of peripheral PsA (enthesophytes).

Short tau inversion recovery (STIR) and T2 weighted (T2w) fast/turbo spin-echo fat suppressed sequences are very effective for bone oedema and soft tissue inflammation, joint effusion, bursitis and tenosynovitis (Roemer et al., 2005, Eshed et al., 2007) and may therefore be preferable in PsA. However, T2w images are more time-consuming to acquire and therefore more susceptible to movement artefact (McQueen et al., 2007a).

Given the superiority of MRI over ultrasound for visualisation of the axial skeleton, many of the trials of MRI assessment of enthesitis have been performed in general SpA patients, and more specifically those with AS, who have predominantly axial disease. However, meaningful conclusions can be drawn from these data for patients with axial PsA given the pathological similarities between the seronegative spondyloarthropathies. Indeed, the hypothesis that enthesitis is the common primary pathogenic mechanism shared in the spondyloarthropathies arose from a MRI-based study of patients with inflammatory arthritis, including PsA. McGonagle and colleagues were the first to describe characteristic MRI entheseal changes involving the knee joints of ten patients with SpA (including three with PsA) and ten with RA with a swollen knee joint of recent onset. Three patients with SpA and one with RA had evidence of enthesitis and focal bone marrow oedema was seen exclusively in SpA patients (six out of ten). All ten SpA patients showed perientheseal high signal outside of the joint compared with four in the RA group (McGonagle et al., 1998b).

1.6.2.1 MRI Definition of Entheseal Disease

Unlike ultrasound, there is no standardised definition of enthesitis on MRI. The Assessment of SpondyloArthritis (ASAS) International Society and OMERACT MRI working group describe active enthesitis at the SI joint as ‘a hyperintense signal on STIR images and/or contrast enhanced, T1 weighted, fat saturated images at sites where ligaments and tendons attach to bone, including the retroarticular space (interosseous

ligaments). The signal may extend to bone marrow and soft tissue' (Rudwaleit et al., 2009).

Barozzi et al characterised the MRI features of enthesitis as 'swelling and deviation from the normally uniform low signal intensity of tendons and ligaments, distension of adjacent bursae by fluid collection, peritendinous soft tissue swelling and inflammation of bone adjacent to the insertion' (Barozzi, 1988). This was supported by the description from Eshed at al (Eshed et al., 2007), in which the group advise that to adequately assess an MRI image for enthesitis, the following should be evaluated:

- 'Thickness and signal intensity of tendons and ligaments'
- 'Perientheseal soft tissues for swelling or oedema'
- 'Adjacent bone marrow to detect oedema, best appreciated as high signal in fat suppressed sequences'
- 'Adjacent bone for erosions (cortical bone defects and contour irregularities)' and enthesophytes (extensions of marrow contents isointense to the medullary bone), both best appreciated on T1-weighted sequences'
- 'Additional findings in adjacent structures (joint or bursal fluid for example)'

1.6.2.2 Conventional MRI in Enthesitis

MRI has been used to investigate the presence of enthesitis at several sites in patients with PsA and SpA. Emad and colleagues confirmed the findings in the knee from McGonagle et al with enhanced MRI scanning in three groups of patients (SpA, established RA and undifferentiated arthritis). Enthesitis was a common feature in the SpA group (n=15), completely absent in the RA group (n=15) and observed in three patients in the undifferentiated arthritis group (n=25) (Emad et al., 2009). In a second study, the group also found enthesitis in the knees of 56 patients with SpA, including 30 with PsA. The most commonly involved enthesis was the medial collateral ligament (40.0%), followed by the patellar tendon insertion (23.3%), lateral collateral ligament (16.7%), biceps femoris tendon (10.0%) medial patellofemoral ligament (6.7%) and lateral patellofemoral ligament (3.3%) (Emad et al., 2010).

In the heel, Kamel et al reported on a cohort of 32 patients with SpA. MRI showed tendon enlargement (62.5%) with loss of the normal hypointense appearance and focal thickening at the insertion site (31.2%), and diminished signals within the pre-Achilles fat pad due to inflammatory oedema. 40.6% had associated osteitis. Entheseal abnormalities of the heel were also frequently identified on MRI in a different cross-sectional study of patients with SpA and symptomatic heel pain (81%). However, interesting in this study, a surprising proportion of SpA patients without heel pain and control subjects (with mechanical back pain) also had abnormalities at the heel (53% and 67% respectively, p=0.045). The most common abnormalities in the control subjects

were abnormal intertendinous signal (Achilles tendon 20.83%, plantar fascia 41.67%) peri-aponeurosis signal (35.42%), enthesophytes (Achilles tendon 16.67%, plantar fascia 31.25%) and Achilles tendon thickening (20.83%). Only oedema of the calcaneum on MRI was specific enough (94%) to distinguish SpA from control subjects but was not sufficiently sensitive for diagnosis (22% of all patients with SpA). 15% of the patients with SpA in this study also had psoriasis, but the specific SpA diagnoses were not disclosed (Feydy et al., 2012).

In the upper limb, only the entheses adjacent to the joints of the hands, fingers and wrists have been studied with MRI in patients with PsA. Most studies compare MRI changes to those in patients with RA; a few reports have shown that inflammation is localised within the joint capsule in RA, which is in contrast to PsA, where extra-capsular involvement is also present (Jevtic et al., 1995, Schoelnast, 2006, Marzo-Ortega et al., 2009, Giovagnoni, 1995, Savnik et al., 2001). In the most recent study, Narvaez and colleagues performed MRI scanning on the hands and wrists of patients with both early PsA and RA, with duration of clinical symptoms of less than 12 months. Enthesitis was seen exclusively in the PsA cohort, with 12 out of 17 patients exhibiting diffuse bone marrow oedema and florid inflammatory soft tissue changes adjacent to the insertion site (Narvaez et al., 2012). MRI could therefore hold value as a diagnostic tool to differentiate between the two conditions, although this concept has not been definitively established or validated in patients with early, inflammatory arthritis.

1.6.2.3 Whole-Body MRI in Enthesitis

Two studies have assessed the use of WB-MRI for widespread detection of enthesitis in patients with PsA (Poggenborg et al., 2014b, Poggenborg et al., 2014a, Weckbach et al., 2011) and several more in axial SpA (Karpitschka et al., 2013, Althoff et al., 2013, Song et al., 2011a). Reliability analysis of WB-MRI assessments within some of these studies has revealed encouragingly high inter-rater correlation coefficients (>0.85) within axial SpA (Song et al., 2011a, Karpitschka et al., 2013). Only one study has included patients with PsA and found variable inter-reader ICCs, ranging from 0.31-0.85 for synovitis, bone marrow oedema and erosions, 0.62-0.68 for bone marrow oedema and fat infiltration in the spine, 0.81-1.0 for bone marrow oedema, fat infiltration, erosion and ankylosis in the SI joints and 0.58 for enthesitis (Poggenborg et al., 2014a, Poggenborg et al., 2014b). It should be noted that this study had a small sample size (only ten participants were re-scored after a 12 month interlude) and there was poor readability at certain sites, particularly for enthesitis (Poggenborg et al., 2014a).

In the first ‘proof of concept’ study to assess whether WB-MRI was feasible in PsA, 30 patients with established PsA were scanned using STIR and T1w gradient echo sequences and the images assessed for the presence of bone marrow oedema,

effusions, synovitis, enthesitis, bursitis, osseous erosions and osseous destructions. Good quality images of the axial skeleton were obtained in 87% of cases and of the hands and feet in 53%. Enthesitis was classified as oedema in the attaching tendon and in the tendon attachment site of bone, and it was the most common visible finding in the hip region. Topographically, enthesitis was closely related to bone marrow oedema like signal alterations, extending beyond the joint capsule away from the joint and associated with oedema-like alterations in adjacent soft tissues. The areas most frequently affected by enthesitis were the hips (66.0%), spine (lumbar, 60.0%; thoracic, 43.3%; cervical 36.6%) and symphysis pubis (23.3%), followed by the feet (6.7%), SI joints (3.3%) and knees (3.3%). Enthesitis within the spine was most commonly seen in the interspinal ligaments, adductor tendons and glutei muscle attachment sites. Comparing the number of regions of enthesitis detected by clinical examination, WB-MRI was statistically superior ($p<0.001$), with more locations being identified on WB-MRI in 80% of patients. However, more sites were scanned than were included in the clinical assessment. (Weckbach et al., 2011).

Poggenborg and colleagues performed WB-MRI on patients with peripheral PsA (n=18), axial SpA (n=18) and healthy volunteers (n=12) to assess the presence and pattern of inflammatory and structural lesions in axial and peripheral joints, with the aim developing a WB-MRI global inflammation and structural damage scoring system (Poggenborg et al., 2014b). In a separate publication, the group reported specifically on enthesitis within this cohort, and compared the WB-MRI findings to clinical measures of enthesitis including the MASES, SPARCC and LEI. WB-MRI allowed adequate visualisation of 53% of all entheseal sites investigated, with the pelvic entheses, supraspinate tendons, greater femoral trochanters and medial femoral condyles being most easily viewed (>94% of patients). The poorest areas were the anterior chest wall and elbows, being in the field of view in only 29% and 1% of cases respectively. Within all 888 entheses visualised, 17% demonstrated enthesitis, defined as ‘the presence of bone marrow oedema, soft tissue oedema, change in tendon thickness, erosions or enthesophytes in adjacent bones, and additional findings such as fluid around tendons or adjacent to bursa, alone or in combination’. Patients with PsA had enthesitis on WB-MRI in 18% of entheses examined, compared to 14% of entheses in healthy subjects. The sites and frequencies at which lesions were identified in these groups are described in Table 1.14.

Anatomical Site	Enthesis	PsA (%)	Healthy Subject (%)
Lower Limb	Greater femoral trochanter	64	58
	Achilles tendon insertion	36	28
	Medical femoral condyle	12	25
	Quadriceps insertion into patella	0	13
Upper Limb	Supraspinate tendon insertion at the humerus	28	13
Pelvis	Ischial tuberosity	18	8
	Posterior superior iliac spine	17	0

Table 1.14. Frequencies of enthesitis found on WB-MRI in patients with PsA (n=18) and healthy subjects (n=12).

The high rates of enthesitis in healthy subjects seen on both clinical examination (8%) and WB-MRI (14%) was attributed by the authors to the possible presence of subclinical enthesitis (related to other conditions inducing high mechanical stress such as obesity or overuse due to physical activity, e.g. long-distance running) (Poggenborg et al., 2014a). Studies in conventional MRI have shown high levels of enthesitis in the shoulders (Lambert et al., 2004) and Achilles tendon (Feydy et al., 2012) in asymptomatic patients with axial SpA and healthy subjects.

1.6.2.4 MRI in Subclinical Enthesitis

The majority of studies investigating subclinical joint pathology in psoriasis have used ultrasound, although one small study has utilised MRI specifically for this purpose. 25 patients with active psoriasis but no clinical evidence of PsA had a non-contrast MRI scan of their hand. 17 patients had one or more signs of arthritis on MRI, including capsular distension (n=11), periarticular oedema (n=9) and erosions (n=7) at and around the MCP and interphalangeal joints. No articular features of PsA were seen in the healthy control group with the exception of a bone cyst in one participant (Offidani et al., 1998).

Emad and colleagues investigated entheseal related changes shown among patients with several forms of spondyloarthropathy. They included six patients with psoriasis without clinical signs of synovitis that were not receiving any systemic immunosuppressant or biologic therapy. One patient had bone marrow oedema, and enthesitis was detected in five patients at the patellar tendon insertion, and one patient at the medial patellofemoral ligament (Emad et al., 2010).

The same group later published data from 48 patients with psoriasis and no clinical evidence of peripheral or axial enthesitis or synovitis and 20 age and sex matched

controls without arthritis. Amongst the 96 knees scanned in psoriasis patients, 90 entheseal lesions were identified in addition to soft tissue oedema (n=52), bone marrow oedema (n=20), perientheseal bone marrow oedema (n=3), cartilaginous erosions (n=42) and bone erosions (n=27). Enthesitis was significantly and positively correlated with soft tissue oedema (r=0.304, p=0.036) and cartilaginous erosions (r=0.304, p=0.036). The control patients showed no evidence of enthesitis; five had cartilaginous erosions and two had bone marrow oedema (Emad et al., 2012). Erdem and colleagues performed clinical and MRI examination of the feet of 26 seronegative patients with psoriasis (and no signs or symptoms of PsA) and 10 healthy subjects. 24 patients had abnormalities on MRI, most commonly Achilles tendonitis (57%), retrocalcaneal bursitis (50%), joint effusion/synovitis (46%), soft tissue oedema (46%) and para-articular enthesophytes (38%). Enthesopathy, described as 'abnormalities at ligamentous attachments such as enthesitis, enthesophyte and [bone] marrow oedema adjacent to the insertion', was seen in 23% at the Achilles tendon and 15% at the plantar fascia attachment. No abnormalities were found in any of their healthy control cases, who were aged between 20 and 63 years (mean 42.9 +/- 12.9) (Erdem et al., 2008).

1.6.2.5 Limitations of MRI in Enthesitis

In comparison to ultrasound, MRI is considerably more expensive, less widely available, and has lower spatial resolution, thus limiting its use in the assessment of enthesitis to clinical trials at the present time.

Conventional MRI can only be used to scan one joint region of interest at a time and this is a limitation when assessing a phenotypically heterogeneous disease such as PsA. The advent of WB-MRI has largely overcome this problem, however it is less sensitive for detecting bone marrow oedema, which in entheseal disease, is a significant limitation. 'Readability' has been a problem in studies using WB-MRI to assess the entheses, with a high degree of artefact preventing interpretation. In one study, 16 of 35 sites were readable in less than 70% of cases. The Achilles tendon was out of the field of view in 21% of cases and impossible to evaluate in 8%, and readability was compromised at several other sites, including the patellar ligament insertion into the patella and tibia (readable in 5% and 2% respectively) and the elbow (readable in 1%) (Poggenborg et al., 2014a). In the peripheral skeleton, it is reported that it can be a challenge to image the elbow, wrist and finger joints due to the configuration of coils (Mager et al., 2009). Nevertheless, despite these problems, much useful data can be obtained from conventional and WB-MRI in its current form, and with advances in scanner technology coupled with operator experience, such limitations should be overcome in time.

1.6.2.6 Sensitivity to Change of MRI in Entheseal Disease

Several trials have used MRI to assess enthesitis before and after treatment. The sensitivity to change with TNF inhibitor therapy was first demonstrated in 10 patients treated with etanercept, with 86% of MRI-detected lesions improving or resolving after 6 months of therapy (Marzo-Ortega et al., 2001). Similarly, Karpitschka et al demonstrated a 94.3% reduction in MRI enthesitis scores after one year of etanercept (Karpitschka et al., 2013), and a significant decrease in bone marrow oedema and synovitis was seen on MRI after 20 weeks of infliximab (Marzo-Ortega et al., 2007). Superiority of etanercept over sulphasalazine in the treatment of enthesitis has been shown using whole body MRI, with no change demonstrated in the latter group after 48 weeks (Song et al., 2011a). Only one study has failed to show any resolution in MRI-detected bone marrow oedema with etanercept compared with placebo, which was in notable contrast to the patient reported outcomes where improvement was significant (Dougados et al., 2010). MRI was also used assess the response to a different TNF inhibitor, adalimumab, in a 19-year-old male with Achilles enthesitis and plantar fasciitis. Resolution of bone marrow oedema, soft tissue oedema and retrocalcaneal bursitis occurred within six months of treatment (Mancarella et al., 2010).

1.6.2.7 MRI Evaluation Vs. Clinical Examination for Enthesitis

Several investigators have compared the rate of enthesitis found on clinical examination with that seen on MRI. None have found a significant correlation between clinical and MRI findings, and there is discrepancy between which method detects the most enthesitis. Weber et al investigated the involvement of individual entheses of the anterior chest wall and found no association between clinical examination and WB-MRI findings (Weber, 2012). This was affirmed by Song and colleagues, who found no significant correlations between an MRI enthesitis score and clinical parameters of disease activity (Song et al., 2011a). The percentage agreement between WB-MRI and clinical enthesitis was 68-100% for all entheseal sites in the cohort studied by Poggenborg et al, with the exception of the medial femoral condyle (64%), Achilles tendon (52%) and greater trochanter (49%). Frequently in this study, more enthesitis was detected by clinical examination than by WB-MRI (22% and 17% respectively). Tenderness was most frequently elicited over the first and seventh costochondral joints (in 32%), whereas no enthesitis was found on WB-MRI in the anterior chest wall, supporting the observations of Weber et al (Poggenborg et al., 2014a, Weber, 2012). This may be partially explained by the fact that the first rib is a synchondrosis or a synostosis, with no movement at the anterior joint (Maksymowych and Lambert, 2007). To capture the relevant joints, along with varying types of motion, selection of the second and seventh anterior joints may have produced better correlation.

An opposing relationship was found in the cohort studied by Weckbach and colleagues, who reported MRI enthesitis at more locations than at clinical examination in 80% of patients with PsA. However, clinically they only assessed those entheses included in the MASES index, and their WB-MRI scored more entheseal sites which may account for the discrepancy (Weckbach et al., 2011).

1.6.2.8 MRI in the Distinction Between Psoriatic Enthesopathy and Other Inflammatory Arthritides

There is a small body of evidence to support the use of MRI in the differentiation of peripheral inflammatory arthritis, especially with regard to PsA and RA at several different anatomical locations. Data from MRI in PsA and RA suggest two principle imaging patterns; one where inflammatory changes are primarily based in the synovium ('RA phenotype', where synovitis is the primary process), and another where periarticular entheses are inflamed and associated with intense oedema of the adjacent bone ('SpA phenotype' where enthesitis is the primary process and synovitis occurs a secondary event) (Jevtic et al., 1995). Looking beyond the enthesis is therefore necessary for differentiation of PsA from other inflammatory arthritides.

The combination of MRI findings of enthesitis, multifocal bone marrow oedema, periostitis and extracapsular enhancement, in association with synovitis and tenosynovitis in the hands, is almost diagnostic of PsA (Tan et al., 2006a, Spira, 2011, Narvaez et al., 2012). Several reports have demonstrated extracapsular inflammation in PsA, in contrast to RA with active synovitis and pannus formation where inflammatory changes were always localised within the joint capsule (Jevtic et al., 1995, Schoelnast, 2006, Marzo-Ortega et al., 2009, Giovagnoni, 1995, Savnik et al., 2001). This phenomenon was first described by Jevtic and colleagues, however it was not uniform across their series of 16 patients with PsA, with half having only intra-capsular disease and no extracapsular inflammation. This could be explained by the proposal that PsA is a heterogeneous condition where some patients have a predominantly synovial disease (like RA), whilst others who have an extracapsular focus of their inflammation have an entheseal driven disease. However, the authors do also raise the possibility that they could have included some cases of seronegative RA who also had co-existent psoriasis and fulfilled the Moll and Wright criteria for PsA (Jevtic et al., 1995).

McGonagle et al showed that demonstration of peri-entheseal bone marrow oedema and focal soft tissue oedema could distinguish patients with early SpA from those with early RA in patients with new onset knee effusion. Entheseal inflammation and bone marrow oedema was much more common in the SpA group, which included patients with PsA (McGonagle et al., 1998b). Similarly, Emad and colleagues found that enthesitis was a common feature on knee MRI in patients with SpA and absent in patients with RA and

undifferentiated arthritis. Enthesitis was most frequently seen in the medial collateral ligament (46.7%) followed by the patellar tendon (33.3%), posterior cruciate ligament (26.7%) and biceps femoris insertion (13.3%) (Emad et al., 2009).

1.6.2.9 MRI Scoring Systems for Enthesitis

Enthesitis is not included in the main MRI scoring system designed for use in peripheral PsA (the OMERACT Psoriatic Arthritis Magnetic Resonance Imaging Scoring System, PsAMRIS) (Ostergaard et al., 2009) and no other validated scoring systems are available for enthesitis.

In terms of assessment of change, only one measure, the Leeds Scoring System, has been developed to quantify the response specifically in entheseal pathology to therapy in patients with SpA. Marzo-Ortega and colleagues describe a semi-quantitative measure used to score MRI images from ten patients before and after six months of etanercept therapy for inflammatory axial and peripheral SpA in a time blinded order (Marzo-Ortega et al., 2001). Several areas were systematically analysed per joint:

- SI Joint: Lesions were assessed in four quadrants (right upper, left upper, right lower, left lower), each divided into iliac and sacral aspects
- Spine: Lesions were assessed as present in the vertebrae or paraspinal soft tissues
- Peripheral joints: Lesions were assessed in bone and soft tissues

At baseline, the presence or absence of lesions was recorded in addition to the cumulative number of lesions per area scanned. Post-treatment scans were assessed using a semi-quantitative scale:

- - 3 Complete resolution
- - 2 Moderate improvement
- - 1 Mild improvement
- 0 No change
- + 1 Mild deterioration
- + 2 Moderate deterioration
- + 3 Severe deterioration

Although not formally validated, this measure has subsequently been used in other MRI-based studies assessing the response to treatment in patients with SpA (Marzo-Ortega et al., 2005, Bennett et al., 2009). Bennett et al assessed reliability of the Leeds Scoring System in the axial skeleton in patients with AS, who found excellent inter-observer agreement for the identification (100% exact agreement) and grade of lesions in the SI joints (93% exact agreement) with an overall quadratic-weighted kappa of 0.95. In the spine, agreement between different grades of different types of lesions was also

substantial (prevalence-adjusted bias-adjusted kappa scores: Romanus lesions, 0.68; end-plate lesions, 0.90; posterior element lesions, 0.89; spinous process lesions, 0.83; diffuse oedema, 0.90) (Bennett et al., 2009). Reliability has not been tested in enthesopathy.

1.6.2.10 Comparison between Ultrasound and MRI in enthesitis

Several studies have compared the findings of ultrasound and MRI images from the same enthesis in an attempt to determine which modality should be the gold standard for imaging entheseal pathology. Independent studies of the knee and heel have revealed ultrasound to be more sensitive for inflammation at the enthesis and calcifications (Kamel et al., 2003, Kamel et al., 2004). Aydin and colleagues (Aydin et al. 2013b) also found ultrasound to correlate with clinical enthesis, with swollen knee joints exhibiting more hypoechogenicity and thickening at the tendon insertion than non-tender joints. MRI at the same sites showed only increased signal in the surrounding tissues, not the enthesis itself, which was greater at tender sites (Aydin et al. 2013b). Agreement on changes between ultrasound and MRI for individual lesions was very low.

In contrast, in a more recent study of the elbow, perhaps helped by advances in MRI technology, inflammation scores between ultrasound and MRI data from patients with enthesitis and PsA revealed complete agreement in 60% of comparisons (Groves et al., 2017). Both modalities clearly have their role in the assessment of PsA, and given that ultrasound is only amenable to imaging peripheral structures, MRI remains an essential adjunct for the assessment of axial and less accessible peripheral entheses and surrounding tissues.

1.7 Ustekinumab in the Management of Psoriasis and Psoriatic Arthritis

In January 2009, Ustekinumab (CNTO 1275, Stelara®; Janssen Cilag®) was granted marketing authorization by the European Commission for the treatment of moderate to severe chronic plaque psoriasis in adults who failed to respond to, who have a contraindication to or who are intolerant of systemic oral immunosuppressants. This was followed in September 2013 by approval for use in active psoriatic arthritis in adult patients, where the response to previous non-biological DMARD therapy has been inadequate. Unlike all other biologic agents already brought to market, which targeted TNF-α, ustekinumab was the first-in-class anti-interleukin therapy for both psoriasis and PsA, and has set the benchmark for future rational anti-psoriasis drug design.

1.7.1 Pharmacodynamics and Phamacokinetics of Ustekinumab

Ustekinumab is a fully humanised IgG1κ monoclonal antibody that inhibits IL-12 and IL-23 activity by binding with high affinity and specificity to their shared p40 subunit. IL-12 and IL-23 bioactivity is therefore inhibited by preventing their binding to IL-12 receptor β1 (IL-12Rβ1) on the surface of immune cells (Janssen, 2012) .

IL-12 and IL-23 are heterodynamic cytokines secreted by activated antigen presenting cells such as dendritic cells and activated macrophages in psoriatic lesional skin (Yawalkar et al., 2009). Both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of naïve $CD4^+$ T cells into Th1 cells which produce IFN-γ and TNF-α (Murphy and Reiner, 2002), while IL-23 promotes the expansion of Th17 cells and the production of IL-17 and IL-22 (Langrish et al., 2005, Harrington et al., 2005). Abnormal regulation of IL-12 and IL-23 are highly implicated in the pathogenesis of psoriasis and PsA (Di Cesare et al., 2009, Lowes et al., 2008). Psoriasis and PsA have considerable genetic overlap and similar susceptibility loci (Hebert et al., 2012); IL-12β single nucleotide polymorphisms and variations in the IL-23 receptor (IL-23R) are associated with susceptibility to both psoriasis and PsA (Filer et al., 2008).

The pharmacokinetic properties of ustekinumab appear to be similar in patients with psoriasis and PsA in terms of mean values for apparent volume of distribution, clearance and absorption-rate constant (Zhu et al., 2010). The median time to reach the maximum serum concentration is 13.5 days and 7 days, after a single subcutaneous injection of ustekinumab 45mg or 90mg, respectively. Following multiple subcutaneous doses of ustekinumab, steady-state serum concentrations are achieved by week 28 after initial subcutaneous doses at weeks 0 and 4, followed by dosing every 12 weeks thereafter. There is no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every twelve weeks. The apparent volume of distribution for ustekinumab is reported in one psoriasis cohort as 161(+/-65)ml/kg for the 45mg dose and 179(+/-85)ml/kg for the 90mg dose. In terms of metabolism, the metabolic pathway of ustekinumab has not been characterised, but as a human IgG1κ monoclonal antibody, it is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. The mean systemic clearance of ustekinumab in patients with psoriasis following a single intravenous dose ranges from 1.90(+/-0.28) to 2.22(+/-0.63)ml/kg/day. The mean half-life ranges from 14.9(+/-4.6) to 45.6(+/-80.2) days across all studies following intravenous or subcutaneous administration (EMA, 2009).

Patient body mass and levels of anti-drug antibodies to ustekinumab significantly affect the pharmacokinetic properties (Zhu et al., 2010), although the clinical significance of such antibodies has yet to be determined (Hsu and Armstrong, 2013). Median systemic

clearance in patients with a body mass in excess of 100kg is approximately 55% higher compared to patients who weigh less than 100kg. Other variables, such as age, sex, race, smoking and alcohol consumption, disease duration and baseline PASI score show no significant effects on the volume of distribution or clearance values (Zhu et al., 2010, Zhu et al., 2013, EMA, 2009). In patients with PsA, concomitant use of NSAIDs, oral corticosteroids, methotrexate or prior TNF inhibitor use does not affect drug clearance (Janssen, 2012).

In the UK, ustekinumab is supplied in pre-filled syringes. Each vial contains 45mg ustekinumab in 0.5ml of solution. The recommended posology is an initial dose of 45mg administered subcutaneously, followed by 45mg four weeks later, and then every 12 weeks thereafter. In patients with a body weight in excess of 100kg, 90mg (two pre-filled syringes) should be used due to the higher rate of systemic clearance and lower volume of distribution (EMA, 2009).

1.7.2 Ustekinumab in the Management of Psoriasis

1.7.2.1 Phase I and II Clinical Trials in Psoriasis

Reductions in lesional gene expression of IL-12p40, IL-23p19 and other inflammatory cytokines were observed as early as two weeks post treatment in the initial phase I studies, suggesting ustekinumab may have therapeutic potential in psoriasis (Gottlieb et al., 2007, Kauffman et al., 2004, Toichi et al., 2006). The drug was well tolerated and appeared to have low immunogenic potential. In some patients, a single intravenous or subcutaneous dose resulted in a pronounced clinical response that was sustained for 16–24 weeks (Gottlieb et al., 2007, Kauffman et al., 2004, Toichi et al., 2006). These observations were followed by an initial phase II double-blind, placebo-controlled trial to assess dose response. 320 patients were randomised to one of five groups: placebo, one 45mg dose, one 90mg dose, four weekly 45mg doses or four weekly 90mg doses. Patients assigned to received ustekinumab received one additional dose at week 16 if their PGA was greater than three. Patients assigned to placebo crossed over at week 20 to receive one 90mg dose of ustekinumab. The primary endpoint (PASI 75 response at week 12) was reached in all four active treatment groups (45 mg once only, 51.5%; 90mg once only, 59.4%; four weekly 45 mg doses, 67.2%; four weekly 90 mg doses, 81.3%) and reached statistical significance when compared to placebo (1.6%, $p<0.001$ for each comparison). Clinical responses were maintained out to week 24 before deterioration and were supported by substantial improvements in the Dermatology Life Quality Index (DLQI). Serious adverse events were not statistically higher in any group (Krueger et al., 2007).

1.7.2.2 Phase III Clinical Trials in Psoriasis

The safety and efficacy of subcutaneous ustekinumab were initially evaluated in three large randomised, controlled trials involving 2899 adult patients with moderate to severe psoriasis (defined as PASI >12, PGA ≥3 or BSA >10% BSA) of at least six months' duration and who were eligible for treatment with a systemic immunosuppressant or phototherapy. Run in parallel, both PHOENIX I (ClinicalTrials.gov #NCT00267969) (Leonardi et al., 2008) and PHOENIX II (ClinicalTrials.gov #NCT00307437) (Papp et al., 2008) were randomized, double-blind, placebo-controlled, multi-center trials with similar objectives, methods and outcomes (primary endpoint: PASI 75 at week 12). The third trial, ACCEPT (ClinicalTrials.gov #NCT00454584), shared the same primary endpoint but differed in that the efficacy of ustekinumab was compared to etanercept rather than placebo (Griffiths et al., 2010). The study design and primary outcomes for these trials are described in Table 1.15.

Trial	Study Design	Comparator	(n=)	Duration	Randomisation and Dosing	Primary endpoint	% achieving primary endpoint		
							45mg	90mg	Comparator
PHOENIX I Leonardi et al, 2008	Randomised, double-blind, placebo-controlled, phase III trial	Placebo	766	76 weeks	1:1:1 randomisation to UST 45mg, UST 90mg or placebo, at week 0, 4 then every 12 weeks thereafter. Crossover at week 12 for placebo arm with loading at week 12 and 16. 12 weekly thereafter. Re-randomisation at week 40.	PASI 75 at week 12	67.1	66.4	3.1 (placebo)
PHOENIX II Papp et al, 2008	Randomised, double-blind, placebo-controlled, phase III trial	Placebo	1230	52 weeks	1:1:1 randomisation to UST 45mg, UST 90mg or placebo, at weeks 0 and 4. 12 weekly thereafter for UST arms. Crossover at week 12 for placebo arm with loading at week 12 and 16. 12 weekly thereafter. Re-randomisation at week 28.	PASI 75 at week 12	66.7	75.7	3.7 (placebo)
ACCEPT Griffiths et al, 2010	Randomised, blinded, active comparator, phase III trial	Etanercept	903	64 weeks	3:3:5 randomisation to UST 45mg, UST 90mg or ETN 50mg. UST given at weeks 0 and 4. If PGA ≥2 at week 12, further dose given at week 16. ETN given BiW for 12 weeks. If PGA ≥2, UST 90mg given at weeks 16 and 20.	PASI 75 at week 12	67.5	73.8	56.8 (ETN)

Table 1.15. Three initial phase III trials of ustekinumab in moderate-to-severe psoriasis. (UST: ustekinumab, ETN: Etanercept, BiW: Bi-weekly)

53% of patients recruited into PHOENIX I were either non-responsive to, intolerant of, or had a contraindication to other systemic therapy. Randomisation was stratified by study site, weight (≤90mg or ≥90mg) and the number of systemic therapies to which the patient had had an inadequate response, intolerance or contraindication (<3 or ≥3). Primary endpoint data can be found in Table 1.15. Re-randomisation occurred at week 40 and was again stratified according to study site and weight:

- Participants that had achieved a PASI 75 response at weeks 28 and 40 were maintained on the same dose or given placebo until loss of response.
- Participants that had achieved a partial response (defined as PASI 50-74) had their dosing interval shortened from 12 to 8 weeks.
- Participants randomised to initially receive placebo crossed over to receive ustekinumab (45mg or 90mg) at week 12 and 16, followed by 12 weekly administration thereafter.

This study design allowed not only comparison of ustekinumab with placebo, but also assessment of long-term efficacy, duration of therapeutic response after withdrawal and the effect of dose escalation in partial responders.

Significant improvement in psoriasis severity was found at both active treatment arms at week 12 compared to placebo ($p<0.0001$). Improvement was rapid, regardless of dose, with many achieving PASI 50 by week 2. Efficacy was maximal at week 24 for both dosing regimens (76.1% and 85.0% PASI 75 for 45mg and 90mg respectively) and similar results were found in those initially treated with placebo after the same period of active therapy.

After the second randomisation at week 40, preservation of PASI 75 response was significantly better at week 76 in those continuing on ustekinumab (84.0%) compared to those who were switched to placebo (19.0%). In the latter group, PASI scores began to deteriorate by week 44 (16 weeks after their last injection), and accelerated after week 52, demonstrating that continuous therapy is required for sustained suppression of psoriatic skin inflammation. In total, 195 participants needed to restart treatment as their PASI improvement from baseline fell below 50%. 85.6% of these patients regained a PASI 75 response within 12 weeks of reinstating ustekinumab (Leonardi et al., 2008).

Fingernail psoriasis was assessed in PHOENIX I using the Nail Psoriasis Severity Index (NAPSI) on a target fingernail, in addition to a nail PGA and assessment of the mean number of fingernails involved (Rich et al., 2014). Of the 766 patients randomised to participate, 545 (71.1%) had nail psoriasis at baseline. NAPSI scores were significantly improved from baseline as early as week 12 for both doses of ustekinumab compared with placebo (45mg, $p<0.001$ and 90mg, $p=0.001$). By week 24, the percentage improvement from baseline NAPSI score was 46.5% (95% CI 39.5-53.4) and 48.7% (95% CI 42.0-55.3) for ustekinumab 45mg and 90mg, respectively. Among patients

receiving placebo who crossed over to ustekinumab at week 12, by week 24, percentage improvements in NAPSI score were comparable with week 12 results for patients randomised to receive the active drug from baseline. Improvements in the less sensitive nail PGA scores were generally not observed in the nail psoriasis cohort at week 12; however, significant improvements were noted by week 24, with over 75% of participants with a PGA ≥3 achieving improvement by at least one point (Rich et al., 2014).

In an extension arm to the PHOENIX I trial, patients were subsequently followed to week 244 (5 years) in order to assess longer-term efficacy and safety (Kimball et al., 2013, Papp et al., 2013). 517/753 (68.7%) participants from the initial trial (who had received at least one dose of ustekinumab) were evaluated. Clinical responses were generally maintained through to week 244 (PASI 75: 63.4% and 72.0%; PASI 90: 39.7% and 49.0%; PASI 100: 21.6% and 26.4% for 45mg and 90mg respectively) (Kimball et al., 2013). Analysing 8998 patient years of follow up, adverse event rates were comparable between the two doses and no increasing trend was seen over time. Rates of overall mortality and malignancies were comparable with the general population in the United States (Papp et al., 2013). Per 100 patient years, adverse events were as follows (45mg, 90mg respectively) (Kimball et al., 2013):

- All adverse events: 220.92, 209.05
- All serious adverse events: 5.26, 5.43
- Serious infections: 0.84, 1.21
- Non-melanoma skin malignancies: 0.65, 0.26
- Other NMSC malignancies: 0.59, 0.38
- Major Cardiovascular Adverse Events (MACE): 0.52, 0.13

In PHOENIX II, 61% of patients were either non-responsive to, intolerant of, or had a contraindication to other systemic therapy. Overall, a significant improvement in PASI score was achieved by week 12 for both doses of ustekinumab (Table 1.15), although maximal efficacy was not reached until week 20 (45mg, 74.9% and 90mg, 83.5%), with similar outcomes seen in the placebo group after cross over to active therapy. The median response by the end of the study (week 52) was PASI 95 for those receiving 45mg, and PASI 96 for those receiving 90mg ustekinumab.

Secondary randomisation occurred earlier than in PHOENIX I, at week 28. Patients were categorised as responders (PASI 75 achieved), partial responders (PASI 50-74) or non-responders (PASI <50). Patients who achieved PASI 75 by week 28 continued on the same dose 12-weekly, and maintained their improvement through to week 52. Non-responders discontinued therapy and partial responders were randomised to either continue their current regimen or reduce their dosing regimen to 8-weekly. Partial responders accounted for 22.7% of patients receiving the 45mg dose and 15.8% of those receiving 90mg from baseline. Compared to responders, patients in this group were of greater body mass, had more severe PGA scores, a longer duration of psoriasis, a

greater incidence of PsA, a higher failure rate with previous systemic immunosuppressant therapies and lower serum drug levels at week 28. Alteration of the dosing regimen in this group permitted analysis of the number of visits between weeks 28 and 52 where PASI 75 response was achieved for the two different dosing schedules. For those receiving 90mg, a reduction in the dosing interval did equate to a greater number of visits where a PASI 75 was achieved, but this was not the case for those receiving 45mg every 8 weeks (Papp et al., 2008).

In terms of safety, the PHOENIX I and II trials reported similar outcomes during the placebo-controlled phase. Adverse events occurred in 54.5% and 50.5% of patients receiving ustekinumab and 48.2% and 49.8% receiving placebo in PHOENIX I and II respectively. Serious adverse events occurred with a low frequency across groups in both studies (1.2% ustekinumab vs. 0.8% placebo in PHOENIX I; 1.6% ustekinumab vs. 2.0% placebo in PHOENIX II). Anti-drug antibodies were mostly of low titre and were found in 5.1% of patients by week 72 in PHOENIX I and 5.4% of patients by week 52 in PHOENIX II (Papp et al., 2008, Leonardi et al., 2008).

The ACCEPT trial differed from the PHOENIX trials in that efficacy was compared with the active biological therapy etanercept rather than placebo (Griffiths et al., 2010). Randomisation was again stratified according to study site and patient weight (<90mg or ≥90mg). Patients in the etanercept group who did not respond (classified as moderate, marked or severe on the PGA) by week 12 (primary endpoint) were given a 90mg dose of ustekinumab at weeks 16 and 20, and those who did not respond in the ustekinumab arm were given one further additional dose of ustekinumab at week 16. No further doses were given to responders (classified as mild, minimal or clear) after week 12. Primary endpoint data can be found in Table 1.15. The time to improvement was more rapid in the ustekinumab treated group and a significantly higher number of patients achieved PASI 90 (36.4% ustekinumab 45mg; 44.7% ustekinumab 90mg; 23.1% etanercept) ($p<0.001$).

Among the non-responders to etanercept, 48.9% achieved PASI 75 and 23.4% achieved PASI 90 12 weeks after cross over to ustekinumab. For those who were graded as responders to any therapy at week 12 and therefore had therapy withdrawn, the median time to recurrence was 14.4 weeks, 18.1 weeks and 7.3 weeks for ustekinumab 45mg, ustekinumab 90mg and etanercept, respectively. Of the 633 patients who were retreated after re-emergence of moderate to severe psoriasis, 534 (84.4%) were classed as having mild, minimal or no psoriasis within 12 weeks.

In terms of safety, adverse events occurred with similar frequency across all three treatment arms. At least one adverse event occurred in 66.0% of patients receiving ustekinumab 45mg, 69.2% receiving ustekinumab 90mg and 70.0% receiving etanercept:

- Most adverse events were minor, with only four patients in each group experiencing a serious adverse event.
- Discontinuation of therapy was necessary in similar proportions (ranging from 1.2-2.3%).
- Injection site reactions were noticeably more frequent in patients treated with etanercept (24.8%) compared to ustekinumab (4.3%, 45mg; 3.7%, 90mg), although the higher number of injections necessitated by the dosing schedule for etanercept must be taken into account (twice weekly compared to week 0, 4 and every 12 weeks thereafter for ustekinumab).
- Infections occurred with a similar frequency in all three treatment arms:
    - 30.6% ustekinumab 45mg
    - 29.7% ustekinumab 90mg
    - 29.1% etanercept
- NMSCs only occurred in patients treated with ustekinumab but with low frequency (3 patients by week 12 and a further 9 by week 64) (Griffiths et al., 2010).

Several other small phase III clinical trials have assessed the efficacy and safety of ustekinumab in non-western populations and have reported similar clinical outcomes to the PHOENIX and ACCEPT trials. In the 36-week, multicentre, double-blind PEARL trial, 121 Taiwanese and Korean patients with moderate-to-severe psoriasis were randomised to receive ustekinumab 45mg (week 0, 4 and 16) or placebo (week 0 and 4) followed by ustekinumab 45mg (week 12 and 16). PASI 75 was achieved by 67.2% in the ustekinumab treated group and 5.0% in the placebo arm at the primary end point of 12 weeks ($p<0.001$). Efficacy was maintained by week 28 in the group treated with ustekinumab from baseline. Adverse events were similar in both groups, with no deaths, malignancies or MACE reported (Tsai et al., 2011).

An identical study design was used in a 72-week, phase II/III clinical trial of 158 Japanese patients, but with the addition of third arm (ustekinumab 90mg). At the primary endpoint (week 12), 59.4% and 67.7% of patients treated with ustekinumab 45mg and 90mg respectively achieved PASI 75, compared with 6.5% of patients receiving placebo ($p<0.0001$). Rates of infections were comparable between groups (20.3%, ustekinumab 45mg; 24.2%, ustekinumab 90mg; and 18.8% placebo). Only single, isolated cases of serious infections and non-cutaneous malignancies were reported (both in the ustekinumab 90mg group), but no deaths, NMSC or MACE (Igarashi et al., 2012).

1.7.2.3 Factors Influencing Clinical Response to Ustekinumab in Psoriasis

HLA-Cw06 is widely accepted as the psoriasis susceptibility gene with the greatest effect. Latterly, observations have now suggested that this genetic polymorphism may

also serve as a pharmacogenetic marker to predict clinical response to immunomodulatory agents including ustekinumab (Warren and Griffiths, 2005). Ustekinumab efficacy has been shown to be superior in HLA-Cw06 patients (PASI 75 response at week 12: 96.4% compared to 65.2% in HLA-Cw06 negative patients) by Talamonti and colleagues. The time to response was also faster, with 89.3% of HLA-Cw06 positive patients achieving PASI 50 at week 4 (after a single dose) compared to 60.9% of HAL-Cw06 negative patients. No significant association was found between clinical response and other psoriatic genetic markers studied (TNFAIP3rs610604 polymorphism and LCE3B/3C gene deletion) (Talamonti et al., 2013). Genetic susceptibility can vary amongst different racial groups, however this finding has been replicated in Chinese patients with psoriasis (Chiu et al., 2014). A more modest improvement in PASI 75 repsonse (17.9%) between those who are HLA-Cw06 positive and negative was found in a larger retrospective analysis at week 12, with smaller differences still noted at later timepoints for PASI 90 (11.8% at week 24) and PASI 100 (10.2% at week 28). This raises the possibility that the findings by Talamonti may have been an overestimation of the true effect (Li et al., 2016).

Aside from genetic factors, obesity has been recognised as an important factor related to both the incidence and severity of psoriasis (Naldi et al., 2005). Obesity can induce overproduction of multiple proinflammatory cytokines in adipose tissue, including TNF-α, IL-6 and IL-8, all of which are implemented in psoriasis pathogenesis (Hamminga et al., 2006). In patients enrolled into the PHOENIX I and II trials, those with a body mass greater than 100mg had a reduced efficacy to ustekinumab. The proportion of patients with a body mass less than or equal to 100kg achieving PASI 75 was 76.9% compared to 54.6% in those weighing more than 100kg at the 45mg dose, and 80.8% (≤100kg) compared to 74.2% (>100kg) at the 90mg dose. Serum drug concentrations were also affected by weight (Lebwohl et al., 2010b). Together these phase III findings provided adequate rationale for the higher dose to be subsequently licensed for patients whose weight exceeds 100kg.

1.7.2.4 Quality of Life Studies in Psoriasis

Quality of life indices were investigated in the PHOENIX I and II trials (Lebwohl et al., 2010a, Langley et al., 2010) and a phase II/III trial by the Japanese Ustekinumab Study Group (Nakagawa et al., 2012), but not recorded in the ACCEPT trial (Griffiths et al., 2010).

In PHOENIX I, in excess of 97% of participants had a score of one or more on the DLQI at baseline, and the average score was greater than 10, indicating a significant impact on patients' quality of life. A significantly greater proportion of patients treated with ustekinumab achieved normalisation of the DLQI (≤1) compared to placebo (53.2%

ustekinumab 45mg and 52.4% ustekinumab 90mg vs. 6.0% placebo; p<0.001 for all comparisons) by week 12. Similarly, impressive improvements were recorded in the Medical Outcomes Study Short Form 36 (SF-36) survey in terms of the mental (25.5% ustekinumab 45mg, 31.3% ustekinumab 90mg, 14.8% placebo) and physical (23.1% ustekinumab 45mg, 33.7% ustekinumab 90mg, 15.6% placebo) component scores, and like the DLQI responses, these improvements were maintained in ustekinumab-treated patients at week 52. Greatest normalisation was recorded in the social functioning and bodily pain domains (Lebwohl et al., 2010a).

In PHOENIX II, the Hospital Anxiety and Depression Score (HADS) replaced the SF-36. Again, the high psychological impact of psoriasis was evident at baseline with 40.3% (45mg dose) and 26.7% (90mg dose) of patients receiving ustekinumab therapy reporting symptoms of anxiety and depression. 54.6% of patients scored ten or more on the DLQI. By week 12, the absolute mean reduction in DLQI was by 9.3 (+/- 7.1) points in the group dosed with ustekinumab 45mg, and by 10.0 (+/-6.7) points in the 90mg group compared to a reduction of only 0.5 (+/-5.7) points in the placebo arm. The proportion of patients with baseline symptoms of mild to severe anxiety decreased in both the ustekinumab 45mg and ustekinumab 90mg groups, from 38.2% to 25.7% and 41.0% to 27.1% respectively (both p<0.01 vs. placebo). This represented a combined relative reduction of 34% from baseline by week 12, compared to a 1.4% increase in the placebo group. More impressive results were found in patients with mild to severe symptoms of depression at baseline, with a relative reduction of 55% from baseline in ustekinumab-treated patients compared to an increase of 10% in the placebo arm (Langley et al., 2010).

In addition to the DLQI and SF-36, the Psoriasis Disability Index (PDI) was assessed in a cohort of 156 Japanese patients with psoriasis, treated with either ustekinumab or placebo (Nakagawa et al., 2012). The PDI examines the effect of psoriasis on five different aspects of patients' quality of life: (i) daily activities; (ii) performance at work or school; (iii) personal relationships; (iv) leisure; and (v) treatment. A maximum score of 45 indicates the greatest impairment. (Finlay and Kelly, 1987). Significant improvements in PDI scores from baseline to week 12 were observed in patients dosed with ustekinumab (45mg, 8.6+/-9.6; 90mg, 12.0+/-11.8) compared with placebo (-0.1+/-4.2) (p<0.0001 for both comparisons). Improvements in PDI scores were generally maintained through to week 64 in ustekinumab-treated patients, and those in the placebo arm who crossed over to receive ustekinumab at week 12 achieved improvements similar to those observed in the first 12 weeks in patients randomised to receive ustekinumab from baseline (Nakagawa et al., 2012).

Looking more closely at the specific impairments in quality of life in patients with psoriasis, sexual difficulties appeared prevalent in patients recruited to the PHOENIX I and II trials. Impaired sexual function was recorded if any patient scored 'very much' or

'a lot' for question 9 of the DLQI. 27.1% of women and 20.8% of men reported sexual impairment at baseline, and this was significantly associated with psoriasis severity. Effective treatment with ustekinumab (at either dose) reduced the proportion of patients reporting sexual difficulties from 22.6% to 2.7% within 12 weeks, compared to no change in the cohort dosed with placebo ($p<0.001$ for all comparisons). A greater mean improvement in PASI score related to a greater reduction in sexual difficulties caused by psoriasis (Guenther et al., 2011).

1.7.3 Ustekinumab in the Management of Psoriatic Arthritis and Enthesitis

In 2013, marketing approval for ustekinumab was extended by the European Commission to include the treatment of PsA, in adults who have had an inadequate response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapies. In 2015, approval was granted by NICE for prescription in PsA in England and Wales, when treatment with TNF inhibitors are contraindicated or have failed to achieve an adequate response using the PsARC at 24 weeks. Identical to the license for chronic plaque psoriasis, ustekinumab was the first non-TNF-inhibitor to be granted marketing authority for use in PsA, finally providing an alternative treatment approach in those whom TNF inhibition had failed. In recognition of this position within the rheumatologists therapeutic armamentarium, the manufacturers undertook two similar phase III, multi-centre, double-blind, placebo-controlled trials in PsA (McInnes et al., 2013, Ritchlin et al., 2014), with the second (PSUMMIT-2) addressing the issue of previous TNF-inhibitor exposure (Ritchlin et al., 2014).

1.7.3.1 Phase I and II Clinical Trials in Psoriatic Arthritis

The first phase II, double-blind, randomised, placebo-controlled and crossover study of ustekinumab in PsA was published in 2009 (Gottlieb et al., 2009). 146 patients with active PsA (defined as ≥3 swollen joints and either an elevated C-reactive protein (CRP) or morning stiffness lasting ≥45 minutes) and current psoriasis were recruited from the dermatology clinic. Random allocation took place into one of three groups:

- Subcutaneous ustekinumab (63mg) at week 0, 1, 2 and 3 followed by placebo at weeks 12 and 16 (n=76).
- Placebo at weeks 0, 1, 2 and 3, followed by ustekinumab at weeks 12 and 16 (n=70).

The primary endpoint was the percentage of patients achieving a 20% or greater improvement in the American College of Rheumatology (ACR20) criteria at week 12 (Figure 1.8). At week 12, 42.1% of patients treated with ustekinumab from baseline

achieved an ACR20 response compared to 14.3% of the placebo-dosed group. By week 36, despite no further doses of ustekinumab for 33 weeks, three quarters of the former group retained their ACR20 response. In the group initially treated with placebo followed by ustekinumab at weeks 12 and 16, 45.0% achieved ACR20 by week 24. Median percentage improvement in morning stiffness at week 12 was 50% in the ustekinumab-treated cohort compared to no change (0%) in the placebo group (Gottlieb et al., 2009).

As patients in this study were recruited from dermatology, not rheumatology clinics, the population was not comparable with those of phase II and III trials of other TNF-inhibitors (adalimumab, etanercept and infliximab) in PsA. The baseline characteristics of these patients differed from those seen in trials conducted through rheumatology clinics largely in terms of concomitant medications. The number of patients in this study prescribed methotrexate and NSAIDs was low (20% and 50% respectively) compared to those recruited to trials involving TNF-inhibitors who were nearly all taking concomitant NSAIDs, oral corticosteroids and/or methotrexate. Safety outcomes were not reported. However, despite these considerations, this study did show that PsA patients appear to respond well to ustekinumab, supporting the progression to larger scale, phase III trials to investigate the efficacy and safety of ustekinumab in active PsA.

1.7.3.2 Phase III Clinical Trials in Psoriatic Arthritis

The 52-week PSUMMIT-1 trial (Clinicaltrials.gov#NCT01009086) included 615 TNF-inhibitor naïve patients with active PsA (defined by ≥5 tender and ≥5 swollen joints and CRP ≥3.0mg/l) for six or more months (McInnes et al., 2013). Participants were randomised 1:1:1 to receive 45mg ustekinumab, 90mg ustekinumab or placebo at week 0, 4 and every 12 weeks thereafter. Stratification between groups was based on weight (≤100 or >100kg) and baseline methotrexate use (yes or no). At week 16, patients with less than 5% improvement from baseline in both tender and swollen joint counts could escalate (placebo to 45mg ustekinumab, 45mg ustekinumab to 90mg ustekinumab, no escalation if already taking 90mg ustekinumab). Patients taking placebo who did not escape at week 16 crossed over to receive 45mg ustekinumab at week 24 and week 28, and 12-weekly thereafter. Concomitant drug use had to remain stable until week 52. The primary outcome measure was the percentage achieving ACR20 response at week 24.

Significant differences between the groups, in favour of ustekinumab, were seen (22.8%, 42.4% and 49.5% for placebo, ustekinumab 45mg and ustekinumab 90mg, respectively) (Table 1.16). Concomitant use of methotrexate appeared not to impact on efficacy (ACR20 rate with methotrexate 44.5%, without methotrexate 47.5%). Maximal efficacy was achieved at week 28.

Of the patients with dactylitis at baseline, significantly lower proportions in the ustekinumab groups (45mg ustekinumab, 56.6%; 90mg ustekinumab, 55.8%) compared

to placebo (76.1%) had digits with dactylitis at week 24 (p=0.0013, p=0.0050 and p=0.0038 respectively). Of patients with spondylitis at baseline, a significantly higher proportion in the ustekinumab groups achieved responses in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) than in the placebo group.

In terms of safety, at week 16, the proportions of patients experiencing adverse events were similar in the ustekinumab and placebo groups (41.8% vs. 42.0%). Nasopharyngitis (4.6%), upper respiratory tract infections (3.4%) and headache (3.4%) were the most common adverse events in ustekinumab treated patients. The proportion of patients and type of adverse events did not differ in relation to concomitant methotrexate therapy. No opportunistic infections (including tuberculosis), death or malignancies were reported by the end of the trial (week 52), but three MACEs were reported in the ustekinumab groups in the first 30 weeks of treatment (McInnes et al., 2013).

Reduction in the functional impact of PsA was also demonstrated in PSUMMIT-1. Improvements in HAQ-DI scores were significantly greater in patients given ustekinumab (median change -0.25) compared to those given placebo (no change, 0.00; p<0.001 for all comparisons). An improvement of 0.3 or more in HAQ-DI score is deemed clinically meaningful (Mease, 2004), and this was achieved by 47.7% and 28.2% of ustekinumab-treated and placebo-treated patients respectively (p<0.0001). Significant improvements were also recorded in the summary scores of the SF-36 survey (both physical and mental components) and DLQI at week 24 in the ustekinumab group, with the exception of the mental component of the SF-36 for those treated with the 45mg dose which did not reach statistical significance (McInnes et al., 2013).

A similar study design was employed in the PSUMMIT-2 trial, however, just over half of the 312 adult participants had prior TNF-inhibitor exposure. Of these, the majority had used more than one agent, with 70% having discontinued the drug(s) because of an inadequate response. The same primary endpoint as in PSUMMIT-1 (ACR20 rate at week 24) was achieved, with ustekinumab showing superior efficacy over placebo despite the more challenging population and smaller sample size. 43.7% of ustekinumab 45mg-treated patients, 43.8% of ustekinumab 90mg-treated patients and 20.2% of placebo-treated patients achieved ACR20 at week 24 (p<0.001) (Table 1.16).

	PSUMMIT-1				PSUMMIT-2			
	Week 12	Week 24			Week 24 (all patients)			Week 24*
	ACR20	ACR20	ACR50	ACR70	ACR20	ACR50	ACR70	ACR20
Placebo	21	23	9	2	20	7	3	15
UST 45mg	41	42	25	2	44	18	7	37
UST 90mg	41	50	28	14	44	23	9	35

Table 1.16 Percentage primary (ACR 20) and secondary endpoint (ACR 50/70) rates for PSUMMIT-1 and PSUMMIT-2 (*TNF experienced patients only)

As expected, response rates in patients in TNF-inhibitor experienced patients were inferior to TNF-inhibitor naïve patients, but still significantly better than placebo. By week 24, ACR20 rates of 35.6% in ustekinumab treated patients compared to 14.5% for those receiving placebo. Again, outcomes were independent of concomitant methotrexate use, but not weight, with patients weighing over 100kg not responding as well in the ustekinumab 90mg group.

In 127 patients with dactylitis at baseline, a greater improvement was noted in patients receiving ustekinumab 90mg compared to placebo, although this was not statistically significant. By week 52, a 95% median percentage improvement was seen in dactylitis scores in patients treated with ustekinumab. Similarly, BASDAI response rates were numerically, but not statistically, better in ustekinumab-treated than placebo-treated patients at week 24.

By week 16, adverse events were reported in 61.8% of ustekinumab-treated and 54.8% of placebo-treated patients. Serious adverse events occurred in 0.5% and 4.8% of ustekinumab-treated and placebo-treated patients, respectively. By week 60, in patients treated with ustekinumab, serious infections were reported in two patients, two reported malignancies (breast cancer and cutaneous squamous cell carcinoma; both were TNF inhibitor experienced) and three patients experienced MACEs. There were no deaths and no cases of tuberculosis (Ritchlin et al., 2014).

In terms of functional impairment, in PSUMMIT-2, improvements in HAQ-DI scores at week 24 were significantly greater among ustekinumab-treated than placebo-treated patients ($p<0.001$). A clinically meaningful change of 0.3 or more was reported in 34.0% of patients dosed with ustekinumab 45mg, 38.1% dosed with ustekinumab 90mg and 16.3% dosed with placebo ($p<0.01$ and 0.001 respectively). Not surprisingly, changes from baseline in HAQ-DI were lower in TNF-inhibitor experienced patients compared to those who were biologic naïve. Changes in the SF-36 were not significantly different in terms of the mental component, but were for the physical component at week 24, with a change from baseline of 3.3 for all ustekinumab treated patients compared to 0.0 for those receiving placebo ($p<0.01$). The mean decrease in DLQI was 6 points for those treated with ustekinumab, resulting in 35.6% (45mg dose) and 42.6% (90mg dose) achieving a score of 0 or 1 at week 24 (compared to 11.1% of placebo-treated patients; $p<0.001$) (Ritchlin et al., 2014).

To date, the only other available safety data for ustekinumab in PsA is found in meeting abstracts. Pooled analyses from trials of psoriasis and PsA were reported at the ACR meeting in 2013 (McInnes, 2013) and 2014 (Kalb, 2014). No worrying safety signals were raised for serious infections or malignancies. However, MACEs appeared to occur with greater frequency in those treated with ustekinumab, although confidence intervals did overlap with the placebo rates (rates of events per 100 patient years of exposure (95% CI): placebo 0 (0-1.69), ustekinumab 1.23 (1.40-2.87)). In a separate pooled analysis

from 2014, data from a two year period contradicts this increase, with no greater MACEs occurring at either dose (45mg or 90mg) of ustekinumab (Kavanaugh, 2014).

Radiographic progression was subsequently reviewed in an integrated data analysis of PSUMMIT-1 and PSUMMIT-2 patients, in order to provide an adequate sample size (n=927). Using the PsA-modified Sharp van der Heijde (mSvdH) score (maximum score 528), ustekinumab-treated patients (regardless of dose) showed less radiographic progression at week 24 compared to placebo-treated patients ($p<0.02$), and this was maintained out to week 52. However, the mean progression rates (change in mSvdH scores) were low across the whole cohort (0.4 for both ustekinumab groups, 1.0 for placebo) and the percentage of patients with a radiographic change score that was less than the smallest detectable difference was high (91.7%, ustekinumab 45mg; 91.9%, ustekinumab 90mg; 83.8% placebo). No data was available on new bone formation, a key radiographic change in PsA, as this is not included in the mSvdH score. A further limitation of the pooled analyses was the high rate of missing data (approximately 10% overall), especially in the group of TNF-inhibitor experienced patients in the placebo arm (Kavanaugh et al., 2014b).

1.7.3.3 Ustekinumab in Psoriatic Enthesitis

The majority of data for ustekinumab in the treatment of enthesitis is in the form of secondary endpoint analyses from clinical trials involving patients with established and active PsA. In the PSUMMIT-1 trial, 69.3% of ustekinumab 45mg-treated, 75.5% of ustekinumab 90mg-treated and 70.4% of placebo-treated patients had enthesitis at baseline. Entheseal tenderness was assessed at 15 body sites as part of the PsA-modified MASES index, with mean baseline scores of 4 (placebo and ustekinumab 45mg groups) or 5 (ustekinumab 90mg group) sites involved. When compared to placebo at week 24, patients in the ustekinumab-treated groups had significantly greater improvements in enthesitis scores (45mg group $p=0.0019$, 90mg $p<0.0001$) (McInnes et al., 2013). Further improvements were seen by week 52 and week 100 (McInnes et al., 2013, Kavanaugh, 2014) (Table 1.17).

	Week 24 (% change)			Week 52 (% change)			Week 100 (% change)		
	Placebo	UST 45mg	UST 90mg	Placebo to UST 45mg	UST 45mg	UST 90mg	Placebo to UST 45mg	UST 45mg	UST 90mg
PSUMMIT-1	0.00	-42.9	-50.0	-87.5	-79.2	-74.2	-87.1	-100	-100
PSUMMIT-2	0.00	-33.3	-48.3	-33.3	-36.7	-60.0	N/A	N/A	N/A

Table 1.17. Median percentage change from baseline in enthesitis score in PSUMMIT-1 and PSUMMIT-2 clinical trials.

Similar proportions of patients had enthesitis at baseline in PSUMMIT-2 (70.2%, 69.9% and 72.4% for placebo, ustekinumab 45mg and ustekinumab 90mg, respectively). Again, the PsA-modified MASES was used to assess entheseal tenderness at 15 sites, with baseline scores of 4 (placebo), 6 (ustekinumab 45mg) and 5 (ustekinumab 90mg) in the different groups. Among the 221 patients with enthesitis, significantly lower proportions of ustekinumab-dosed, than placebo-dosed patients had residual enthesitis at week 24 (all $p<0.05$) (Table 1.17). Patients treated with ustekinumab 90mg exhibited significantly greater reductions in their MASES at week 24 versus placebo ($p<0.01$). By week 52, the median percent reduction in enthesitis scores amongst ustekinumab treated patients was 50.0%.

The ECLIPSA study is the only study to investigate enthesitis as a primary endpoint, in patients with active PsA. This prospective, randomised-controlled, open-label study of 47 patients compared the efficacy of treatment with ustekinumab (n=23) and TNF inhibitors (n=24) in completely clearing enthesitis at six months, as measured by the SPARCC index. After six months, 17 out of 24 patients (70.8%) receiving ustekinumab, and 10 out of 26 (38.4%) receiving a TNF inhibitor, achieved a SPARCC score of 0. Logistic regression predicting enthesitis-free state of disease was significantly related to study treatment only, with patients receiving ustekinumab being more likely to show no signs of enthesitis at month six (OR=0.037; p=0.005) (Araujo et al., 2017).

While limited, these data collectively support a role for the use of IL-23/IL-17 pathway inhibitors in patients with entheseal driven-disease, although further studies are needed with enthesitis as the primary endpoint, ideally with imaging as an outcome to support clinical assessment. There are no reported clinical trials or observations of ustekinumab efficacy in patients with subclinical enthesitis or very early psoriatic arthritis, although these data provide the basis for the hypothesis that early, asymptomatic entheseal disease may respond to ustekinumab, and may ultimately be able to limit the progression to symptomatic PsA.

Thesis Hypotheses and Aims

Primary Care Cohort

The detection of psoriatic arthritis among patients with psoriasis in primary care can be improved through the provision of educational material detailing the link between arthritis and skin disease, and through the use of a novel psoriatic arthritis screening questionnaire based on the most discriminate questions of existing tools.

By inviting patients with psoriasis to attend for an assessment with a rheumatologist and dermatologist, this work aims to:

i. Evaluate the effect of educational material on attendance rates for screening in primary care.
ii. Prospectively test the performance of a novel psoriatic arthritis screening questionnaire in the primary care setting, compared against the current standard (Psoriasis Epidemiology Screening Tool; PEST).

Secondary Care Cohort

A significant proportion of patients with moderate-to-severe psoriasis have subclinical entheseal disease (compared with the general population), the inflammatory aspect of which can be attenuated through the use of skin-directed therapy with an IL-12/IL-23 inhibitor. Subsequently, demographic and clinical parameters can be used to predict response.

By studying treatment-naïve individuals presenting to secondary care for the management of moderate-to-severe psoriasis, this work aims to:

i. Evaluate the role of grey scale and power Doppler ultrasound in the assessment of peripheral subclinical enthesopathy amongst asymptomatic patients and develop a comprehensive scoring system incorporating the entire synovio-entheseal complex to quantify the burden of disease.
ii. Explore the utility of whole body magnetic resonance imaging in quantifying subclinical enthesopathy in both the peripheral and axial skeleton.
iii. Establish whether skin-directed therapy with ustekinumab impacts on the presence and severity of inflammatory and chronic damage abnormalities detected by both imaging modalities, and whether any demographic or clinical parameters influence therapeutic response within the musculoskeletal system.

Summary of Thesis Chapters

Chapter 1 aims to provide a comprehensive review of the literature relating to the presentation and pathogenesis of enthesitis and psoriatic disease, and appraise the available data regarding the detection and management of subclinical enthesopathy.

Chapter 2 aims to determine the rates of undiagnosed PsA in a diverse primary care population and to test whether educational material explaining the risks of PsA improves the attendance of patients with psoriasis for screening. In addition, the two CONTEST questionnaires are prospectively tested alongside the PEST in this primary care cohort.

Chapter 3 aims to assess the prevalence of subclinical enthesitis in new, asymptomatic patients presenting to the dermatology clinic for treatment of moderate-to-severe psoriasis, and to establish the pattern of inflammatory and chronic damage abnormalities to determine the feasibility of an ultrasound screening programme in secondary care.

Chapter 4 aims to provide reference thresholds for entheseal thickness for those tendons where values have not been published, for use in a novel sonographic scoring system based on a consensus definition of enthesopathy. This scoring system is used to further assess the feasibility of using ultrasound for the detection of subtle abnormalities at the synovio-entheseal complex in asymptomatic patients with psoriasis compared to healthy volunteers. Finally, this chapter aims to assess the utility of the PEST questionnaire in a cohort of psoriasis patients with subclinical enthesitis and compares responses with clinical examination and ultrasound findings.

Chapter 5 aims to assess if subclinical ultrasound abnormalities within the synovio-entheseal complex alter in response to therapy with anti-interleukin (IL)-12/IL-23 p40 monoclonal antibody therapy (ustekinumab), assessed at 12, 24 and 52 weeks. It also aims to test the feasibility of a large randomised controlled trial comparing ustekinumab with other treatment modalities for the management of subclinical psoriatic joint disease in patients with psoriasis. Further aims include the analysis of any correlation between clinical entheseal assessments, skin and nail outcomes and demographic details and the change in sonographic subclinical enthesopathy following ustekinumab therapy.

Chapter 6 aims to analyse the utilisation of WBMRI to assess the extent, distribution, severity and type of inflammatory abnormalities and structural changes in both the peripheral and axial skeleton in asymptomatic patients with psoriasis, and compares those findings with a cohort of healthy volunteers.

Chapter 7 aims to investigate the change in active inflammatory lesions and structural abnormalities in the axial and peripheral skeleton seen on WBMRI, following skin directed treatment with ustekinumab.

Chapter 2
Identification of Undiagnosed Psoriatic Arthritis in Patients with Psoriasis in Primary Care

2.1 Introduction

In the UK, an estimated 1.82 million people have psoriasis and have consulted with their General Practitioner (GP) according to the Clinical Practice Research Datalink (CPRD), a large-scale primary care epidemiology database (Springate et al., 2017). Up to 30% will develop psoriatic arthritis (PsA), which can be heterogeneous in its clinical manifestations, including arthritis, enthesitis, dactylitis and axial disease (Christophers et al., 2010, Gelfand et al., 2005, Radtke et al., 2009). The majority of people with PsA have antecedent psoriasis (70%) (Gladman, 1998), but many cases of established PsA remain unidentified for some time despite presenting to primary care for skin directed treatment (Reich et al., 2009). Possible causes of this are patients' lack of understanding of the link between skin and arthritis, the lack of musculoskeletal expertise in primary care and the incorrect assumption that symptoms are attributable to mechanical and degenerate-related pains and arthritis. It follows that a simple method of screening for PsA in people with psoriasis would enable earlier treatment, to prevent the development of progressive joint damage and functional limitation which has been shown to occur in the first few years of disease onset (McHugh et al., 2003, Kane et al., 2003, Gladman et al., 1990). This has been acknowledged in the most recent consensus guidelines for psoriasis from both the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN), who recommend annual screening for PsA including those followed up only in primary care (NICE, 2012, SIGN, 2001).

Many patient-reported screening questionnaires for PsA have been developed, but they have not been widely adopted in clinical practice. NICE acknowledge that the optimal screening tool is not yet established, but based on available data, recommend the Psoriasis Epidemiology Screening Tool (PEST) (Ibrahim et al., 2009). In the CONTEST study, where three of the most frequently used screening tools were compared head-to-head in a number of UK dermatology clinics, the PEST seemed to perform slightly better than the Psoriatic Arthritis Screening and Evaluation (PASE) and Toronto Psoriatic Arthritis Screen (ToPAS), but the specificity was much lower than in the development cohort (Coates et al., 2013). Of the patients invited to take part in this study, only 70% responded to the questionnaires, and of those contacted for a rheumatological assessment, only 61% attended. This was despite a detailed patient information sheet explaining about the link between skin and arthritis and the rationale for the study.

Recently, a new questionnaire ('CONTEST') has been created incorporating the most discriminative items from the PEST, PASE and ToPAS questionnaires and tested retrospectively in similar secondary care PsA screening datasets in Utah and Dublin (Coates et al., 2014). Both the simple CONTEST questionnaire (questions only) and the CONTEST questionnaire with the addition of joint mannequin (to reflect that featured in the PEST questionnaire) performed better than the PEST questionnaire. It is not known how these questionnaires would perform in a primary care setting and if they would offer any advantage over the PEST.

One of the main limitations of screening and identifying PsA is that many patients are unaware of the risk of PsA and the consequences of delayed diagnosis and treatment, and so do not immediately present to their primary care physician when joint symptoms develop. The opportunity to educate patients in secondary care is far more achievable than in primary care due to the regularity of follow up. Health promotion campaigns in both dermatology and rheumatology that have included the use of patient education leaflets have shown improvements in patient awareness and attendance for investigation and treatment (Tomlinson et al., 2004, Richard et al., 1999, Geller et al., 2006), but this has never been tested in psoriatic patients in the primary care setting.

The aims of this chapter are to determine the rates of undiagnosed PsA in a socioeconomically diverse primary care population and to test whether educational material explaining the risks of PsA will improve the attendance of patients with psoriasis for screening. In addition, the two CONTEST questionnaires will be prospectively tested alongside the PEST in this primary care cohort, where a full spectrum of psoriatic disease activity can be found.

2.2 Methods

Ethical approval was granted by the National Research Ethics Committee (Reference 13/NE/0058).

2.2.1 Participant Recruitment

Patients with psoriasis were identified from five primary care practices across Yorkshire with varied socio-economic backgrounds. The practices varied in size from 2908 to 19850 patients (Table 2.2), and four of the five practices did not have any GPs with a special interest in either dermatology or rheumatology. The fifth practice had two GPs with an interest in dermatology. Each surgery performed a database search to identify potential participants, and were eligible if they were aged 18 or over, had a diagnostic label of psoriasis (see below) but did not have a coexistent diagnosis of PsA, ankylosing spondylitis or rheumatoid arthritis. A random sample was taken from each practice using

random number tables to select participants. Information regarding the study was posted by the surgery to those selected. Patients were randomised 1:1 to receive study information in isolation, or the study information with an educational leaflet about PsA (Figure 2.1). The education leaflet was a brightly coloured, small folded card with stylised graphics depicting the ways in which PsA can present, with sources for further information.

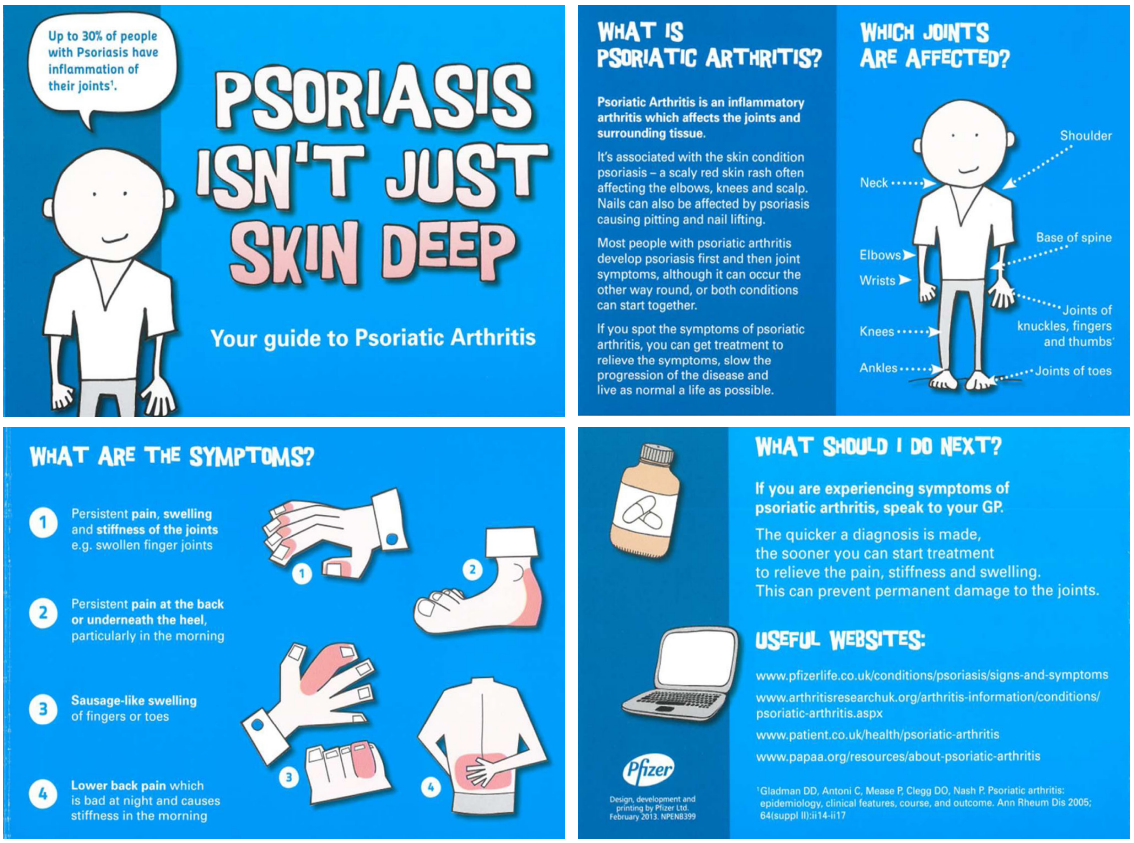

Figure 2.1. Psoriatic arthritis education leaflet sent with study information.

Patients were asked to return a reply slip if they were willing to attend one visit at their GP surgery for an assessment by both a dermatologist (the candidate, LJS) and a rheumatologist (LC, PH or AM). Clinics were held in the evenings to aid attendance. The dermatologist and rheumatologist were blind to whether the patient had received the leaflet or not.

2.2.2 Inclusion/Exclusion Criteria

2.2.2.1 Inclusion Criteria

- Age 18 years or older
- Diagnostic label of psoriasis (Read code M161, x506Y or M16Y)
- Able to attend the surgery for one evening visit

2.2.2.2 Exclusion Criteria

- Age less than 18 years
- Diagnostic label of psoriatic arthritis (read code M160), ankylosing spondylitis (read code N100) or rheumatoid arthritis (read code N40)

2.2.3 Data Collection

Recruitment and data collection took place over twelve months (November 2013 to November 2014). Data relating to dermatological assessment was collected by the candidate (LJS), and rheumatological assessment by the assessing rheumatologist (LC, PH or AM), immediately on to a paper case report form (CRF). Once written consent was obtained, two types of data were collected and recorded for research purposes: participant-reported data and clinical data. Participant-recorded data comprised of demographics, past medical and surgical history, history of skin and joint disease, family history, medications (current prescribed, over-the-counter and psoriasis-specific/arthritis-specific medications, and any previous therapies), age of psoriasis symptom onset, areas ever affected by psoriasis, areas currently affected by psoriasis and current or previous musculoskeletal symptoms, diagnoses and treatments.

Clinical data was collected to assess the type, distribution and severity of psoriasis, the severity of psoriatic nail disease and the presence of any clinical signs of psoriatic arthritis (joint swelling and/or tenderness, clinical enthesitis, dactylitis or axial disease).

Data was transcribed from the paper case report forms (CRFs) into an encrypted, password-protected database stored on a secure drive within the University of Leeds. Paper CRFs are stored in a locked filing cabinet within a locked room within LIRMM, in accordance with the University's Information Security Policy.

2.2.4 Clinical Assessment

Following informed written consent, patients were asked to self-complete a questionnaire booklet including the PEST questionnaire (Appendix 1) and two CONTEST questionnaires (Appendix 2), a Dermatology Life Quality Index (DLQI) (Appendix 3) (Finlay and Khan, 1994), a PsA Quality of Life (PsAQoL) questionnaire (Appendix 4) (McKenna et al., 2004) and a Health Assessment Questionnaire (HAQ) (Appendix 5) (Fries et al., 1980). Consent was sought to use their clinical and questionnaire data for research purposes in addition to data storage.

2.2.4.1 Psoriasis Severity

Patients were reviewed by a dermatologist (the candidate, LJS), and assessment included a detailed history regarding the duration of psoriasis symptoms, areas of involvement, family history of psoriasis and previous therapies used. Examination involved assessment of the type and pattern of psoriasis, calculation of the Psoriasis Area and Severity Index (PASI) (Fredriksson and Pettersson, 1978), modified Nail Psoriasis Area and Severity Index (mNAPSI) (Cassell et al., 2007) and body surface area (BSA). Patients with moderate to severe skin or nail psoriasis were offered referral to secondary care for treatment if they wished.

2.2.4.2 Psoriatic Arthritis

Patients were independently assessed by a rheumatologist (LC, PH or AM) and any history of musculoskeletal symptoms was recorded in addition to any family history of PsA, plus any previous investigations and treatments. Clinical examination included an assessment of entheseal tenderness at sites covered by the Leeds Enthesitis Index (LEI) (Healy and Helliwell, 2008), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) (Heuft-Dorenbosch et al., 2003) and Spondyloarthritis Research Consortium of Canada score (SPARCC) (Maksymowych et al., 2009b), dactylitis digit count and 68 tender and 66 swollen joint counts. The Classification of PsA (CASPAR) criteria were applied to patients with features of inflammatory arthritis (Taylor et al., 2006). Patients with PsA or other symptomatic arthritis were offered a referral to secondary care if they wished.

2.3 Statistical Analysis

To compare the response rates according to the provision of the educational leaflet, it was assumed that a 20% difference in response rate would be of clinical significance (50% response without the leaflet, 70% with the leaflet). Using this 20% difference and a two-sided test, a sample size calculation was performed using an alpha level of 0.05 and a beta of 0.9, which provided a sample size of 124 per group (248 in total). This was the number of screening invitations sent out to patients. Response rates to the leaflet were compared using Pearson's χ^2 test.

To examine the sensitivity and specificity of the CONTEST questionnaire in this new primary care cohort, a minimum sample size of 191 patients attending for examination was required. This was based on a minimum accuracy of 10% and a confidence interval of 95% and assuming a prevalence of 0.3. This study therefore aimed to recruit a total of 191 participants from the minimum number of 248 invitations posted to eligible patients. Receiver operator characteristic (ROC) curve analysis was used to assess the

PEST and CONTEST questionnaires using rheumatologist diagnosis as the gold standard. The sensitivity and specificity of potential cut points were examined.

The relationship between specific anatomical sites of psoriasis and the presence of PsA were examined using Pearson's χ^2 and Fishers exact test. An independent two-sample Mann-Whitney U test was used to assess the difference in psoriasis severity between those with and without PsA. Missing values were excluded. Analysis was performed using IBM© SPSS© version 22.0.

2.4 Results

2.4.1 Response to Invitation for Screening for Psoriatic Arthritis

In total, it was necessary to post out 932 invitations to eligible patients from the five GP practices to recruit 191 participants who agreed to attend for assessment. The response rate to the study was considerably lower than predicted at 20.5%. Response rates varied widely from 14.7% to 30.6% depending on the practice (Table 2.1). The response rate was not significantly higher when patients received the educational leaflet (22.8 vs. 18.3%, p=0.088).

Practice	Deprivation Index	Information Leaflet Provided	No. of Invitations Sent	Response Rate (%)	*p* value
A	10	Yes	54	29.6	0.835
		No	54	31.5	
B	3	Yes	46	30.4	<0.0001
		No	54	3.7	
C	10	Yes	150	21.3	0.976
		No	151	21.2	
D	10	Yes	136	21.3	0.741
		No	137	19.7	
E	7	Yes	75	18.7	0.166
		No	75	10.7	

Table 2.1. Response rates for individual GP practices based on educational leaflet provision.

In terms of demographic and clinical factors, there were no significant differences between those who received the leaflet and those who did not. Median (IQR) age (59 (55,62) vs 58 (55,61) years, *p*=0.821), duration of psoriasis (27 (23,31 vs. 27 (24,31) years, *p*=0.960), the presence of active psoriasis (58% vs. 55%) and subsequent

diagnosis of PsA following clinical examination (9% vs. 9%) were broadly similar in both groups.

Socioeconomic data of the registered patients at each practice were obtained from Public Health England (PHE, 2017). National General Practice Profile statistics on deprivation were used to allocate each practice a decile score (range 1-10, where 1 represented the most deprived area, and level 10 the least deprived). The deprivation index for surgeries included in this study ranged from 3 to 10 (Table 2.1). Analysing the impact of the leaflet on response rates by decile score, there was a significant increase in response from those who received the leaflet for the practice for the surgery in the most deprived area (response rate 30.4% vs. 3.7%, $p<0.0001$). No significant differences were identified in the other practices. In the practice with the deprivation index of 7, a descriptive difference was observed between response rates (18.7% vs. 10.7%), but it did not reach statistical significance. Only a small proportion of invitations were sent out from this practice (150 of 932 in total) which may have been too few to detect a small but significant difference.

2.4.2 Prevalence of Psoriatic Arthritis Amongst Patients in Primary Care

Of the 191 patients attending for assessment, 169 (88.5%) were found to have current or previous psoriasis, with the remaining 22 (11.5%) being misdiagnosed or coded incorrectly. Other diagnoses include ichthyosis vulgaris, eczema, seborrhoeic dermatitis and actinic keratosis. The majority of patients had active psoriasis, but the severity was generally mild with a median PASI score of 2.6 (1.1, 5.4). Only twelve patients had a PASI score greater than 10, indicating moderate to severe psoriasis, and referrals were recommended to made to secondary care where appropriate. The majority of patients had chronic plaque psoriasis (79.2%), with the remainder having small plaque disease (9.0%), palmoplantar psoriasis (2.8%) and guttate psoriasis (1.4%). In terms of therapies, only 49.1% were currently using at least one active topical therapy. Four patients were currently under the care of a dermatologist, with two receiving narrowband UVB phototherapy, and two receiving oral treatment (acitretin/methotrexate).

Previously undiagnosed PsA was identified in 17 (10.1%) of patients. 53.3% were found to have another musculoskeletal diagnosis, and 36.7% had no musculoskeletal problems. Alternative musculoskeletal diagnoses included osteoarthritis and mechanical joint pain (74 patients), tendinopathy (seven patients), gout (two patients), fibromyalgia (two patients), palindromic arthritis (one patient), Morton metatarsalgia (one patient) and joint hypermobility (one patient). Using data from the practices and correcting for the misdiagnosis of psoriasis, the estimated prevalence of PsA in the entire primary care cohort was 18.1% (95% C.I. 16.2-20.1%) (Table 2.2).

Practice	A	B	C	D	E	Total
List Size (n)	2908	13300	19850	10102	9768	55928
Patients coded as PsO (n)	118	360	433	450	313	1674
Patients coded as PsO and PsA (n)	8	12	16	14	18	68
Patients coded as PsA (n)	2	28	36	2	7	75
Total coded as PsA (n)	10	40	52	16	25	143
Patients seen in study (n)	333	16	64	56	22	191
New PsA diagnosed (n)	3	1	4	7	2	17
PsO misdiagnosis (n)	4	2	7	6	3	22
Misdiagnosis rate of PsO (%)	12.1	12.5	10.9	10.7	13.6	11.5
Correctly likely patients with PsO (n)	105	320	391	404	274	1494
Corrected prevalence of PsO (%)	3.61	2.41	1.97	3.99	2.80	2.67
Estimated PsA in Patients with PsO not seen (n)	7	19	20	47	24	117
Total actual and predicted PsA (n)	20	60	76	70	51	277
Estimated PsA prevalence in those with PsO (%)	18.9	18.1	19.4	17.4	18.7	18.5

Table 2.2. The proportion and prevalence of patients in each practice diagnosed with psoriasis (PsO) and psoriatic arthritis (PsA) according to read code.

The demographics of the 169 patients diagnosed with psoriasis are shown in Table 2.3. Looking at potential clinical predictors of PsA, the incidence of PsA was not significantly greater in those with disease of the scalp (p=0.701), retroauricular areas (p=0.359), gluteal cleft (p=0.762) or nail (p=0.394), possibly due to the small number of cases of PsA. No significant associations were observed between the presence of PsA and gender (p=0.872), median age (p=0.234), PASI score (p=0.986), mNAPSI score (p=0.987) or duration of psoriasis (p=0.863).

	Psoriasis (n=169)	**Psoriatic Arthritis (n=17)**	**Alternative MSK diagnosis (n=90)**	**No MSK diagnosis (n=62)**
Male gender [n (%)]	83 (49.1)	8 (47.0)	41 (46.0)	34 (55.0)
Age (years) [median(IQR)]	61.0 (48.0,68.0)	52.0 (47.5,62.5)	61.0 (50.0,69.0)	62 (46.8,68.3)
PsO duration (years) [median (IQR)]	28.0 (14.0,39.5)	30.0 (19.5,43.0)	30.5 (13.3,43.0)	25.0 (12.5,37.0)
Active PsO [n (%)]	144 (85.2)	12 (71.0)	75 (83.0)	57 (92.0)
BSA (%) [median (IQR)]	3 (3,5)	5 (0,5)	3 (2,5)	5 (3,5)
PASI [median (IQR)]	2.6 (1.1,5.4)	2.5 (0.0,5.5)	1.8 (1.0,3.6)	3.6 (1.3,5.9)
Active nail disease [n (%)]	39 (23.1)	6 (35.0)	19 (21.0)	14 (23.0)
mNAPSI score (median {IQR)]	16.0 (8.0,28.0)	16.0 (11.0,23.3)	17.0 (0.0,35.0)	12.5 (8.0,34.3)
CASPAR criteria met (score ≥3) [n (%)]	10 (5.9)	8 (47.0)	2 (2.0)	0 (0.0)
CASPAR score ≥2 [n (%)]	18 (10.6)	14 (82.0)	4 (4.0)	0 (0.0)
No. of swollen joints (0-66) [median (IQR)]	0 (0.0,0.0)	1 (0.0,2.5)	0 (0.0,0.0)	0 (0.0,0.0)
No. of tender joints (0-68) [median (IQR)]	0 (0,2.0)	1 (0.5,3.5)	1 (0.0,4.0)	0 (0.0,0.0)
Active enthesitis [n (%)]	61 (36.1)	7 (41.0)	41 (46.0)	13 (21.0)
Enthesitis score [median (IQR)]	2.0 (1.0,4.5)	1.0 (1.0,6.0)	3.0 (1.0,5.0)	2.0 (1.0,2.5)
Active dactylitis [n (%)]	1 (0.6)	1 (6.0)	0 (0.0)	0 (0.0)
Dactylitis score [median {IQR}]	1	1	0	0
DLQI score [median (IQR)]	2.0 (1.0,5.0)	3.0 (1.0,4.3)	2.0 (1.5,5.0)	2.0 (1.0,5.0)
PsAQoL score [median (IQR)]	1.0 (0.0,7.0)	5.0 (0.0,12.0)	2.0 (0.0,9.0)	0.0 (0.0,3.0)
HAQ score [median (IQR)]	0.0 (0.0,0.4)	0.4 (0.0,0.6)	0.0 (0.0,0.5)	0.0 (0.0,0.0)
PEST score [median (IQR)]	2.0 (1.0,3.0)	2.5 (1.8,4.0)	2.0 (1.0,4.0)	1.0 (0.0,2.0)
CONTEST score without mannequin [median (IQR)]	2.0 (1.0,4.0)	4.0 (2.8,5.5)	3.0 (1.0,4.0)	1.0 (0.0,3.0)
CONTEST score with mannequin [median (IQR)]	2.0 (1.0,5.0)	4.0 (3.5,6.5)	3.0 (1.0,5.0)	1.0 (0.0,3.0)

Table 2.3. Demographics of the study participants with psoriasis (PsO), psoriatic arthritis (PsA), other musculoskeletal (MSK) diagnoses or no MSK problems.

Clinical enthesitis was common amongst patients with psoriasis, and did not discriminate between those with PsA (41.0%) and those with other musculoskeletal diagnoses (46.0%). 13% of patients without any musculoskeletal symptoms also had tender entheseal points. In the 17 patients with a diagnosis of PsA, three had a polyarthritis, eleven had oligoarthritis, two had pure axial disease, and one had symptomatic and clinically inflamed entheseal disease. Three patients with peripheral PsA also had axial involvement.

Scores for quality of life indices were uniformly low, with the exception of the PsAQoL, which was noticeably higher in patients with PsA. One patient, who subsequently revealed he was unaware of the link between skin and joint disease, scored 12 out of 20, highlighting the significant impact his symptoms are having on his quality of life and the need for urgent secondary care assessment and treatment.

2.4.3 Performance of CONTEST Questionnaires in Primary Care

Using ROC curve analysis, all three screening questionnaires showed a significant ability to identify PsA. The areas under the curve for the CONTEST questionnaires (with or without the mannequin) were marginally higher than that of the PEST, but no statistically significant differences were seen between any of the questionnaires (Figure 2.2).

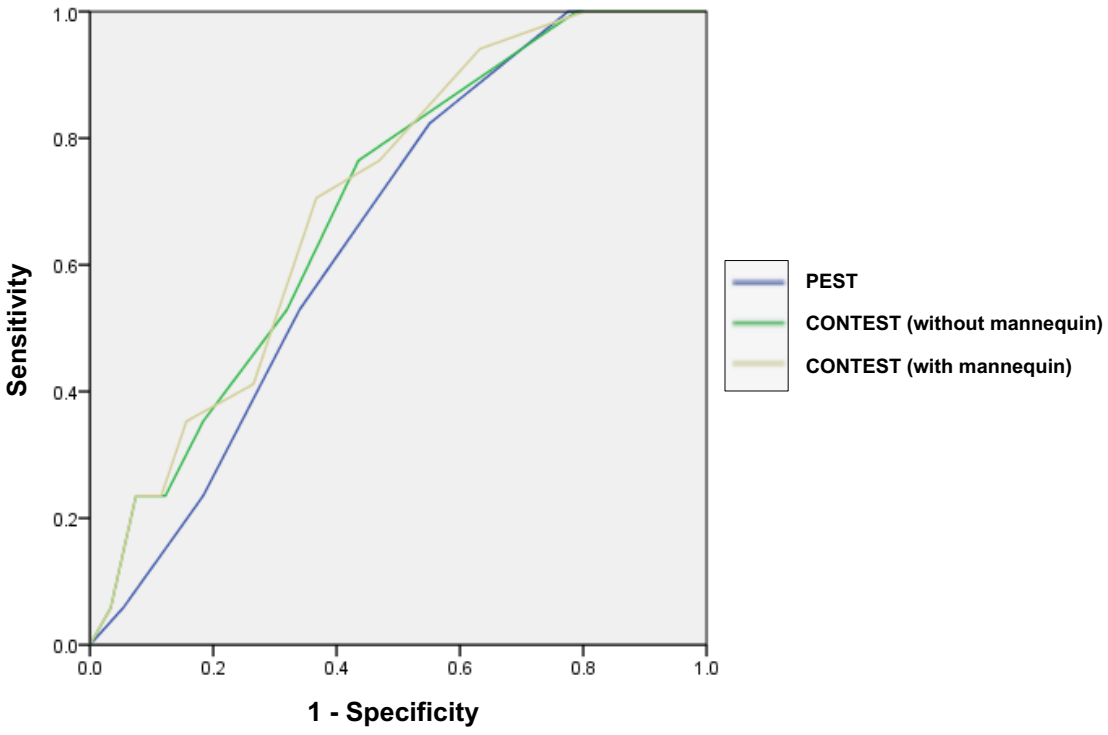

Figure 2.2. Receiver operator characteristic (ROC) curve analysis for the Psoriasis Epidemiology Screening Tool (PEST) and CONTEST questionnaires (with and without a joint mannequin). n=164 (missing data for five patients).

Examining the sensitivities and specificities for the different cut points in this cohort, optimal scores for the CONTEST questionnaires (with and without the joint mannequin) were 3 and 4 respectively. A score ≥3 is advised as the cut off for a diagnosis of PsA using the PEST questionnaire (Ibrahim et al., 2009), but a PEST score ≥2 performed better in this cohort (Table 2.4). Using the validated cut off of 3, eight patients in this cohort had false negative results. Seven of eight of these patients answered 'yes' to the presence of a swollen joint, with the other questions being positive in only one patient each, leading to a score of 2 for most of these patients. Five of these participants had axial involvement, two of which had pure spinal disease, and the absence of questions in the PEST relating to axial symptoms may have accounted for these falsely negative questionnaires. However, despite specific questions on spinal pain, only one of these patients was identified by the CONTEST questionnaire.

Questionnaire	Score	Area Under the Curve	Sensitivity	Specificity
PEST	2	0.652	0.824	0.449
	3	0.652	0.529	0.660
	4	0.652	0.235	0.816
CONTEST (without joint mannequin)	2	0.694	0.882	0.388
	3	0.694	0.765	0.565
	4	0.694	0.529	0.680
	5	0.694	0.353	0.816
CONTEST (with joint mannequin)	2	0.704	0.941	0.367
	3	0.704	0.765	0.531
	4	0.704	0.706	0.633
	5	0.704	0.412	0.735

Table 2.4. Area under the curve, sensitivity and specificity for different cut points for the Psoriasis Epidemiology Screening Tool (PEST) and CONTEST questionnaires (with and without joint mannequin). n=164 (missing data for five patients).

50 patients had falsely positive PEST questionnaires. The majority of these (82.0%) had other MSK diagnoses, typically osteoarthritis or mechanical joint pain. Again, most patients reported swollen joints (96.0%). 78% reported having previously had a swollen and painful digit, 70% reported that they had previously been told they had arthritis, 70% reported heel pain, and 56% reported nail psoriasis. Within this group, the HAQ and PsAQoL scores were similar to those with PsA (median HAQ 0.25 (0.0,0.75); median PsAQoL 5.0 (0.0,12.0)), implying a significant burden of musculoskeletal disease on their quality of life.

2.5 Discussion

Within this primary care cohort across five diverse GP surgeries, the provision of an educational leaflet about PsA did not significantly alter the response rate to an invitation for PsA screening with the exception of the practice with the lowest deprivation index. There was a numerical suggestion of higher uptake in the second most deprived surgery (deprivation index 7) for those sent a leaflet, but the difference did not reach significance. Only 150 of a total of 932 invitations were sent from this practice, so this may represent a type II error.

The anticipated response rate was 50/70% (no leaflet/leaflet), but only 18% (without) and 23% (with leaflet) accepted the invitation for screening. The predicted response rate was based on previous study experience in secondary care, however, this was an unsolicited postal invitation, albeit from their primary care provider, where the patient may not have consulted for some time, or believe their psoriasis to ‘be not that bad’. Patients in secondary care are typically seen on a more frequent basis, have more severe disease, are often more informed about their condition and have usually built a relationship with their treating dermatologist or rheumatologist, which is likely to improve response rates. Basing the sample size calculation on an assumed 50% response rate may have therefore underpowered the study and introduced a further type II error.

The use of an educational leaflet does appear to have played a useful educational role in low socioeconomic areas. Traditionally, patients are less engaged in such areas and attendance for screening is poor. However, giving this information in an easy to read, cartoon format, particularly if given in person by a healthcare practitioner, may be a step forward towards identifying PsA in patients with psoriasis. The response rate without the leaflet was only 3%, increasing to 30% with the leaflet, similar to the maximum response rate at any of the practices.

The assumption that screening to identify undiagnosed PsA is worthwhile has not been formally assessed, but is based on several observational studies in which earlier diagnosis is associated with better disease outcomes (Gladman et al., 2011, Tillett et al.,

2013). Indeed, in this cohort, a number of patients had significant symptoms that, reflected in their PsAQoL and HAQ scores, were clearly having a profound impact on their quality of life. Clearly, both patients and GPs need more awareness and education about the risks associated with undiagnosed PsA. Around 10% of patients with psoriasis had previously been diagnosed (and coded) with PsA, but an additional 10% were found to have undiagnosed PsA on examination. This is in keeping with a recent meta-analysis which found an overall prevalence of undiagnosed PsA in psoriasis patients of 15.5% (Villani et al., 2015). The problem is compounded by the fact that many patients with relatively mild psoriasis do not regularly see their GP, and are less likely to connect their joint symptoms with a small amount of psoriasis. Further education also appears necessary for GPs with regards to the diagnosis of psoriasis, with around 10% of this sample being incorrectly diagnosed (or miscoded). Similarly, it is likely that within the practices, some patients will have psoriasis but have not been coded as such, perhaps because they have not consulted with their doctor or have not had the correct diagnosis made, and therefore a limitation of this study is that some patients may have been inadvertently excluded.

For those that have a diagnosis of psoriasis and do engage with their GP, national guidelines recommend annual screening for PsA (NICE, 2012, SIGN, 2001), although anecdotal evidence suggests this has not been widely adopted. These guidelines acknowledge that the optimal screening questionnaire has not yet been established, although recommend the PEST questionnaire based on available data. PEST was originally developed in a primary-care population and subsequently validated in dermatology clinics. The new CONTEST questionnaires (with and without the joint mannequin) were developed in two secondary care dermatology populations, and have not been previously tested in primary care. In this primary care population, all of these questionnaires were able to identify PsA, with no questionnaire significantly out-performing the others. A much larger study would be required to identify a significant difference in the sensitivity and specificity of the questionnaires.

Interestingly, the optimal cut points of all of the questionnaires seem to be lower in this cohort than in their development cohorts. ROC curve analysis identified a PEST score ≥ 2, rather than the advised cut off of ≥ 3, to be most accurate in identifying PsA, although this was at the expense of specificity; given that 50 patients had false positive PEST questionnaires using the validated cut off of ≥ 3, even more patients with mechanical joint pain, osteoarthritis and other MSK complaints would be incorrectly identified as having PsA using a cut off of ≥ 2. A number of these false positive patients answered ‘yes’ to the question relating to dactylitis, a PsA-specific presentation, suggesting that this question may need rewording. Of greater concern, the PEST questionnaire failed to detect PsA in two patients examined and diagnosed by a rheumatologist. Similarly, the CONTEST questionnaires, which contain at least two questions about spinal pain failed

to capture either of the only two patients with pure axial disease in the study, even when the cut-off was lowered from 4 to 3.

With the inaccuracies of screening questionnaires for PsA highlighted in this and other studies (Coates et al., 2013, Haroon et al., 2013, Walsh et al., 2013a, Mease et al., 2014b, Mishra et al., 2017), the question arises as to what other methods can be used to identify PsA amongst patients with psoriasis. One previous large retrospective population-based study identified a number of cutaneous clinical features associated with a higher likelihood of PsA including nail dystrophy, scalp lesions and intergluteal/perianal psoriasis (Wilson et al., 2009). However, no clinical predictors of PsA were identified in this cohort, but this is not surprising given that only 17 patients had PsA and the study was powered to assess the performance of the screening questionnaires rather than to look at the performance of PsA predictors.

In terms of musculoskeletal examination, it is recognised that certain clinical features can help differentiate PsA from osteoarthritis, rheumatoid and other forms of arthritis (Helliwell and Wright, 1998). Included among these distinguishing clinical features is the presence of enthesitis. Entheses are widely distributed in the body, but the major entheses of the lower limb around the calcaneum provide the hallmark features of enthesitis in PsA and other spondyloarthropathies, which accounts for the question relating to heel pain in the PEST and CONTEST questionnaires (Ibrahim et al., 2009, Coates et al., 2014). Enthesitis is a classification criterion for PsA (CASPAR classification) (Taylor et al., 2006) and is now generally accepted as the primary pathological lesion in PsA (McGonagle et al., 1998a, McGonagle et al., 2002a). Enthesitis has therefore been proposed as an important domain of assessment and outcome in PsA (Gladman et al., 2007b), and is the basis of several examination indices, including the LEI (Healy and Helliwell, 2008), MASES (Heuft-Dorenbosch et al., 2003) and SPARCC (Maksymowych et al., 2009b) which were tested in this cohort. However, far from discriminating those patients with PsA from others with different musculoskeletal disorders, high levels of tender entheseal points were found in patients with mechanical joint pain or osteoarthritis (46%), and also in patients without a musculoskeletal diagnosis (13%), suggesting examination alone, especially for early disease, is insufficient. Imaging is the gold standard for the assessment of enthesitis, but is not widely available in primary care.

The difficulties of capturing psoriasis patients for PsA screening in primary care, the limitations of clinical examination, and the problem of low specificity with screening questionnaires, have been highlighted in the findings of this chapter. Even the new CONTEST questionnaires, formulated from the best performing questions within existing tools, did not improve on the current recommendation of the PEST. PsA is a heterogeneous disease, and developing a questionnaire or examination technique to identify cases precisely, while excluding other causes of musculoskeletal pain, seems

problematic. It may well be the case that existing tools cannot be improved upon and the deficiencies should be accepted and acknowledged, and simply by promotion of their existence in national guidelines may serve to increase awareness of the link between skin and joints amongst GPs. In turn, education of psoriasis patients is also key to the earlier recognition and diagnosis of PsA, and the addition of a simple leaflet may be beneficial if provided in person by a healthcare provider, especially in lower socioeconomic areas.

2.6 Conclusion

Health promotion campaigns, including the use of educational leaflets, have previously shown improvements in health awareness and attendance for investigation. In this cohort, provision of educational material only had an impact in the most deprived practices. Low response rates to the invitation for screening made detection of any true impact difficult. In hindsight the study was underpowered, with sample size estimates incorrectly based on previous response rates in secondary care studies. 10.1% of cases of PsA identified among those that did attend were newly diagnosed. All three screening questionnaires analysed showed a significant ability to detect PsA, with the two CONTEST questionnaires (with and without joint mannequin) being marginally better than the PEST, although this difference did not reach statistical significance and therefore does not warrant a change in current practice.

Chapter 3
Identification of Early Psoriatic Arthritis in Patients with Psoriasis in Secondary Care

3.1 Introduction

Psoriasis affects approximately 2% of the western population, and up to 30% will develop psoriatic arthritis (PsA) (Gelfand et al., 2005, Reich et al., 2009, Radtke et al., 2009, Christophers et al., 2010). The majority of patients will develop the skin manifestations of psoriatic disease first, and as such, dermatologists in the secondary care setting are often well placed to identify PsA as it develops. The recognition that PsA can lead to significant musculoskeletal damage and consequent functional limitation, disability and impairment to quality of life has modified the disease management approach and treatment paradigm. While outcomes can be variable, patients with psoriasis often experience progressive and irreversible joint damage over a relatively short period of time. PsA is erosive and deforming in 40-60% of untreated patients where joint damage has been seen to occur within the first few years after disease onset (McHugh et al., 2003, Kane et al., 2003, Gladman et al., 1990). A window of opportunity is said to exist, whereby delay in first encounter with a rheumatologist for six months, or a diagnostic delay of greater than one year, can contribute to the development of peripheral joint erosions and worse long-term physical function (Haroon et al., 2014a). However, as discussed in the previous chapter, a lack of both patient and physician awareness of the link between the skin and arthritis has a profound negative impact on early diagnosis. The concept of ‘early PsA’ remains relatively new, and still lags behind the wealth of literature on early rheumatoid arthritis (RA) and the “window of opportunity” that exists to treat RA early in order to minimise disability (Quinn and Emery, 2003).

Though the potential advantages of early diagnosis and effective management of PsA have been highlighted, in the absence of a predictive/diagnostic serological biomarker such as anti-citrullinated antibody in RA, identifying such patients early in the disease course remains a challenge. No association between the severity of skin disease and the likelihood of developing PsA has been found, making screening of this prevalent disease difficult at the population level. Another key problem is the wide clinical spectrum of PsA, which can include the synovial joints, entheses, dactylitis, axial skeleton and nails either concomitantly or in isolation. Furthermore, there are erratic temporal associations between the skin and joint disease, with psoriasis predating joint disease in 70%, occurring prior to skin disease in 15% and occurring concurrently in 15% of cases (Jones et al., 1994, McGonagle et al., 2011, Gladman et al., 1987).

Several screening questionnaires have been developed to assist dermatologists to identify patients with PsA amongst their psoriasis cohorts. However, the most widely used have been shown to have suboptimal sensitivity and specificity in head to head studies, identifying many cases of musculoskeletal disease rather than PsA specifically (Coates et al., 2013, Haroon et al., 2013, Mishra et al., 2017, Mease et al., 2014b, Walsh et al., 2013a). Where they do identify PsA, patients have often had symptoms for several years and the 'window of opportunity' is often missed.

Despite the introduction of these questionnaires, the prevalence of undiagnosed PsA remains high in secondary care, estimated at 15.5% in one recent meta-analysis of published studies of newly diagnosed PsA in patients with psoriasis (Villani et al., 2015), although on review of dermatology patients within secondary care by a rheumatologist, some centres have reported finding up to 85% of cases of PsA within their psoriasis cohort were undiagnosed (Reich et al., 2009). Additional approaches are therefore desperately needed to try identify PsA much earlier in patients with psoriasis in order to target effective treatment strategies and prevent progressive joint damage.

Identification of subclinical musculoskeletal disease, very early in the disease course, could play a vital role in the patients' management. Histological analysis remains the gold standard, although is invasive and impractical outside of the research setting. Ultrasound has shown to be an effective means of detecting asymptomatic inflammation at the entheses and in surrounding structures, in addition to osseous destructions and new bone formation at various sites in patients with psoriasis (Naredo et al., 2011, Gutierrez et al., 2011, Gisondi et al., 2008, Balint et al., 2002, De Simone et al., 2011, Ozcakar et al., 2005, Moshrif et al., 2017, Acquacalda et al., 2015). However, given the wide clinical spectrum of joint involvement in PsA, very few studies have looked beyond more than a handful of sites. There are no published studies providing a comprehensive assessment of accessible entheses in the upper and lower limbs that could be used to guide a screening protocol for patients with psoriasis. This chapter aims to assess the prevalence of subclinical enthesitis in new, asymptomatic patients presenting to the dermatology clinic for treatment of moderate-to-severe psoriasis, and establish the pattern of inflammatory and chronic damage abnormalities to determine the feasibility of an ultrasound screening programme in secondary care.

3.2 Methods

This study was conducted in one centre (Chapel Allerton Hospital, part of Leeds Teaching Hospitals NHS Trust). Ethical approval was obtained from the National Research Ethics Committee (Reference 12/YH/0483) and the Medicines and Healthcare Products Regulatory Authority (Reference 16767/0264/001-0001).

3.2.1 Participant Recruitment

Recruitment of patients was undertaken within the Leeds Centre for Dermatology at Chapel Allerton Hospital (Leeds Teaching Hospitals Trust). All new routine referrals from Primary Care to the Department of Dermatology were screened for a diagnosis of psoriasis as made by the patients' General Practitioner. Referrals were excluded if the letter made reference to previous treatment with any systemic immunosuppressant, PUVA phototherapy or biologic agent. Similarly, any patients with a confirmed diagnosis of psoriatic arthritis were excluded.

Adult patients (aged 18 and over) identified from the screening of referrals were booked into a dedicated psoriasis clinic. Within Leeds Teaching Hospitals NHS Trust, patients are routinely advised of their initial clinic appointment by standard NHS letter. Patients were booked under the named consultant (MDG) who is the Lead Clinician for the psoriasis service within the Trust, but the candidate (LJS) conducted all of the consultations.

No modification was made to the initial clinical consultation, except for the addition of questionnaires and an invitation to participate in ultrasound screening of the peripheral joints. Questionnaires to screen for co-morbidities such as psoriatic arthritis and depression are recommended by the National Institute for Health and Care Excellence (NICE) and their use within these psoriasis clinics served as a pilot for guideline implementation and service improvement. During the consultation, patients were informed about the link between psoriasis and psoriatic arthritis, asked about any joint symptoms and briefly examined for any clinical signs of the disease, as recommended by NICE. All patients completed a Dermatology Life Quality Index (DLQI) questionnaire in line with the current standard of the psoriasis clinic.

Patients who were clinically eligible were offered the opportunity to undergo a brief (20-30 minute) ultrasound scan of their peripheral joints. Whilst this is not routine practice, it did form part of a service development plan within the Trust. Findings from this study will form part of a pilot to see if there are any trends that may identify who should be targeted for ultrasound screening in future psoriasis clinics. Ideally, all psoriasis patients would undergo ultrasound screening of their joints, but the prevalence of psoriasis is such that this is not economically or logistically possible. To develop the service, a targeted approach is needed.

Patients indicating a willingness to undergo an ultrasound scan of their peripheral joints were given a verbal explanation about the procedure and the potential findings. They were also provided with a generic leaflet about musculoskeletal ultrasound produced by the Department of Rheumatology within Leeds Teaching Hospitals NHS Trust. If they decided they would like to have the ultrasound, they were booked into the next mutually convenient appointment, usually within a week. Patients were reassured that if any

pathology was seen at ultrasound, a referral would be made to a Consultant Rheumatologist at Chapel Allerton Hospital.

Written consent was obtained from all patients undergoing a screening ultrasound prior to the investigation. Consent was sought to use their clinical, questionnaire, serological and imaging data for research purposes in addition to data storage.

3.2.2 Inclusion/Exclusion Criteria

Male and female patients over the age of 18 with moderate to severe chronic plaque psoriasis (Psoriasis Area and Severity Index (PASI) ≥10) were included. They must have had psoriasis for a minimum of 12 months and not previously received treatment with any systemic immunosuppressant, PUVA phototherapy or biologic agent, which could have potentially had an impact on the musculoskeletal system. Patients with symptoms consistent with inflammatory arthritis, or who fulfilled the CASPAR criteria for psoriatic arthritis were excluded, as were patients with a diagnosis or symptoms of any other rheumatological disorder (Taylor et al., 2006).

3.2.3 Data Collection

Recruitment and data collection took place over two years (May 2013 – May 2015), through all four seasons to allow for natural variation in psoriasis severity related to outdoor ultraviolet levels. Data collection was solely carried out by the candidate (LJS) onto paper case record forms (CRF) and then transposed into encrypted password-protected databases on the University of Leeds server for analysis within seven days. Paper record forms are stored in a locked filing cabinet within a locked room within LIRMM, in accordance with the University's Information Security Policy. All clinical data collection took place within the first visit, and imaging data collection within the subsequent visit. Two experienced musculoskeletal sonographers (LH and AJ) performed ultrasound scans within the Leeds Musculoskeletal Biomedical Research Unit (LMBRU) at Chapel Allerton Hospital.

Once written consent was obtained, three types of data were collected and recorded for research purposes: participant-reported data, clinical data and imaging data. Participant-recorded data comprised of demographics, skin type, social history (smoking, alcohol and employment), past medical and surgical history, history of skin and joint disease, family history, medications (current prescribed, over-the-counter and psoriasis-specific medications, and any previous psoriasis therapies), age of psoriasis symptom onset, areas ever affected by psoriasis, areas currently affected by psoriasis and current or previous musculoskeletal symptoms.

Clinical data was collected to assess the severity of psoriasis, the severity of any psoriatic nail disease, baseline observations (height, weight, blood pressure and heart rate) and the presence of any clinical signs of psoriatic arthritis (joint swelling and/or tenderness, clinical enthesitis or dactylitis).

3.2.4 Clinical Assessment

3.2.4.1 Psoriasis Severity

Following on from a detailed history (see Data Collection above), patients were fully undressed (down to their underwear) and a full clinical examination conducted as would occur in a standard dermatology consultation. Clinical assessment included documentation of the anatomical location of psoriatic plaques, body surface area (BSA) involvement, PASI score and modified NAPSI score. Impact of psoriasis on quality of life was assessed using the patient-completed Dermatology Life Quality Index (DLQI) questionnaire.

3.2.4.2 Psoriatic Arthritis

While the patient was undressed for their skin examination, several entheseal sites were examined for tenderness. Direct pressure was applied with sufficient force to just blanche the examiners fingernail. Clinical examination was performed prior to ultrasound to prevent bias. The following sites were evaluated:

- 1st and 7th costochondral joints
- Supraspinatus insertion
- Medial and lateral epicondyles of the humerus
- Anterior and posterior superior iliac spines
- Iliac crest
- 5th lumbar process
- Greater trochanter
- Medial condyle of the femur
- Quadriceps insertion at the patella
- Inferior pole of the patella
- Tibial tubercle
- Proximal Achilles
- Plantar fascia insertion

These sites were chosen as they form part of commonly used clinical entheseal scores. The fingers and toes were assessed for any fusiform swelling or tenderness consistent

with dactylitis. All peripheral joints were examined for gross evidence of joint disease. All clinical assessments were performed by the candidate (LS).

3.2.5 Laboratory Assessment

To ensure that patients did not have rheumatoid arthritis or any other rheumatological disorder, a number of serological assessments were performed.

- C-reactive protein (CRP) was measured by the standard nephelometry (mg/l).
- Rheumatoid Factor was measured by nephelometry (IU/ml)
- Anti-citrullinated peptide (Anti-CCP) antibody was measured by multiplex bead technology (bioplex) (U/ml)
- Anti-nuclear antibody (ANA) was measured by indirect immunofluorescence using Hep-2 substrate and results were expressed in titres of 1/40 or higher.

All of the tests above were measured using commercial kits in the hospital diagnostic laboratory.

3.2.6 Ultrasonography

Grey scale ultrasound and power Doppler (PD) examinations were performed by two dedicated research sonographers (AJ and LH) fully trained in musculoskeletal ultrasound using a Logiq E9 machine (General Electric, Wauwatosa, Wisconsin USA). The ultrasound equipment is maintained and optimised through regular servicing, routine calibration and quality assurance testing. This is in accordance with the Society of Motion Picture and Television Engineers (SMPTE), the manufacturers' (General Electric) directions and the Leeds Teaching Hospitals NHS Trust Medical Physics department procedures. Adherence to these measures should result in a reduction of random error in the measurements.

The sonographers were aware of the patients' diagnosis of psoriasis but not aware of the findings from their history and clinical examination. Patients were asked not to communicate with the sonographer about their medical history during the examination. All joints and tendon insertions were examined using a multi-frequency linear probe at 6-15MHz with a B-mode frequency of 12-15MHz. A multiplanar scanning technique was performed according to the indications provided by the EULAR guidelines for musculoskeletal ultrasound in rheumatology (Backhaus et al., 2001). The PD settings were standardised with a pulse repetition frequency of 0.5-0.8KHz, a colour mode frequency of 7.5-10MHz, a gain of 15dB and low wall filters. The colour gain was increased to the maximum level that did not generate PD signals under the bony cortex.

A broad range of anatomical sites were included with the aim of capturing very early psoriatic arthritis that may only affect one or two entheses, in addition to investigating which entheses are most commonly involved. The majority of published studies looking at subclinical enthesitis in patients with psoriasis have concentrated only on the large entheses in the lower limbs. Several peripheral upper and lower limb sites were scanned to look for entheseal pathology and associated bursitis in addition to synovitis of associated peripheral joints. Table 3.1. summarises the tendon entheses and corresponding bone insertion sites scanned and Table 3.2 lists the joints examined for synovitis.

Anatomical Site	Tendon Enthesis	Bone Insertion Point
Thumb	Flexor pollicis longus	Base of distal phalynx
	Extensor pollicis longus	Base of distal phalynx
Index Finger	Flexor digitorum profundus	Base of distal phalynx
	Extensor digitorum	Base of distal phalynx
Middle Finger	Flexor digitorum profundus	Base of distal phalynx
	Extensor digitorum	Base of distal phalynx
Ring Finger	Flexor digitorum profundus	Base of distal phalynx
	Extensor digitorum	Base of distal phalynx
Little Finger	Flexor digitorum profundus	Base of distal phalynx
	Extensor digitorum	Base of distal phalynx
Elbow	Common extensor	Lateral epicondyle of humerus
	Common flexor	Medial epicondyle of humerus
	Distal brachial triceps	Olecranon process of ulna
Knee	Quadriceps	Superior pole of patella
	Proximal patellar	Inferior pole of patella
	Distal patellar	Anterior tibial tuberosity
Foot and Ankle	Peroneal brevis	5^{th} metatarsal base lateral tuberosity
	Achilles	Superior pole of calcaneus
	Plantar fascia	Inferior pole of calcaneus

Table 3.1. Tendon entheses and bone insertion sites scanned (grey scale and power Doppler assessments).

Limb	Joint
Upper Limb	Wrist
	Elbow
	Thumb interphalangeal
	Thumb carpometacarpal
	Index finger distal interphalangeal
	Index finger proximal interphalangeal
	Index finger metacarpophalangeal
	Middle finger distal interphalangeal
	Middle finger proximal interphalangeal
	Middle finger metacarpophalangeal
	Ring finger distal interphalangeal
	Ring finger proximal interphalangeal
	Ring finger metacarpophalangeal
	Little finger distal interphalangeal
	Little finger proximal interphalangeal
	Little finger metacarpophalangeal
Lower Limb	Knee
	Ankle

Table 3.2. Joints scanned for grey scale hypertrophy and power Doppler signal.

All structures were examined in at least two perpendicular planes and care taken to obtain comparable contralateral views. Patients were positioned prone with the legs extended and feet over the end of the examination couch, with the ankle dorsiflexed to 90 degrees to facilitate assessment of the Achilles tendon and plantar aponeurosis insertions (superior and inferior calcaneal poles, respectively). Examinations of the perineal brevis insertion at the fifth metatarsal base and associated functional entheses in the foot and ankle were performed in the supine position with the knee semi-flexed to 30 degrees and the foot flat on the couch, as were assessments of the quadriceps tendon insertion (superior pole of the patella), patellar ligament origin (inferior pole of the patella) and the distal patellar tendon insertion (tibial tuberosity). The knee was then extended to a neutral position (in order to reduce vascular compression) to confirm the presence of any power Doppler signal seen in the semi-flexed position. Assessment of the elbow tendon insertions occurred with patients seated sideways on the examination couch facing the sonographer. With their arms resting on a pillow, palms together in a prayer position and with the elbow flexed to 90 degrees, the common extensor tendon insertion was examined at the lateral epicondyle. Each arm was then fully extended and the forearm supinated to allow access to the medial epicondyle to assess the common flexor tendon enthesis. Finally, the palms were placed on the pillow with the fingers touching,

the arms were abducted to raise the elbows and the elbows brought forward to permit scanning of the distal brachial triceps tendon insertion at the radial tuberosity. With the elbows relaxed, the hands separated and the lateral border of the hand resting on the pillow, compartment 1 of the posterior wrist was scanned over the lateral wrist crease. The forearm was then pronated and the remaining compartments (2-6) were scanned with the palms resting on the pillow. This position was maintained for examination of the thumb extensor pollicis longus and finger extensor digitorum tendons, and then the hands turned to permit scanning of the thumb flexor pollicis longus and finger flexor digitorum profundus tendons with the palms facing upwards.

3.2.6.1 Ultrasound Image Interpretation

Ultrasound images were interpreted at the time of scanning for changes included in the OMERACT definition of enthesopathy (see Figure 3.1 below). The following entheseal parameters were assessed:

- Tendon thickness at its bony attachment site
- Hypoechoic change within the tendon at the bony attachment site
- Power Doppler signal within the tendon at the bony attachment site
- Calcification within the tendon at the bony attachment site
- Enthesophytes arising around the tendon attachment site
- Erosions arising within the bone around the tendon attachment site
- Irregularities within the usually smooth bony cortex around the tendon attachment site

> ***OMERACT definition of enthesopathy:*** *'Abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity.'*

Figure 3.1. OMERACT definition of enthesopathy (Wakefield et al., 2005).

Synovitis was assessed using the OMERACT definition of synovial hypertrophy (see Figure 3.2 below). The following parameters were assessed:

- Hypoechoic change within the intraarticular tissue
- Power Doppler signal within the synovial intraarticular tissue

OMERACT definition of synovial hypertrophy: *'Abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intraarticular tissue that is non-displaceable and poorly compressible and which may exhibit Doppler signal.'*

Figure 3.2. OMERACT definition of synovial hypertrophy (Wakefield et al., 2005).

All parameters were scored as 1 for present and 0 for absent. Abnormalities must be seen in two perpendicular planes (longitudinal and transverse) to be deemed present. A maximum score of 266 was possible for entheseal changes (7 parameters assessed in 38 entheses – 19 per side), and a maximum score of 72 was possible for synovial changes (2 parameters assessed in 36 joints – 18 per side). The total entheseal score was composed of two sub scores – an inflammation score (maximum possible 114) and a chronic damage score (maximum possible 152). Scores were expected to be low as patients were included on the basis of no known rheumatological disease and no persistent symptoms in keeping with a diagnosis of psoriatic arthritis.

3.3 Statistical Analysis

Categorical data are expressed as frequencies, and continuous variables are given as means (standard deviation, s.d.) or medians (interquartile range, IQR), depending on the distribution. Correlations between demographic (age, skin type, BMI, smoking history, alcohol consumption) and clinical parameters (age of psoriasis onset, duration of psoriasis, PASI, BSA, mNAPSI, DLQI) were analysed by Spearman rank correlation or rank biserial r_b (Somers *D*) depending on the type of data analysed; absolute rho values >0.3 and d values >0.4 are considered to indicate substantive correlation. For categorical variables (gender, family history of psoriasis, anatomical location of psoriasis plaques, presence/absence of ultrasound inflammation), associations were explored using Student's *t*-tests, Mann-Whitney *U* tests or Pearson's χ^2 tests according to whether the associating variable was normally-distributed interval-scaled data, skewed interval or ordinal data, or categorical data respectively. *p* values <0.05 were regarded as statistically significant. Statistical analysis was performed using IBM© SPSS© version 24.0.

3.4 Results

3.4.1 Patient Characteristics

75 patients with moderate to severe psoriasis were approached, of which 73 agreed to undergo a brief ultrasound of their peripheral joints and consented for their data to be used for research purposes. Two declined due to holiday commitments within the two weeks following their consultation.

Of the 73, 45 were male and 28 were female. The age of participants ranged from 18 to 74 years, with a median of 40 years. Mean BMI was 28.7(5.70)kg/m^2. The majority of patients were Caucasian (skin type I, n=8; skin type II, n=40, skin type III, n=22), with three patients being of Asian or Afro-Caribbean ethnicity (skin type IV=0, skin type V=2, skin type VI=1). The age of onset of psoriasis symptoms varied greatly from 4 years to 60 years, with a median of 18 years. 60 patients had type I psoriasis (i.e. onset prior to the age of 40 years) and 13 had type II psoriasis (i.e. onset from 40 years or older). Participants had had psoriasis symptoms for an average [median(range)] of 14 (1-55) years. 43 participants had a family history of psoriasis, and 9 had a family history of psoriatic arthritis. Median PASI score was 17.6 (10.0-56.3) and BSA 20% (10-80%). 46 patients (63%) had nail involvement with a median mNAPSI score of 16 (2-89) out of a possible maximum of 140. Every participant had a positive DLQI questionnaire, with a mean total of 15 (7.65) out of a possible maximum of 30.

Despite not reporting any musculoskeletal symptoms, and all having a PEST score of two or less, 11 (15.1%) of 73 patients examined had tender entheseal points clinically. All 11 had evidence of entheseal inflammation on ultrasound at the corresponding site. No patient with a negative ultrasound had tender entheseal sites on clinical examination. The number of sites found to be tender on clinical examination was 1 in six patients, 2 in three patients, 4 in one patient and 12 in one patient. These scores were too low to warrant calculation of formal entheseal indices such as the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) for comparison.

Patient characteristics in all 73 cases were further studied dependant on whether the patient had a ‘positive’ or ‘negative’ ultrasound. As these chronic changes can occur as a result of trauma, repeated stress from heavy exercise or load bearing (e.g. through occupation) and as part of the ageing process, only those with abnormally hypoechoic or thickened entheses (with or without power Doppler signal) were classified as having a positive ultrasound scan and active subclinical enthesitis.

44 (60.3%) of 73 patients scanned had at least one abnormality on ultrasound, although of these 44, only 36 (49.3%) had changes in keeping with inflammatory enthesopathy (i.e. abnormally hypoechoic and/or thickened tendon at its bony attachment, with or without power Doppler signal). The remaining 8 patients had evidence of chronic damage

(entheseal calcification, enthesophytes, bone erosions and/or bone cortex irregularities) but no changes in keeping with active entheseal inflammation.

Patients with a positive ultrasound (i.e, abnormally hypoechoic and/or thickened tendon at its bony attachment, with or without power Doppler signal) were older than patients without subclinical enthesitis (p<0.001), and also are likely to have never smoked (p=0.005). No differences were seen in terms of gender, skin type or amount smoked if ever a smoker or alcohol consumption. Patients with inflammatory abnormalities on ultrasound were slightly heavier, although this difference did not reach statistical significance (Table 3.3.).

Characteristic		**Positive US (n=36)**	**Negative US (n=37)**	**Difference**
Gender [*n (%)*]	Male	20 (55.6%)	25 (67.6%)	p=0.291
	Female	16 (44.4%)	12 (32.4%)	NA
Age (years) [*Median (IQR)*]		50 (37-58)	31 (23-42)	***p*<0.001**
Skin Type [*n (%)*]	I	4 (11.1%)	4 (10.8%)	p=0.715
	II	18 (50.0%)	22 (59.5%)	NA
	III	13 (36.1%)	9 (24.3%)	NA
	IV	0 (0%)	0 (0%)	NA
	V	1 (2.8%)	1 (2.7%)	NA
	VI	0 (0%)	1 (2.7%)	NA
BMI (kg/m^2) [*Mean (s.d.)*]		30.0 (5.6)	27.5 (5.6)	p=0.059
Smoking Status [*n (%)]*	Never	17 (47.2%)	10 (27.0%)	***p*=0.005**
	Current	8 (22.2%)	22 (59.5%)	NA
	Previous	11 (30.6%)	5 (13.5%)	NA
	Ever	19 (52.8%)	27 (73.0%)	p=0.074
Cigarette pack years (years) [*Median (IQR)*]		1.75 (0-21)	4 (0-19)	p=0.587
Alcohol consumption (units per week) [*Median (IQR)*]		10 (10-20)	10 (5-33)	p=0.945

Table 3.3. Comparison of demographic characteristics between psoriasis patients categorised according to ultrasound outcome. p<0.05 denotes significance. (US: ultrasound; NA: not applicable; IQR: interquartile range; s.d.: standard deviation).

3.4.2 Skin and Nail Disease Characteristics

Table 3.4 summaries the differences in psoriasis duration and severity, lesion distribution and impact on quality of life between patients with and without evidence of inflammatory subclinical enthesitis on ultrasound. No statistically significant differences were found

between the two groups. The duration of psoriasis symptoms was marginally longer in patients with inflammatory abnormalities on ultrasound (17 years vs. 13 years), but did not reach statistical significance (p=0.149). This was despite patients with an abnormal (positive) ultrasound being of older age at symptom onset (28.5 years vs, 19.4 years, p=0.05).

Characteristic		**Positive US** (with inflammatory changes) **(n=36)**	**Negative US** (normal/chronic changes only) **(n=37)**	**Difference**
Age at psoriasis onset (years) [*Mean (s.d.)*]		28.5 (15.86)	19.4 (10.55)	p=0.050
Duration of psoriasis symptoms (years) [*Median (IQR)*]		17 (7.25-29.25)	13 (4.5-22.0)	p=0.149
Positive family history of psoriasis [*n (%)*]		20 (55.6%)	23 (62.2%)	p=0.566
Positive family history of PsA [*n (%)*]		5 (13.9%)	4 (10.8%)	p=0.689
PASI Score [*Median (IQR)*]		17.1 (11.9-25.4)	18.5 (11.8-25.5)	p=0.903
BSA (%) [*Mean (s.d.)*]		28.6 (19.24)	27.5 (16.19)	p=0.784
mNAPSI Score *Median (IQR)*		8 (0-29.5)	6 (0-23)	p=0.575
DLQI Score *Median (IQR)*		15.5 (10.3-22.0)	15.0 (10.5-21.0)	p=0.916
Nail involvement [*n (%)*]	Current	23 (63.9%)	23 (62.2%)	p=0.879
	Ever	23 (63.9%)	24 (64.9%)	p=0.931
Scalp involvement [*n (%)*]	Current	30 (83.3%)	33 (89.2%)	p=0.467
	Ever	36 (100%)	36 (97.3%)	p=0.572
Retroauricular involvement [*n (%)*]	Current	25 (69.4%)	30 (81.1%)	p=0.249
	Ever	31 (86.1%)	33 (89.2%)	p=0.689
Gluteal cleft involvement [*n (%)*]	Current	22 (61.1%)	21 (56.8%)	p=0.705
	Ever	27 (75.0%)	29 (78.4%)	p=0.733
Umbilical involvement [*n (%)*]	Current	13 (36.1%)	17 (45.9%)	p=0.393
	Ever	23 (63.9%)	23 (62.2%)	p=0.879
Facial involvement [*n (%)*]	Current	15 (41.7%)	15 (40.5%)	p=0.922
	Ever	22 (61.1%)	19 (51.4%)	p=0.401

Characteristic		Positive US (with inflammatory changes) (n=36)	Negative US (normal/chronic changes only) (n=37)	Difference
Upper limb involvement [*n (%)*]	Current	35 (97.2%)	37 (100%)	*p*=0.539
	Ever	36 (100%)	37 (100%)	*p*=0.984
Dorsal hand involvement [*n (%)*]	Current	19 (52.8%)	23 (62.2%)	*p*=0.417
	Ever	23 (63.9%)	27 (73.0%)	*p*=0.404
Trunk involvement [*n (%)*]	Current	35 (97.2%)	35 (94.6%)	*p*=0.572
	Ever	35 (97.2%)	36 (97.3%)	*p*=0.984
Lower limb involvement [*n (%)*]	Current	35 (97.2%)	37 (100%)	*p*=0.539
	Ever	36 (100%)	37 (100%)	*p*=0.984
Flexural involvement [*n (%)*]	Current	18 (50.0%)	17 (45.9%)	*p*=0.729
	Ever	23 (63.9%)	20 (54.1%)	*p*=0.393
Genital involvement [*n (%)*]	Current	11 (30.6%)	14 (37.8%)	*p*=0.512
	Ever	16 (44.4%)	20 (54.1%)	*p*=0.411
Perianal involvement [*n (%)*]	Current	5 (13.9%)	9 (24.3%)	*p*=0.258
	Ever	10 (27.8%)	16 (43.2%)	*p*=0.168
Involvement of the palms [*n (%)*]	Current	6 (16.7%)	3 (8.1%)	*p*=0.266
	Ever	7 (19.4%)	6 (16.2%)	*p*=0.719
Involvement of the soles [*n (%)*]	Current	6 (16.7%)	5 (13.5%)	*p*=0.782
	Ever	9 (25.0%)	4 (10.8%)	*p*=0.113

Table 3.4. Comparison of skin and nail disease characteristics between psoriasis patients categorised according to ultrasound outcome. $p<0.05$ denotes significance. (BSA: Body Surface Area; PASI: Psoriasis Area and Severity Index; mNAPSI: modified nail psoriasis area and severity score; DLQI: Dermatology Life Quality Index; US: ultrasound; IQR: interquartile range; s.d.: standard deviation).

3.4.3 Serological Characteristics

There were very few serological abnormalities in all 73 patients, and no significant differences were identified between the group with and the group without positive

ultrasound findings. CRP was elevated above the standard cut off of <10.0mg/l in 5 patients, three of which were within the group with no sonographic abnormalities. The highest measurement in all patients was marginally elevated at 15.4mg/l, indicative of a very low level of inflammation. All patients with a slightly elevated CRP reported symptoms consistent with an acute, self-limiting viral or bacterial illness such as an upper respiratory tract infection in the preceding month.

ANA was positive at low titre in only one patient (positive ultrasound group) as was Rheumatoid Factor (27iu/ml – upper limit of normal <20iu/ml) (negative ultrasound group). Anti-CCP antibody was normal in all patients. Little difference was found in the number of patients with elevated plasma viscosity (PV) levels, with six in the positive ultrasound group, and five in the negative ultrasound group.

3.4.4 Ultrasound Characteristics

3.4.4.1 Entheseal Changes

In total, 2774 entheses were scanned in 73 patients (38 per patient) with moderate to severe psoriasis. 44 patients had at least one entheseal change (either inflammatory, chronic or both) on ultrasound and in these, a total of 640 abnormalities were seen, equating to 23.1% of entheses scanned being abnormal (Table 3.5). Frequencies of these abnormalities are as follows (in descending order):

- Entheseal thickening in 264 entheses (9.5%)
- Enthesophytes in 97 entheses (3.5%)
- Hypoechogenicity in 92 entheses (3.3%)
- Calcifications in 72 entheses (2.6%)
- Bone cortex irregularities in 61 entheses (2.2%)
- Power Doppler signal in 5 entheses (0.2%)
- Bone erosions in 5 entheses (0.2%)

In total, inflammatory lesions (thickening, hypoechogenicity and power Doppler signal) were identified in 13.0% of all entheses scanned, whereas chronic entheseal abnormalities (enthesophytes, calcifications, bone erosions and bone cortex irregularities) occurred in 8.5%. Figure 3.3 and Figure 3.4 demonstrate these abnormalities within participants.

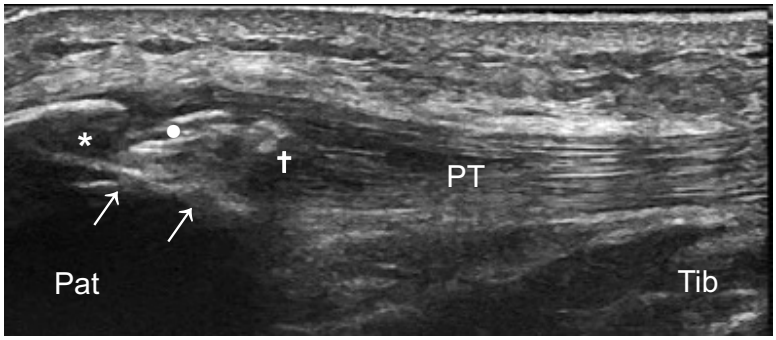

Figure 3.3. Entheseal thickening (†, grade 2), hypoechogenity (✶, grade 2), calcification (•, grade 2), bone cortex irregularities and enthesophytes (↑, grade 1) in the right proximal patellar tendon enthesis of an asymptomatic patient with moderate-to-severe psoriasis. PT: Patellar tendon; Pat: Patella; Tib: Tibia.

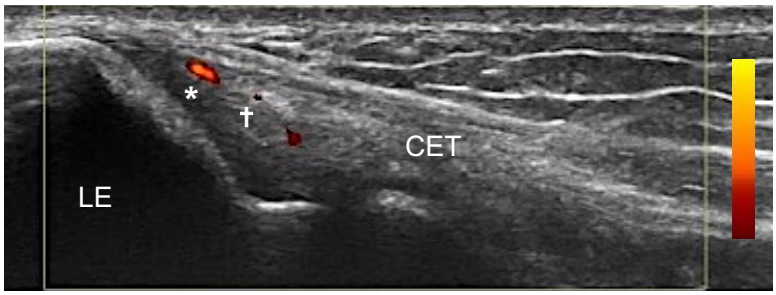

Figure 3.4. Entheseal thickening (†, grade 2), hypoechogenity (✶, grade 1) and power Doppler signal (red) in the left common extensor tendon enthesis of an asymptomatic patient with moderate-to-severe psoriasis. CET: Common extensor tendon; LE: Lateral epicondyle.

Burseal hypertrophy occurred in 3 of 730 (0.4%) bursae scanned (in 5 sites bilaterally per patient) (Figure 3.5).

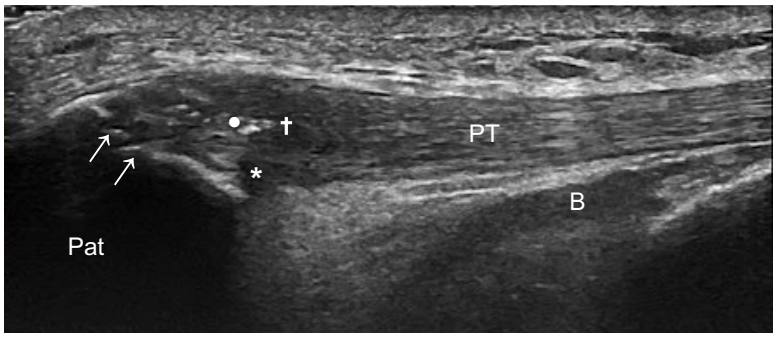

Figure 3.5. Right deep infrapatellar burseal hypertrophy (B) associated with proximal patellar tendon entheseal thickening (†, grade 2), hypoechogenicity (✶, grade 2), calcification (•, grade 1) and bone cortex irregularities (grade 1) in an asymptomatic patient with moderate to severe psoriasis. PT: Patellar tendon; Pat: Patella.

In the 36 patients with a positive ultrasound, inflammatory enthesopathy scores ranged from 1 to 19, with a median (interquartile range, IQR) of 6 (2-11) out of a possible 114.

Chronic damage changes were rarely seen without accompanying signs of active inflammation. 8 (11.0%) of the 44 patients with at least one lesion on ultrasound had signs of chronic damage only, with the remaining 36 of 44 (81.8%) having at least one potentially modifiable inflammatory entheseal abnormality.

In all patients scanned, chronic damage enthesopathy scores ranged from 0-24, with a median of 1 (0-5) out of a possible 182. In those with a at least one inflammatory lesion on ultrasound, the median was 5 (1.25-8.75).

Total enthesopathy scores ranged from 0 to 37 in all participants, with a median of 2 (0-11.5) out of a possible total of 266. In the 36 patients with a positive ultrasound, the median was 11.5 (4.0-20.25).

Tendon		Parameter	Within all entheses (max = 146)		Within patients with at least one inflammatory lesion (n=x/73, max. 36)		Within in patients with only chronic damage lesions (n=x/73, max. 8)	
			n	%	n	%	n	%
Thumb	Flexor pollicis longus	Thickening	9	6.2	7	9.6	0	0.0
		Hypoechogenicity	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	0	0.0
		Enthesophytes	4	2.7	3	4.1	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	15	10.3	11	15.1	0	0.0
	Extensor pollicis longus	Thickening	4	2.7	4	5.5	0	0.0
		Hypoechogenicity	1	0.7	1	1.4	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	0	0.0
		Enthesophytes	6	4.1	4	5.5	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	7	4.8	6	8.2	0	0.0
Index Finger	Flexor digitorum profundus	Thickening	5	3.4	5	6.8	0	0.0
		Hypoechogenicity	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	2	1.4	2	2.7	0	0.0
		Enthesophytes	1	0.7	1	1.4	0	0.0
		Bony erosions	1	0.7	1	1.4	0	0.0
		Bone cortex irregularities	5	3.4	4	5.5	0	0.0
	Extensor digitorum	Thickening	3	2.1	2	2.7	0	0.0
		Hypoechogenicity	2	1.4	1	1.4	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	1	0.7	1	1.4	0	0.0
		Enthesophytes	3	2.1	3	4.1	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	7	4.8	4	5.5	0	0.0

Tendon		Parameter	Within all entheses (max = 146)		Within patients with at least one inflammatory lesion (n=x/73, max. 36)		Within in patients with only chronic damage lesions (n=x/73, max. 8)	
			n	%	n	%	n	%
Middle Finger	Flexor digitorum profundus	Thickening	1	0.7	1	1.4	0	0.0
		Hypoechogenicity	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	0	0.0
		Enthesophytes	0	0.0	0	0.0	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	0	0.0
	Extensor digitorum	Thickening	0	0.0	0	0.0	0	0.0
		Hypoechogenicity	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	0	0.0
		Enthesophytes	0	0.0	0	0.0	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	0	0.0
Ring Finger	Flexor digitorum profundus	Thickening	0	0.0	0	0.0	0	0.0
		Hypoechogenicity	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	0	0.0
		Enthesophytes	0	0.0	0	0.0	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	0	0.0
	Extensor digitorum	Thickening	0	0.0	0	0.0	0	0.0
		Hypoechogenicity	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	0	0.0
		Enthesophytes	0	0.0	0	0.0	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	0	0.0

Tendon		Parameter	Within all entheses (max = 146)		Within patients with at least one inflammatory lesion (n=x/73, max. 36)		Within in patients with only chronic damage lesions (n=x/73, max. 8)	
			n	%	n	%	n	%
Little Finger	Flexor digitorum profundus	Thickening	0	0.0	0	0.0	0	0.0
		Hypoechogenicity	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	0	0.0
		Enthesophytes	0	0.0	0	0.0	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	0	0.0
	Extensor digitorum	Thickening	0	0.0	0	0.0	0	0.0
		Hypoechogenicity	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	0	0.0
		Enthesophytes	0	0.0	0	0.0	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	0	0.0
Elbow	Common Extensor	Thickening	13	8.9	8	11.0	0	0.0
		Hypoechogenicity	13	8.9	10	13.7	0	0.0
		Power Doppler signal	2	1.4	2	2.7	0	0.0
		Calcifications	0	0.0	0	0.0	0	0.0
		Enthesophytes	3	2.1	2	2.7	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	6	4.1	4	5.5	0	0.0
	Common Flexor	Thickening	13	8.9	7	9.6	0	0.0
		Hypoechogenicity	8	5.5	5	6.8	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	1	0.7	1	1.4	0	0.0
		Enthesophytes	3	2.1	2	2.7	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	4	2.7	3	4.1	0	0.0

Tendon		Parameter	Within all entheses (max = 146)		Within patients with at least one inflammatory lesion (n=x/73, max. 36)		Within in patients with only chronic damage lesions (n=x/73, max. 8)	
			n	%	n	%	n	%
	Distal Brachial Triceps	Thickening	3	2.1	3	4.1	0	0.0
		Hypoechogenicity	3	2.1	3	4.1	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	6	4.1	5	6.8	0	0.0
		Enthesophytes	9	6.2	5	6.8	2	2.7
		Bony erosions	1	0.7	1	1.4	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	0	0.0
Knee	Quadriceps	Thickening	17	11.6	11	15.1	0	0.0
		Hypoechogenicity	22	15.1	15	20.5	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	26	17.8	17	23.3	1	1.4
		Enthesophytes	31	21.1	15	20.5	5	6.8
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	5	3.4	3	4.1	0	0.0
	Proximal Patellar	Thickening	14	9.6	9	12.3	0	0.0
		Hypoechogenicity	14	9.6	9	12.3	0	0.0
		Power Doppler signal	2	1.4	1	1.4	0	0.0
		Calcifications	5	3.4	3	4.1	0	0.0
		Enthesophytes	6	4.1	4	5.5	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	3	2.1	2	2.7	0	0.0
	Distal Patellar Tendon	Thickening	26	17.8	16	22.0	0	0.0
		Hypoechogenicity	10	6.8	8	11.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	15	10.3	10	13.7	0	0.0
		Enthesophytes	4	2.7	4	5.5	0	0.0
		Bony erosions	1	0.7	1	1.4	0	0.0
		Bone cortex irregularities	3	2.1	3	4.1	0	0.0

Tendon		Parameter	Within all entheses (max = 146)		Within patients with at least one inflammatory lesion (n=x/73, max. 36)		Within in patients with only chronic damage lesions (n=x/73, max. 8)	
			n	%	n	%	n	%
Foot and Ankle	Peroneal Brevis	Thickening	6	4.1	4	5.5	0	0.0
		Hypoechogenicity	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	1	0.7	1	1.4	0	0.0
		Enthesophytes	2	1.4	2	2.7	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	3	2.1	3	4.1	0	0.0
	Achilles	Thickening	7	4.8	6	8.2	0	0.0
		Hypoechogenicity	10	6.8	9	12.3	0	0.0
		Power Doppler signal	1	0.7	1	1.4	0	0.0
		Calcifications	11	7.5	9	12.3	1	1.4
		Enthesophytes	23	15.8	11	15.1	6	8.2
		Bony erosions	1	0.7	1	1.4	0	0.0
		Bone cortex irregularities	3	2.1	2	2.7	0	0.0
	Plantar Fascia	Thickening	11	7.5	9	12.3	0	0.0
		Hypoechogenicity	14	9.6	12	16.4	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0
		Calcifications	4	2.7	4	5.5	0	0.0
		Enthesophytes	2	1.4	2	2.7	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	0	0.0

Table 3.5. Number of entheseal abnormalities by anatomical site and lesion at the entheseal and patient level.

In terms of the location of subclinical enthesitis, by far the majority of all abnormalities occurred in the larger tendon entheses, especially the three knee tendons (quadriceps, proximal patellar and distal patellar), Achilles tendon, plantar aponeurosis and elbow common extensor and flexor tendons. With the exception of bone cortex abnormalities, very few changes were seen in the small tendons of the finger and thumb or the perineal brevis tendon in the foot. Inflammatory lesions (thickening, hypoechogenicity and/or power Doppler signal) occurred with the greatest frequency at knee tendon insertion sites, followed by the elbows and foot and ankle tendon entheses. Figure 3.6 and Table 3.6 describe the total number of inflammatory lesions in all patients by tendon enthesis type.

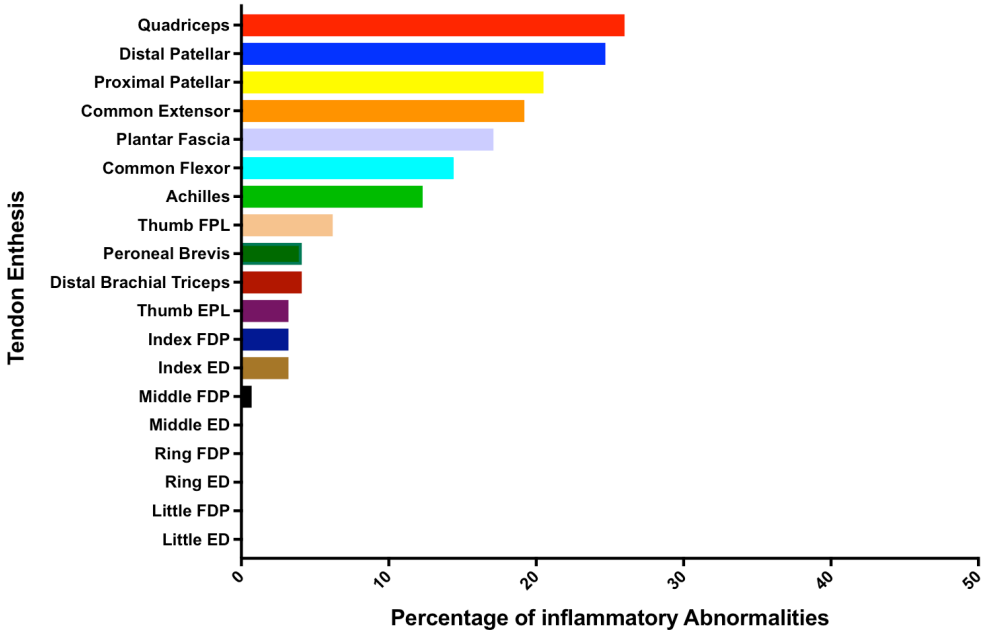

Figure 3.6. Percentage number of inflammatory entheseal lesions by anatomical location (FPL: Flexor Pollicis Longus; EPL: Extensor Pollicis Longus; ED: Extensor Digitorum; FDP: Flexor Digitorum Profundus).

Tendon Enthesis	Total number of lesions in all patients (max =146)
Quadriceps	38 (26.0%)
Distal patellar	36 (24.7%)
Proximal patellar	30 (20.5%)
Common extensor	28 (19.2%)
Plantar fascia	25 (17.1%)
Common flexor	21 (14.4%)
Achilles	18 (12.3%)
Thumb flexor pollicis longus	9 (6.2%)
Peroneal brevis	6 (4.1%)
Distal brachial triceps	6 (4.1%)
Thumb extensor pollicis longus	5 (3.2%)
Index finger flexor digitorum profundus	5 (3.2%)
Index finger extensor digitorum	5 (3.2%)
Middle finger flexor digitorum profundus	1 (0.7%)
Middle finger extensor digitorum	0 (0%)
Ring finger flexor digitorum profundus	0 (0%)
Ring finger extensor digitorum	0 (0%)
Little finger flexor digitorum profundus	0 (0%)
Little finger extensor digitorum	0 (0%)

Table 3.6. Total number and percentage of inflammatory entheseal lesions by anatomical location.

Lesions in keeping with chronic damage (entheseal calcification, enthesophytes, bone erosions and/or bone cortex irregularities) again occurred with high frequency in the larger entheses, although signs of damage were seen in the thumb and index finger insertion sites with a noticeably higher incidence than inflammatory lesions. Figure 3.7 and Table 3.7 describe the total number of chronic damage lesions in all patients by tendon enthesis type.

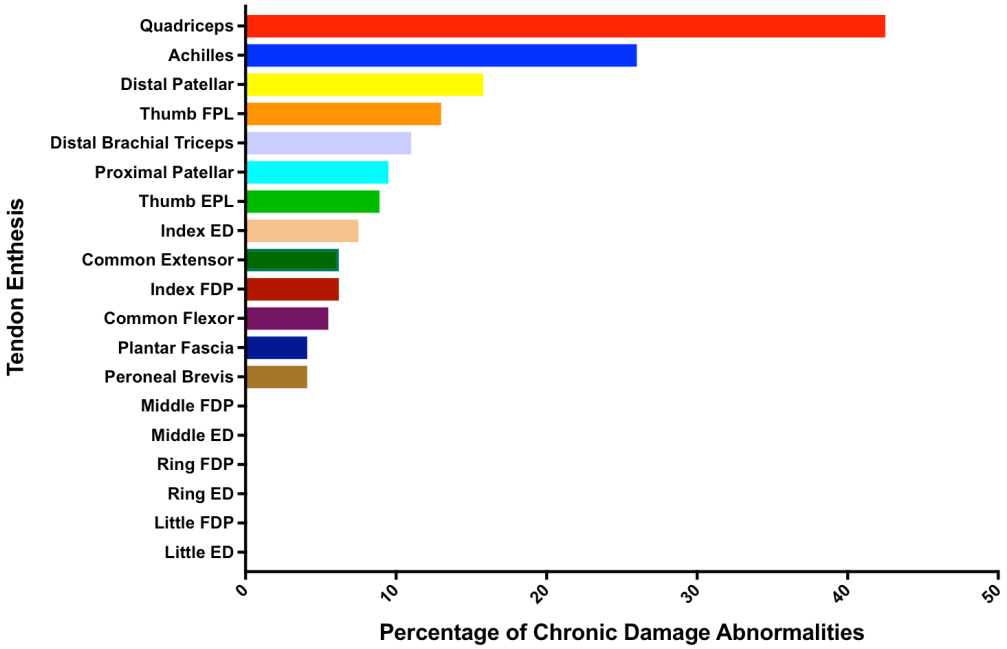

Figure 3.7. Percentage number of entheseal chronic damage lesions by anatomical location (FPL: Flexor Pollicis Longus; EPL: Extensor Pollicis Longus; ED: Extensor Digitorum; FDP: Flexor Digitorum Profundus).

Tendon Enthesis	Total number of lesions in all patients (max.=146)
Quadriceps	62 (42.5%)
Achilles	38 (26.0%)
Distal patellar	23 (15.8%)
Thumb flexor pollicis longus	19 (13.0%)
Distal brachial triceps	16 (11.0%)
Proximal patellar	14 (9.5%)
Thumb extensor pollicis longus	13 (8.9%)
Index finger extensor digitorum	11 (7.5%)
Common extensor	9 (6.2%)
Index finger flexor digitorum profundus	9 (6.2%)
Common flexor	8 (5.5%)
Plantar fascia	6 (4.1%)
Peroneal brevis	6 (4.1%)

Tendon Enthesis	Total number of lesions in all patients (max.=146)
Middle finger flexor digitorum profundus	0 (0%)
Middle finger extensor digitorum	0 (0%)
Ring finger flexor digitorum profundus	0 (0%)
Ring finger extensor digitorum	0 (0%)
Little finger flexor digitorum profundus	0 (0%)
Little finger extensor digitorum	0 (0%)

Table 3.7. Total number and percentage of chronic damage lesions by anatomical location.

3.4.4.2 Synovial Changes

Synovial hypertrophy only occurred in patients with inflammatory entheseal lesions. Cases were most commonly seen in the wrists (26 joints, 17.8%) and carpometacarpal joints of the thumb (22 joints, 15.1%) followed by the metacarpophalangeal joints of the index finger (12 joints, 8.2%) and the knee joints (10 joints, 6.8%) (Figure 3.8).

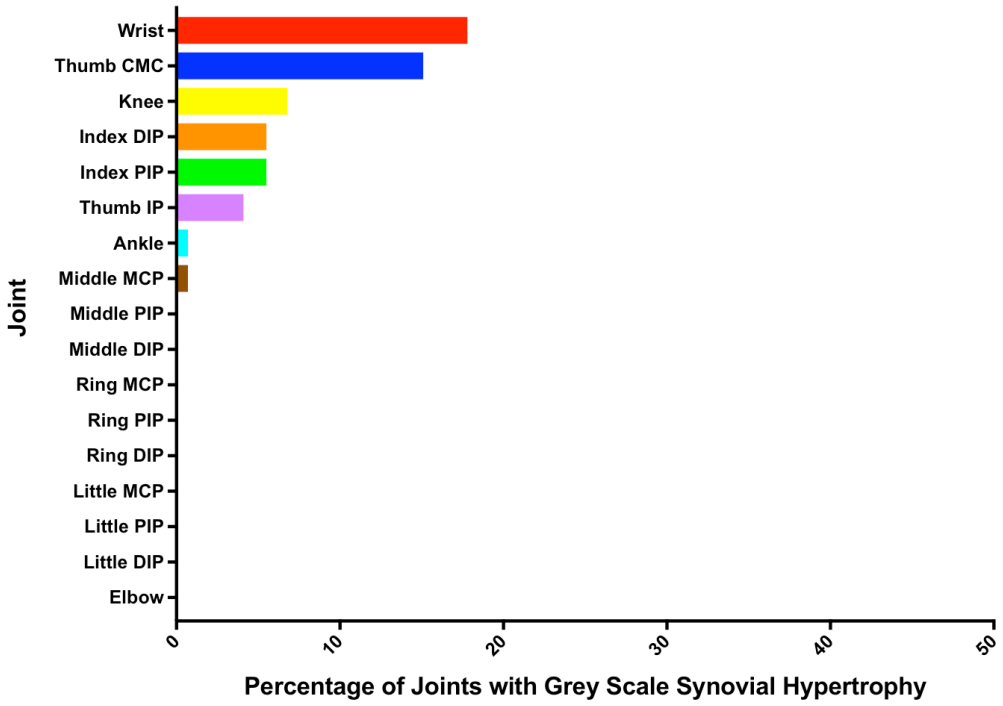

Figure 3.8. Percentage frequency of joints with grey scale synovial hypertrophy (DIP: Distal Interphalangeal; PIP: Proximal Interphalangeal; MCP: Metacarpophalangeal; CMC: carpometacarpal).

Like at the enthesis, the incidence of power Doppler signal was low, only affecting the wrist joints in four patients (one bilateral and three unilateral) and index metacarpophalangeal joints in three patients (one bilateral and two unilateral) (Figure 3.9).

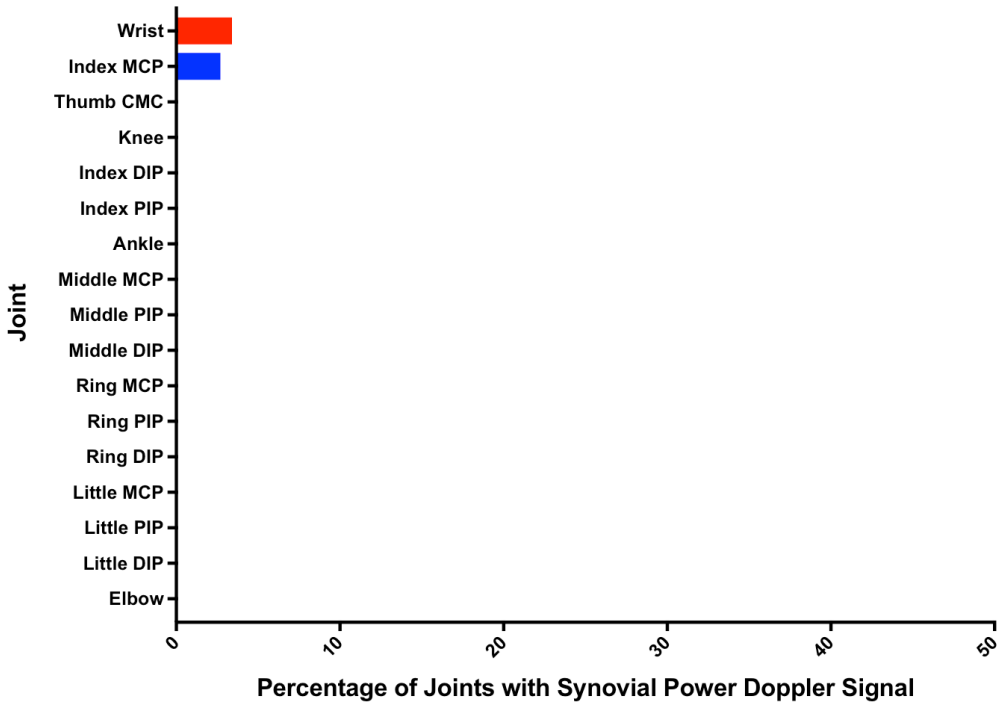

Figure 3.9. Percentage frequency of joints with synovial power Doppler signal (DIP: Distal Interphalangeal; PIP: Proximal Interphalangeal; MCP: Metacarpophalangeal; CMC: carpometacarpal).

Table 3.8 displays the frequencies of grey scale and power Doppler synovial changes by joint.

Joint		Mode	Within all entheses (max = 146)		Within patients with at least one inflammatory lesion (n=x/73, max. 36)		Within in patients with only chronic damage lesions (n=x/73, max. 8)	
			n	%	n	%	n	%
Thumb	Interphalangeal	GS	6	4.1	5	6.8	0	0.0
		PD	0	0.0	0	0.0	0	0.0
	Carpometacarpal	GS	22	15.1	11	15.1	0	0.0
		PD	0	0.0	0	0.0	0	0.0
Index Finger	Distal Interphalangeal	GS	8	5.5	8	11.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0
	Proximal Interphalangeal	GS	8	5.5	5	6.8	0	0.0
		PD	0	0.0	0	0.0	0	0.0
	Metacarpophalangeal	GS	12	8.2	8	11.0	0	0.0
		PD	4	2.7	3	4.1	0	0.0

Joint		Mode	Within all entheses (max = 146)		Within patients with at least one inflammatory lesion (n=x/73, max. 36)		Within in patients with only chronic damage lesions (n=x/73, max. 8)	
			n	%	n	%	n	%
Middle Finger	Distal Interphalangeal	GS	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0
	Proximal Interphalangeal	GS	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0
	Metacarpophalangeal	GS	1	0.7	1	1.4	0	0.0
		PD	0	0.0	0	0.0	0	0.0
Ring Finger	Distal Interphalangeal	GS	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0
	Proximal Interphalangeal	GS	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0
	Metacarpophalangeal	GS	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0
Little Finger	Distal Interphalangeal	GS	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0
	Proximal Interphalangeal	GS	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0
	Metacarpophalangeal	GS	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0
Wrist		GS	26	17.8	14	19.2	0	0.0
		PD	5	3.4	4	5.5	0	0.0
Elbow		GS	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0
Knee		GS	10	6.8	8	11.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0
Ankle		GS	1	0.7	1	1.4	0	0.0
		PD	0	0.0	0	0.0	0	0.0

Table 3.8. Frequency of grey scale synovial hypertrophy and synovial power Doppler signal by joint.

Synovitis scores ranged from 0-11 in all participants, with a median of 0 (0-2.5) out of a possible maximum total of 72. In the 36 patients with at least one inflammatory entheseal lesion, the median was 2.5 (0-4.75).

3.4.5 Associations Between Patient, Clinical and Ultrasound Characteristics

Associations between ultrasound enthesopathy and synovitis scores, and a number of demographic and clinical parameters were analysed using Spearman rank correlation between ordinal (ranked) data or rank biserial r_b (Somers *D*) for ordinal (ranked) and nominal (dichotomous) data correlations. Absolute rho values >0.3 and d values >0.4 were considered to indicate substantive correlation (Table 3.9). Positive correlations were found between enthesopathy scores (inflammation, chronic damage and total), synovitis scores and patient age (all $p<0.05$). Similarly, heavier patients (as assessed using BMI) were more likely to have greater enthesopathy and synovitis scores.

Correlations	Inflammation Score	Chronic Damage Score	Total Enthesopathy Score	Total Synovitis Score
Age	**rho=0.40***	**rho=0.41***	**rho=0.45***	**rho=0.34***
Gender	d=0.13	d=0.12	d=0.11	d=0.28
BMI	**rho=0.32***	**rho=0.32***	**rho=0.35***	**rho=0.30***
PASI	rho=0.00	rho=-0.15	rho=-0.11	rho=-0.01
mNAPSI	rho=0.20	rho=0.21	rho=0.19	rho=0.29
BSA	rho=0.03	rho=-0.09	rho=-0.05	rho=0.04
Duration of Psoriasis	rho=0.13	rho=0.27	rho=0.23	rho=0.14
Age of Psoriasis Onset	rho=0.23	rho=0.16	rho=0.23	rho=0.16
Smoker (ever)	d=-0.09	d=0.03	d=-0.04	d=0.05
Pack years	rho=0.03	rho=0.21	rho=0.13	rho=0.21
No. of PsO sites (current)	rho=0.01	rho=-0.05	rho=-0.04	rho=0.09
No. of PsO sites (ever)	rho=0.05	rho=0.02	rho=0.03	rho=0.14

Table 3.9. Associations between demographic and clinical parameters, and enthesopathy and synovitis scores. rho=Spearman rank correlation coefficient. d=Rank biserial correlation coefficient (Somers *D*). Values in bold represent rho>0.3 and are considered to represent a substantive correlation (PsO: psoriasis). *denotes significance at $p<0.05$ level.

3.5 Discussion

Enthesitis has been indicated as a distinctive pathological condition affecting patients with psoriatic arthritis, and is best identified using grey scale and power Doppler ultrasound where histological analysis is not feasible. These data add further confirmation that entheseal abnormalities can be also be documented in patients with psoriasis, prior to the development of musculoskeletal symptoms. Previous studies have shown asymptomatic inflammatory entheseal abnormalities in 46.4% (Acquacalda et al., 2015), 39.0% (Ash et al., 2012b), 56.0% (Ozcakar et al., 2005), 39.1% (Naredo et al., 2011) and 59.3% (De Simone et al., 2003) of patients with psoriasis, which is comparable with the 49.3% of patients in this cohort. Power Doppler signal was found in 0.2% of entheses, and published data show, where assessed, that either PD signal was absent (Acquacalda et al., 2015) or rates were similarly low with 0.77% (Acquitter et al., 2016), 1.0% (Ash et al., 2012b) and 0.9% of entheses demonstrating PD signal (Gutierrez et al., 2011).

The majority of previous studies in psoriasis patients have concentrated on imaging the larger entheses of the lower limb, studying either the Achilles tendon in isolation (Ozcakar et al., 2005, De Simone et al., 2003) or the five entheses included in the Glasgow Ultrasound Enthesitis Scoring System (quadriceps, proximal patellar, distal patellar, Achilles and plantar fascia tendon insertions) (Gisondi et al., 2008, Bandinelli et al., 2013, Ash et al., 2012b, Moshrif et al., 2017, Gutierrez et al., 2011). Few studies have looked at sites in the upper limb, with only one study including the brachial triceps tendon insertion (Acquacalda et al., 2015), one study including the common extensor and flexor tendon insertions into the medial and lateral epicondyles of the elbow (Acquitter et al., 2016) and two studies including the flexor/extensor tendons of the fingers (Naredo et al., 2011, De Filippis et al., 2005). In all published studies, regardless of anatomical site, entheseal abnormalities were identified in asymptomatic patients with psoriasis, suggesting their inclusion is paramount if a comprehensive assessment of the distribution of entheseal lesions is to be achieved. This is the first study to systematically assess all of these sites with grey scale and power Doppler ultrasound in the upper and lower limbs in addition to the peroneal brevis tendon insertion of the ankle, using agreed definitions for ultrasound pathology in a large population of psoriatic patients without musculoskeletal disease.

Enthesitis is different from enthesopathy, although the two terms, incorrectly, are often used interchangeably in the literature (D'Agostino M et al., 2009). Enthesitis is defined as the presence of inflammation in tendons, ligaments and capsule insertions into the bone, whereas enthesopathy is a term reserved to describe a spectrum of inflammatory and structural damage abnormalities within the enthesis, including calcifications, enthesophytes, bone erosions and cortical irregularities (D'Agostino, 2010). Gandjbakhch showed that many different authors published about enthesitis definition

and consensus was needed, which may account for some of the differences seen between the data in this thesis and that in previously published studies (Gandjbakhch et al., 2011). However, Terslev and colleagues dismissed this observation, demonstrating a high agreement concerning different components of the definition of enthesitis such as hypoechogenicity, thickness of tendon insertion, enthesophytes, calcifications, erosions and power Doppler signal at the entheses ≤2mm near the bony cortex (Terslev et al., 2014). For the purposes of this analysis, where 'enthesitis' has been reported, this has been interpreted to denote only the presence of inflammatory abnormalities, and 'enthesopathy' has been understood to represent the presence of inflammatory lesions and/or structural damage abnormalities.

Using these terms, similar rates of subclinical enthesitis were identified by Naredo et al in their study of 162 asymptomatic patients with psoriasis (11.6% of entheses vs. 13.0%), as were the frequencies of patients with enthesopathy (62.5% vs. 60.3%), and power Doppler signal (7.4% of patients vs. 6.8%) (Naredo et al., 2011). Theirs is the most comprehensive assessment published to date, analysing a total of 9 entheses, 18 joints and 11 tendons bilaterally. A number of entheses included in this investigation were not included (finger extensor tendons, quadriceps tendons, distal brachial triceps tendons, common extensor and flexor tendons of the elbow and peroneal brevis tendons). Both cohorts had a similar mean participant age (42.6 years vs. 40.1 years) and mean duration of psoriasis (13.4 years vs. 16.9 years), although patients in their study had a lower mean PASI score (6.7 vs. 20.0), perhaps reflecting their inclusion of patients recently discontinuing drugs such as methotrexate, ciclosporin and oral retinoids. This is likely to not be of relevance, as this study and several others have found no association between the presence of subclinical enthesopathy on ultrasound and PASI score (Bandinelli et al., 2013, De Simone et al., 2003, Gisondi et al., 2008, Gutierrez et al., 2011, Naredo et al., 2011).

Naredo and colleagues actively chose to exclude the palmar aspect of the finger joints and the metacarpophalangeal joints from the ultrasound examination because, although very sensitive to ultrasound imaging in arthritis, a high frequency of synovitis has been reported in normal subjects (Wiell et al., 2007, Scheel et al., 2005). This was not the experience in this study, where adequate visualisation of the flexor and extensor tendons allowed a clear assessment of these entheses, and relatively low rates of synovitis (<9%) were observed in the distal interphalangeal, proximal interphalangeal and metacarpophalangeal joints, with the exception of the thumb carpometacarpal joint (15.1% had synovitis). No synovitis was seen in the ring and little fingers. Naredo and colleagues observed low rates of enthesopathy in the deep flexor tendons of the fingers (2.4%), with no distinction made between the different digits. In this cohort, no enthesopathy was observed in the middle, ring and index fingers, however 6.2% of thumb and 3.2% of index finger flexor tendons had inflammatory entheseal

abnormalities, alongside 3.2% of thumb and 3.2% of index finger extensor tendons. The difference between fingers is most probably attributable to the difference in function of the index finger and thumb, through which they sustain the most use and frequent microtrauma of all of the digits, which as demonstrated by Benjamin et al, can lead to sustained inflammation and structural damage in genetically primed individuals with psoriatic disease (Benjamin et al., 2007, Benjamin and McGonagle, 2001).

Few other data are available for comparison of entheses of the upper limb, with the majority of previous studies concentrating on the weight-bearing entheses of the lower limbs. Acquacalda and colleagues identified abnormal hypoechogenicity and/or thickening of the tendon/ligament at its bony attachment in a proportion of 22 patients at the distal brachial triceps tendon, although the frequency is not disclosed (Acquacalda et al., 2015). Acquitter et al examined 37 patients with nail, inverse and scalp psoriasis and also identified inflammatory abnormalities in the entheseal attachments at the lateral and medial epicondyles of the elbows, although again, the frequency of abnormalities is not published to facilitate comparison (Acquitter et al., 2016).

The results in this chapter for the lower limb entheses are in accordance with those of previous studies that assessed entheseal abnormalities using (or based on) the Glasgow Enthesitis Ultrasound Scoring System (GUESS) in smaller populations of psoriatic patients (Ash et al., 2012b, Gutierrez et al., 2011, Gisondi et al., 2008, Bandinelli et al., 2013, Moshrif et al., 2017, Acquacalda et al., 2015). Quadriceps enthesitis was the most common site in this study, closely followed by the other knee tendon entheses. Thickness of the quadriceps tendon has been shown to be an independent predictor of the development of PsA in the only published longitudinal study of patients with psoriasis and psoriatic arthritis, where 7 of 28 patients developed inflammatory arthritis (which fulfilled the CASPAR criteria for a diagnosis of PsA) after a mean of 3.5 years (Tinazzi et al., 2011).

Gisondi et al identified similarly high rates to this study of enthesitis at the quadriceps and other knee tendon entheses in an older population with mean age 55.8 years (quadriceps tendon insertion 30.0% vs. 26.0%; proximal patellar tendon 36.6% vs. 20.5%; distal patellar tendon insertion 35.0% vs. 24.7%). Lower rates of enthesitis were observed in the foot and ankle entheses in both studies (Achilles tendon insertion 16.6% vs. 12.3%; plantar fascia insertion into the calcaneus 5.0% vs. 17.1%) (Gisondi et al., 2008). Achilles tendon enthesitis also occurred with comparable frequency (13.2% vs. 12.3% of entheses) in a study of 34 psoriasis patients with a similar mean age (43.5 years vs 40.1 years) and disease duration (16.7 years vs. 16.9 years) (Acquacalda et al., 2015).

Two different authors, Gutierrez and Bandinelli, have also demonstrated a lower incidence of foot and ankle enthesitis compared to the knee. 6.7% and 14.1% of patients, respectively, had thickening of the plantar aponeurosis insertion, and 20.0% and 38% of

patients, respectively, of the Achilles tendon enthesis. At the knee, striking numbers of psoriasis patients were found to have entheseal thickening (distal patellar 68.9% and 59.8% of patients, respectively, compared with 21.9% in this study; proximal patellar 46.7% and 85.8% of patients, respectively, compared with 12.3% in this study; quadriceps tendon 20.0% and 41.3% of patients, respectively, compared with 19.2% in this study) (Gutierrez et al., 2011, Bandinelli et al., 2013). The former study included 45 asymptomatic patients with psoriasis, but no data is published regarding demographic factors such as mean age, PASI score or duration of psoriasis for comparison (Gutierrez et al., 2011). In the latter, Bandinelli studied older patients (mean age 51.6 years) with psoriasis and 'early PsA', defined as musculoskeletal symptom duration of less than one year, which may account for the higher number of patients with entheseal thickening compared with the cohort in this thesis (Bandinelli et al., 2013). Age is likely to be important, with this study and several others reporting a significant correlation between age and the presence of inflammatory enthesitis on ultrasound (Gisondi et al., 2008, Moshrif et al., 2017, Naredo et al., 2011, Ozcakar et al., 2005).

Moshrif et al studied a younger cohort of 50 patients with psoriasis (mean age 33.8 years) with a shorter duration of skin disease (mean 7.7 years), and found much lower rates of asymptomatic ultrasound enthesitis at the knee than Gisondi, Gutierrez and Bandinelli, but similar rates of enthesitis to this study (distal patellar tendon 22.2% vs. 21.9%; proximal patellar tendon 16.7% vs 12.3%; quadriceps tendon 16.7% vs. 19.2% of entheses). However, they observed much higher rates in the Achilles tendon (33.3% vs. 12.3% of entheses) (Moshrif et al., 2017). Most patients within this study had a high BMI, with more than three quarters being overweight and 44% being clinically obese (BMI>30kg/m^2), compared to a mean BMI in this thesis of 28.7kg/m^2. This could translate to a greater burden of microtrauma at these key weight-bearing sites and therefore more enthesitis, although histopathological analysis would have been required to confirm this. Like previous studies, this study found a significant correlation between the presence of ultrasound enthesopathy and BMI (Gisondi et al., 2008, Moshrif et al., 2017). However no association with BMI has been found by others with the presence of ultrasound enthesopathy (Naredo et al., 2011) or mean GUESS score (Gutierrez et al., 2011), although it is observed that mean BMI was notably lower within the latter two studies.

Two other studies have also observed high rates of Achilles tendon enthesopathy (described as either tendon thickening and/or hypoechogenicity), in 56.6% (Ozcakar et al., 2005) and 59.3% (De Simone et al., 2003) of psoriasis patients examined. However, each of these studies included patients with a formal diagnosis of PsA (36.0% and 24.1% respectively) and patients with musculoskeletal signs and symptoms (44.0% and 30.5%, respectively), which is likely to account for the discrepancy between their cohort and those patients in this chapter.

Aside from age and BMI, in terms of other risk factors for subclinical entheseal inflammation, significantly higher rates were observed in this chapter in psoriasis patients who had never smoked (47.2% vs 27.0%, *p*=0.005). The prevalence of smoking has previously been reported to be less among patients with PsA compared with psoriasis patients without arthritis (Eder et al., 2011b, Pattison et al., 2008). Several potential biological mechanisms have been proposed for this observation including the activation of α7 nicotinic acetylcholine receptor by nicotine, which inhibits intracellular pro-inflammatory pathways that are associated with the development of arthritis. Eder et al also demonstrated a protective effect of smoking in the development of PsA, but only in patients who were HLA-Cw06 negative (Eder et al., 2012).

Aside from inflammatory abnormalities, most other studies included assessments of chronic damage lesions such as erosions, enthesophytes and entheseal calcifications. Bone erosions, seen adjacent to 0.2% of entheses in this cohort, were comparably low, reported as 0% (Moshrif et al., 2017, Gisondi et al., 2008, Naredo et al., 2011), 1.1% (Gutierrez et al., 2011), 1.7% (Acquitter et al., 2016) and 3.0% in previous studies (Ash et al., 2012b). Erosions were seen with much greater frequency in those studies which included patients with symptomatic PsA, ranging from 11.8% (Acquacalda et al., 2015) to 21.7% (Bandinelli et al., 2013). In asymptomatic psoriasis patients, enthesophytes are reported with much greater variation, from 0% (Naredo et al., 2011) to 68.3% (Gisondi et al., 2008), but as in this cohort, are reported with the greatest frequency in all studies at the Achilles tendon insertion into the calcaneus (Gisondi et al., 2008, Bandinelli et al., 2013, Ash et al., 2012b). 2.6% of entheses in this cohort demonstrated calcification at the enthesis, which is slightly lower than that identified in other studies of asymptomatic patients with psoriasis by Acquitter et al (4.6%) (Acquitter et al., 2016) and Ash et al (5.0%) (Ash et al., 2012b), and significantly less than that in a study including patients with PsA (25.9%) (Acquacalda et al., 2015), which supports the belief of the progressive nature of structural damage abnormalities between subclinical enthesopathy and symptomatic PsA. No published studies have included the assessment of bony cortex irregularities, seen in 2.2% of entheses in this cohort. No correlations were found between the total chronic damage score and any demographic or clinical parameters.

Beyond the enthesis, sustained inflammation is thought to dissipate to adjacent structures, although few studies have published data in this domain in patients with psoriasis. Only one previous study has included assessments of synovitis, and found more at the knee (23.5% of joints) than the ankle (1.1% of joints) (Naredo et al., 2011). This is mirrored in this cohort, with synovitis identified in 6.8% of knee joints and 1.4% of ankle joints, accompanying adjacent inflammatory entheseal abnormalities. No studies have assessed synovitis in the wrist, elbow and finger joints of asymptomatic patients with psoriasis, but scanning of these joints is warranted given the high frequency of

synovitis seen at the wrist (17.8%) and joints at the base of the thumb and index finger (thumb carpometacarpal joint 15.1%, index finger metacarpophalangeal joint 8.2%).

In terms of feasibility, this study has demonstrated that subclinical enthesopathy, like established PsA, can be very diverse in its presentation and distribution, and requires a broad-reaching sonographic assessment in order to capture the true prevalence of disease. Ultrasound is not able to assess the axial skeleton, and so even with a comprehensive peripheral protocol, there will be patients who are missed unless complementary imaging is performed using MRI or PET scanning. However, it would not be feasible to perform such screening investigations in all patients due to the population prevalence of psoriasis. As shown in previous studies, no associations between the duration of psoriasis (Gisondi et al., 2008, Gutierrez et al., 2011, Naredo et al., 2011) or PASI score (Bandinelli et al., 2013, De Simone et al., 2003, Gisondi et al., 2008, Gutierrez et al., 2011, Naredo et al., 2011), have been found which could help stratify patients for screening.

In the research setting, or in patients where it is desirable to know if there is subclinical enthesopathy, these data show is that it is not adequate to limit the assessment of subclinical arthritis to just the larger entheses of the lower limbs. A high proportion of patients had disease at the elbows (19.2%) and small joints of the hands, particularly the thumbs (6.2%), with a proportion of these patients having no disease at the knee entheses, Achilles tendon and plantar fascia insertions. The inclusion of the small entheses of all fingers meant that the protocol used was lengthy (30-35 minutes). Little useful information was yielded from the middle, ring and index fingers, with only one enthesis showing any inflammatory abnormality and so if removed, could save 15 minutes of scanning time. The thumb and index finger, as discussed, showed significantly higher rates of enthesitis as a consequence of greater use and frequent microtrauma and should therefore continue to be included, but the middle, ring and little finger could be removed from the protocol.

The frequency of power Doppler was low as in previous studies, but should be maintained in the protocol. It requires very little additional time to do, and where seen at entheseal sites, is confirmatory of the presence of abnormal vascularisation which is considered a phenotypical sign of PsA (Aydin et al., 2013a). The assessment of joints for synovitis has rarely been included in previous ultrasound protocols, but as data in this cohort have shown, high rates of synovitis accompany enthesitis, especially in the upper limbs. To further understanding of subclinical arthropathy in patients with psoriasis, future studies should include assessment of joint synovium in addition exploration of other structures within the synovio-entheseal complex, especially those investigating the natural evolution of subclinical enthesopathy or the musculoskeletal response to therapeutic intervention.

3.6 Conclusion

Published prevalence estimates for subclinical enthesitis among patients with psoriasis vary greatly, with low rates influenced by limited parameters used to define enthesopathy and a restriction in the number and distribution of entheses scanned. Using a novel, comprehensive protocol of 19 entheses and 18 joints bilaterally, data in this chapter demonstrate that subclinical enthesitis is very diverse in terms of presentation and distribution, and therefore requires a broad-reaching sonographic assessment including both the upper and lower limb entheses in order to fully capture the true prevalence of disease.

60.3% of patients were found to have an abnormal ultrasound, and 49.3% had at least one potentially modifiable inflammatory abnormality. Older age and higher body mass index demonstrated weak association with the burden of entheseal and synovial inflammation. The larger, weight bearing entheses were most frequently involved especially at the knee, Achilles tendon, plantar fascia and elbows, although up to 6% of digital tendon insertions showed inflammatory changes (thumb and index fingers only). Entheseal thickening was the most prevalent abnormality overall, followed by enthesophyte formation and hypoechogenicity. Power Doppler signal was an uncommon finding (0.2% of entheses/6.8% of patients), reflecting the early stage of musculoskeletal disease in these asymptomatic patients.

Chapter 4
Comparison of the Ultrasound Appearances of Subclinical Enthesitis, Bursitis, Tenosynovitis and Synovitis in Patients with Psoriasis at First Presentation to Secondary Care and Healthy Controls

4.1 Introduction

Enthesitis as the primary lesion in psoriatic arthritis has gained further credibility in recent years from animal models showing the importance of tumour necrosis factor (TNF) and the interleukin (IL)-23/Th17 axis in the development of enthesopathy (Sherlock et al., 2012). Mirroring the mouse model data, it appears that therapies designed to treat psoriasis by antagonising TNF and/or IL-23 in man are effective for entheseal pathology, although available data are only secondary outcomes (McInnes et al., 2013, Kavanaugh et al., 2014b, Kavanaugh et al., 2015). Historically, enthesitis was described as an isolated disorder at the precise point where tendons anchor onto bone, however this notion has been discarded with the introduction of the concept of the synovio-entheseal complex (SEC) (McGonagle et al., 2007). The enthesis is now understood to form an integral part of an 'enthesis organ', whereby normal enthesis-related fibrocartilages are functionally integrated with the adjacent soft tissues, and are dependent on immediately adjacent synovium (Benjamin and McGonagle, 2001, Benjamin et al., 2004). The fibrocartilages adjacent to bones are often located inside joints, which form synovial-lined bursa. Synovium provides lubrication and nutrition to aid the function of the enthesis, and filters debris that occurs as a result of biomechanical stress, which is subsequently removed by resident macrophages. This close functional integration is thought to explain the progression from primary enthesitis to arthritis, whereby there is dissipation of inflammation to adjacent structures over time. This would account for the presence of synovial hypertrophy seen on ultrasound in some of the 73 psoriasis patients with subclinical enthesitis examined in the previous chapter. To obtain a more comprehensive picture of the early subclinical changes that may develop within the entire SEC in patients with moderate to severe psoriasis, it would therefore appear logical to carefully assess the adjacent bursa and joints in patients with enthesopathy and make comparisons with the non-psoriatic population.

SECs can be found at multiple sites around the body, and although they typically arise within the immediate vicinity of insertions and within the joint capsule, may also occur at sites distant to insertion points. In a human TNF transgenic mouse model of inflammatory arthritis akin to spondyloarthritis, serial sacrifice of animals to ascertain the origins of

disease demonstrated infiltration by inflammatory cells in the peritendinous regions that equated with tenosynovitis (Hayer et al., 2007). There was no actual tendon insertion at this location, but inflammation occurred at the site at which the tendon traversed bony prominences. Fibrocartilage was present on the bony surface and adjacent tendon at the point of contact, creating what has been termed a 'function enthesis'. Such regions share an identical insult of mechanical shearing forces and stress, which have been shown to produce entheseal type pathology on magnetic resonance imaging (MRI) (McGonagle et al., 2012). It is therefore postulated that tenosynovitis may also occur in patients with psoriasis and subclinical enthesopathy. Some degree of abnormality in the SEC would also be expected in 'healthy' individuals (without known musculoskeletal disease) as a consequence of high body mass and age-related degeneration, although to what extent is unknown.

Using a refined ultrasound protocol based on the findings of that used in Chapter 3, this chapter aims to determine the full spectrum (lesion type, anatomical location and severity) and frequency of imaging abnormalities within the full synovio-entheseal complex (entheses and adjacent bursa, tendon sheaths and joints) in patients with moderate to severe psoriasis and subclinical enthesitis and compare those imaging abnormalities with a healthy control group of volunteers, to try differentiate between those abnormalities that are likely to be pathological and those that are physiological (due to age and weight-related degeneration).

This chapter also aims to provide reference thresholds for entheseal thickness for those tendons where values have not been published in the literature, to be used in a novel sonographic scoring system based on a consensus definition of enthesopathy. This scoring system will be used to further assess the feasibility of using ultrasound for the detection of subtle abnormalities at the synovio-entheseal complex in asymptomatic patients with psoriasis compared to healthy volunteers, for use in a subsequent research trial of an investigational medicinal product, described in the next chapter. Finally, this chapter aims to assess the utility of the PEST questionnaire in a cohort of patients with psoriasis and subclinical enthesitis and compare the patient-reported responses with clinical examination and ultrasound findings.

4.2 Methods

4.2.1 Participant Identification and Recruitment

4.2.1.1 Patients with Psoriasis

Twenty-eight adult patients (aged 18 and over) with moderate to severe chronic plaque psoriasis, without clinical psoriatic arthritis (PsA) but with ultrasound evidence of active subclinical enthesitis and 23 healthy controls were recruited.

Patients with psoriasis were approached for participation from a pilot study of 73 adult patients with moderate to severe psoriasis (defined as a Psoriasis Area and Severity Index (PASI) score of 10 or more), who consented to undergo a short, non-invasive ultrasound of their peripheral joints and tendons following their first 'new patient' consultation within the Leeds Centre for Dermatology at Chapel Allerton Hospital (Leeds Teaching Hospitals Trust) (Chapter 3). These patients were included in the pilot cohort as they had a diagnosis of chronic plaque psoriasis (confirmed by a dermatologist, the candidate LS), with symptoms for more than twelve months and had not previously received any systemic immunosuppression, PUVA phototherapy or biologic agent that could potentially have had an impact on the evolution of any subclinical musculoskeletal pathology. Patients were excluded if they had any symptoms suggestive of PsA, defined clinically as early morning stiffness (lasting 15 minutes or more in duration) and joint swelling, or if they fulfilled the CASPAR criteria (Taylor et al., 2006).

Of the 73 patients who underwent a short ultrasound, 44 (60.3%) had abnormalities; 8 of these had changes in keeping with chronic damage only (entheseal calcification, enthesophytes, bone erosions and/or bone cortex irregularities), while the remaining 36 had at least one inflammatory lesion (entheseal thickening, hypoechogenic change and or entheseal power Doppler signal). Only those patients with potentially modifiable inflammatory lesions were approached for this study. Psoriasis patients who entered this study were also to be considered for participation in a clinical trial of an investigational biological drug (ustekinumab), and so needed to meet the strict criteria for receiving this therapy (Appendix 6) and not have any contraindications to magnetic resonance imaging (MRI), e.g. a pacemaker or aneurysm coil in situ.

On identification of active subclinical enthesitis at ultrasound, patients were invited back for a longer, more detailed ultrasound scan to assess for bursitis, tenosynovitis and synovitis in addition to enthesopathy, with lesion severity scoring and tendon insertion thickness measurements. Patients were given a written information sheet to take home which provided details of the scan and also about the potential for inclusion in the drug trial. Scans took place within one to three weeks of the initial scan, and a full clinical assessment was performed again immediately beforehand to confirm eligibility, given the fluctuant and unpredictable nature of psoriasis. Written consent was obtained prior to this assessment for any clinical, questionnaire, serological and imaging data to be used in an anonymised format for research purposes, in addition to data storage.

4.2.1.2 Healthy Control Group Volunteers

Healthy controls were recruited from staff members and their family and friends in the Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM) and Leeds Institute of Cancer and Pathology (LICAP) at the University of Leeds. Recruitment was by direct approach or by invitational email to research groups. Volunteers were excluded if they

had a history of psoriasis, PsA or any other rheumatological disorder. Attempts were made to identify healthy controls with similar demographics to patients (age, sex, BMI), although no specific case matching was performed. A detailed information sheet was provided to interested volunteers at least 24 hours prior to participation, and written consent was obtained to use and store any data collected for research purposes.

Participants in both groups were asked to complete the Psoriasis Epidemiology Screening Tool (PEST) (Appendix 1). In addition, patients with psoriasis completed a Dermatology Life Quality Index (DLQI) questionnaire (Appendix 3).

4.2.2 Inclusion/Exclusion Criteria

4.2.2.1 Patients with psoriasis

Male and female patients over the age of 18 with moderate to severe chronic plaque psoriasis (Psoriasis Area and Severity Index (PASI) ≥10) with evidence of active subclinical enthesitis on ultrasound were included. Findings at ultrasound must have included thickening, hypoechogenic change or power Doppler signal in at least one peripheral tendon insertion site. Participants must also not have any contraindications to biologic therapy (Appendix 6) or MRI scanning (Appendix 10). Further detail regarding the inclusion and exclusion criteria can be found in Chapter 3.2.2.

4.2.2.2 Healthy Control Group Volunteers

Males and females over the age of 18 without a personal history of psoriasis, psoriatic arthritis or other rheumatological condition, or history of use of any immunosuppressant or long-term non-steroidal anti-inflammatory therapy (for any indication) were eligible. Volunteers must not have had any contraindications to MRI as they may also have been asked to undergo a scan of their axial skeleton using MRI.

4.2.3 Data Collection

Data collection was solely carried out by the candidate (LS). Recruitment and data collection took place over two years (May 2013 – May 2015), through all four seasons to allow for natural variation in psoriasis severity related to outdoor ultraviolet levels. Two experienced musculoskeletal sonographers (LH and AJ) performed ultrasound scans within the Leeds Musculoskeletal Biomedical Research Unit (LMBRU) at Chapel Allerton Hospital.

Once written consent was obtained, three types of data were collected from psoriasis patients and recorded for research purposes: participant-reported data, clinical examination data and imaging data. Participant-reported data comprised of

demographics, skin type, social history (smoking, alcohol and employment), past medical and surgical history, history of skin and joint disease, family history, medications (current prescribed, over-the-counter, alternative and psoriasis-specific medications, and any previous psoriasis therapies), age of psoriasis symptom onset, areas ever affected by psoriasis, areas currently affected by psoriasis and current or previous musculoskeletal symptoms. Participants also self-completed two questionnaires (DLQI (psoriasis patient group only) and PEST).

Clinical examination data was collected to assess the severity of psoriasis, the severity of any psoriatic nail disease, baseline observations (height, weight, blood pressure and heart rate) and the presence of any clinical signs of psoriatic arthritis (joint swelling and/or tenderness, clinical enthesitis or dactylitis).

Data was collected onto paper case record forms (CRF) and then transcribed into an encrypted, password-protected database held on a secure drive within the University of Leeds. Paper record forms are stored in a locked filing cabinet within a locked room within LIRMM, in accordance with the University's Information Security Policy.

Healthy volunteers provided written consent for the collection of participant-reported and imaging data and for its use for research purposes. Participant reported data included demographics, skin type, social history (smoking, alcohol and employment), past medical and surgical history, history of skin and joint disease, family history and medication history (current prescribed, over-the-counter and homeopathic). Clinical observations were recorded (height, weight, blood pressure and heart rate).

4.2.4 Clinical Assessment

4.2.4.1 Psoriasis Patients

4.2.4.1.1 Psoriasis Severity and Impact

Patients were fully exposed down to their underwear and a detailed assessment made of the distribution, extent, thickness, degree of scaling and redness of psoriatic plaques. BSA and PASI (Appendix 7) were calculated. The nails were assessed for pitting, onycholysis, plate crumbling, leukonychia, red spots in the lunula, oil spot dyschromia and nail bed hyperkeratosis, and a modified Nail Area and Severity (mNAPSI) score calculated (Appendix 8). Impact of psoriasis on quality of life was assessed using the patient-completed Dermatology Life Quality Index (DLQI) questionnaire.

4.2.4.1.2 Psoriatic Arthritis

While the patient was exposed, several entheseal sites were examined for clinical signs of enthesitis. Direct pressure was applied with sufficient force to just blanche the

examiners fingernail to elicit tenderness if present. Clinical examination was performed prior to ultrasound to prevent bias. The following sites were evaluated:

- 1st and 7th costochondral joints
- Supraspinatus insertion
- Medial and lateral epicondyles of the humerus
- Anterior and posterior superior iliac spines
- Iliac crest
- 5th lumbar process
- Greater trochanter
- Medial condyle of the femur
- Quadriceps insertion at the patella
- Inferior pole of the patella
- Tibial tubercle
- Proximal Achilles
- Plantar fascia insertion

From these, three of the most widely published clinical entheseal scores were calculated – the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), the Spondyloarthritis Research Consortium of Canada (SPARCC) score and the Leeds Enthesitis Index (LEI). Table 4.1 details which sites are included in these scores.

Site	MASES	SPARCC	LEI
1st costochondral	+		
7th costochondral	+		
Supraspinatus insertion		+	
Lateral epicondyle humerus		+	+
Medical epicondyle humerus		+	
5th lumbar spinous process (one point)	+		
Posterior-superior iliac spine	+		
Anterior-superior iliac spine	+		
Iliac crest	+		
Greater trochanter		+	
Medial femoral condyle			+
Inferior pole patella		+	
Tibial tubercle		+	
Proximal Achilles	+	+	+
Plantar Fascia Insertion		+	

Table 4.1. Published enthesitis indices. All assess the enthesis bilaterally unless stated. (MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC: Spondyloarthritis Research Consortium of Canada; LEI: Leeds Enthesitis Index).

Fingers and toes were assessed for any fusiform swelling or tenderness consistent with dactylitis. All peripheral joints were examined for tenderness or swelling. The clinical assessments were performed by the candidate (LS). Patients were also asked to self-complete a validated PsA screening questionnaire (PEST) for comparison with clinical and ultrasound outcomes, which was assessed only after the participants had undergone their ultrasound scan.

4.2.4.1.3 Healthy Controls

No clinical examination took place unless the volunteer requested a medical opinion to clarify their eligibility in terms of skin or joint signs, or a participant reported pain or swelling at a particular site on their screening questionnaires.

4.2.5 Laboratory Assessment

To ensure that patients and healthy control group volunteers did not have rheumatoid arthritis or any other rheumatological disorder, a number of serological assessments were performed and are described in Chapter 3.2.5.

In addition, two risk alleles (class I surface antigens) for psoriatic arthritis amongst patients with psoriasis were measured; HLA-B27 and HLA-Cw06:

- HLA-Cw06 and HLA-B27 were measured by single antigen bead testing (median fluorescent intensity, MFI)

All of the tests above were measured using commercial kits in the hospital diagnostic laboratory.

4.2.6 Ultrasonography

4.2.6.1 Ultrasound Equipment and Protocol

All participants were examined with the same ultrasound protocol. Ultrasound was performed using a pulse-echo approach with a brightness-mode (B-mode) display. Grey scale ultrasound and power Doppler (PD) examinations were performed by the same two dedicated research musculoskeletal sonographers (AJ and LH) who performed the initial shorter ultrasound in the patients with psoriasis. It was therefore impossible to blind the sonographers to which participants were in the psoriasis group and which were healthy volunteers as they had often met the psoriasis patients previously. The sonographers were asked not to refer back to the images and results from the previous, shorter ultrasound scan in the psoriasis patient group so as not to influence their findings on the second scan. Further detail regarding the ultrasound equipment and settings can be found in Chapter 3.1.6.

Using the results from the scans of the pilot cohort of 73 patients, it was deemed unnecessary to scan all fingers as there were such negligible rates of subclinical enthesitis and synovitis in the middle, ring and little fingers. In addition, scanning the hands was time consuming, even when just having a 'quick look' without scoring and thickness measurements. The protocol in the pilot study included 20 entheses and 28 joints for both hands, which took as long to scan as the feet, ankles, knees and elbows combined, and yielded only one patient with thickening of the middle finger flexor digitorum profundus enthesis and another with synovitis unilaterally in the middle finger metacarpophalangeal joint. In contrast, at least one thumb tendon enthesis was involved in 9.6% of patients and index finger tendon enthesis in 6.8%. As these two digits are the ones that are likely to sustain the most microtrauma from daily use, it was decided to keep these in the ultrasound protocol to compare with the healthy control group volunteers (Figure 4.1).

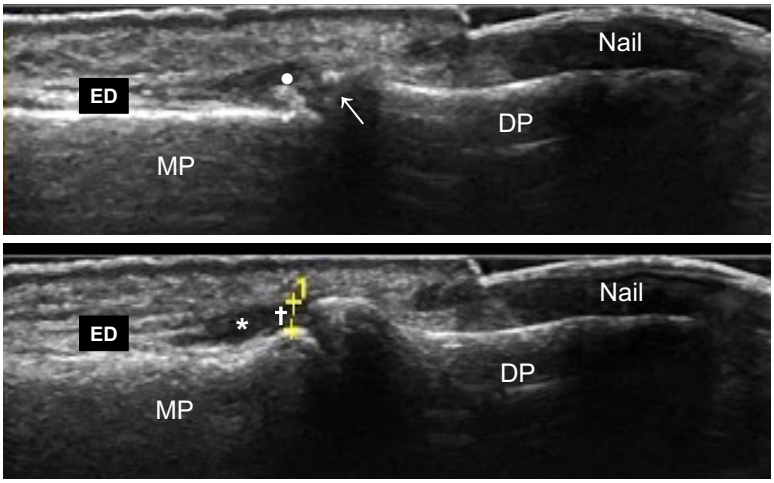

Figure 4.1. Left index finger extensor digitorum tendon enthesis demonstrating entheseal thickening (†, grade 1), hypoechogenicity (✶, grade 2), calcification (•, grade 1), bone cortex irregularities and enthesophytes (↑, grade 2) in an asymptomatic patient with moderate to severe psoriasis. ED: Extensor digitorum; MP: Middle phalynx; DP: distal phalynx.

Given the rates of synovitis seen in the pilot cohort, the ultrasound protocol was extended to include bursal hypertrophy/power Doppler signal at several sites, and tenosynovitis (hypoechoic and/or thickened tissue within the tendon sheath), which all form part of the synovio-entheseal complex (McGonagle et al., 2007). The full ultrasound clinical record form (CRF) can be found in Appendix 9.

Table 4.2, Table 4.3, Table 4.4 and Table 4.5 summarise the tendon entheses and corresponding bone insertion sites, the bursa, the sites for tenosynovitis and the synovial joints scanned.

Anatomical Site	Tendon Enthesis	Bone Insertion Point
Thumb	Flexor pollicis longus	Base of distal phalynx
	Extensor pollicis longus	Base of distal phalynx
Index Finger	Flexor digitorum profundus	Base of distal phalynx
	Extensor digitorum	Base of distal phalynx
Elbow	Common extensor	Lateral epicondyle of humerus
	Common flexor	Medial epicondyle of humerus
	Distal brachial triceps	Olecranon process of ulna
Knee	Quadriceps	Superior pole of patella
	Proximal patella	Inferior pole of patella
	Distal patella	Anterior tibial tuberosity
Foot and Ankle	Peroneal brevis	5th metatarsal base lateral tuberosity
	Achilles	Superior pole of calcaneus
	Plantar fascia	Inferior pole of calcaneus

Table 4.2. Tendon entheses and bone insertion sites scanned (grey scale and power Doppler assessments)

Anatomical Site		Bursa
Upper Limb	Elbow	Olecranon bursa
Lower Limb	Knee	Suprapatellar bursa
		Superficial infrapatellar bursa
		Deep infrapatellar bursa
	Ankle	Retrocalcaneal bursa

Table 4.3. Bursa scanned for grey scale hypertrophy and power Doppler signal.

Anatomical Site		Tendon Sheath
Upper Limb	Thumb	Flexor pollicis longus
		Extensor pollicis longus overlying interphalangeal joint
		Extensor pollicis longus overlying carpometacarpal joint
	Index Finger	Flexor digitorum profundus
		Extensor digitorum
	Wrist	Extensor compartment 1 - Abductor Pollicis Longus and Extensor Pollicis Brevis
		Extensor compartment 2 - Extensor Carpi Radialis, Longus and Brevis
		Extensor compartment 3 - Extensor Pollicis Longus
		Extensor compartment 4 - Extensor Digitorum

Anatomical Site		Tendon Sheath
		Extensor compartment 5 - Extensor Digiti Minimi
		Extensor compartment 6 - Extensor Carpi Ulnaris
Lower Limb	Knee	Quadriceps
		Proximal patella
		Distal patella
	Foot and Ankle	Posterior tibialis
		Flexor digitorum longus
		Flexor hallucis longus
		Anterior tibialis
		Extensor hallucis longus
		Extensor digitorum longus
		Peroneal longus
		Peroneal brevis

Table 4.4. Tendon sheaths scanned for tenosynovitis (grey scale and power Doppler assessments)

Limb	Joint
Upper Limb	Thumb interphalangeal
	Thumb carpometacarpal
	Index finger distal interphalangeal
	Index finger proximal interphalangeal
	Index finger metacarpophalangeal
	Wrist
	Elbow
Lower Limb	Knee
	Ankle

Table 4.5. Joints scanned for synovitis (grey scale and power Doppler assessments)

All structures were examined in at least two perpendicular planes, and care was taken to obtain comparable views of the contralateral side. Joints were continually assessed during the scanning of the tendon insertions and bursae. The positioning of participants is described in Chapter 3.1.6. The retrocalcaneal bursa around the heel was assessed during scanning of the Achilles tendon and plantar aponeurosis insertions while the participant lay prone. Examinations of the medial and lateral tendon sheaths of the foot occurred with the patient sat supine and with the knee flexed to 30 degrees, following assessment of the peroneal brevis tendons. Knee bursae (suprapatellar, superficial

infrapatellar and deep infrapatellar) were also scanned in this position during imaging of the knee tendon entheses. The olecranon bursa was assessed at the time of scanning the distal brachial triceps tendon.

4.2.6.2 Ultrasound Image Interpretation

Ultrasound images were interpreted at the time of scanning. Enthesopathy, bone erosion, tenosynovitis and synovial hypertrophy were identified according to the definitions provided by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Special Interest Group for Musculoskeletal Ultrasound in Rheumatology (Figure 4.2, Figure 4.3, Figure 4.4 and Figure 4.5) (Wakefield et al., 2005). Bursitis was defined as a well circumscribed, localised anechoic or hypoechoic area at the site of an anatomical bursa which was compressible by the transducer with bursal wall thickening, with or without periburseal or intraburseal power Doppler signal (Schmidt et al., 2004).

> ***OMERACT definition of enthesopathy:*** *'Abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity.'*

Figure 4.2. OMERACT definition of enthesopathy (Wakefield et al., 2005).

> ***OMERACT definition of bone erosion: '****An intraarticular discontinuity of the bone surface that is visible in two perpendicular planes'.*

Figure 4.3. OMERACT definition of enthesopathy (Wakefield et al., 2005).

> ***OMERACT definition of tenosynovitis: '****Hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in two perpendicular planes and which may exhibit Doppler signal'.*

Figure 4.4. OMERACT definition of tenosynovitis (Wakefield et al., 2005).

OMERACT definition of synovial hypertrophy: *'Abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intraarticular tissue that is non-displaceable and poorly compressible and which may exhibit Doppler signal.'*

Figure 4.5. OMERACT definition of synovial hypertrophy (Wakefield et al., 2005).

The following parameters were assessed for enthesopathy:

- Tendon thickness at its bony attachment site
- Hypoechoic change within the tendon at the bony attachment site
- Power Doppler signal within the tendon at the bony attachment site
- Calcification within the tendon at the bony attachment site
- Enthesophytes arising around the tendon attachment site
- Erosions arising within the bone around the tendon attachment site
- Irregularities within the usually smooth bony cortex around the tendon attachment site

The following parameters were assessed for tenosynovitis:

- Hypoechoic tendinous sheath thickening
- Power Doppler signal within the tendon sheath

The following parameters were assessed for synovitis:

- Synovial hypertrophy (non-compressible hypoechoic intracapsular area)
- Power Doppler signal within the synovial intraarticular tissue

The following parameters were assessed for bursitis:

- Bursal wall hypertrophy and/or synovial proliferation with a well circumscribed hypoechoic area
- Periburseal or intraburseal Power Doppler signal

4.2.6.3 Ultrasound Scoring

Ultrasound parameters were scored either quantitatively or semi-quantitatively. Thickness measurements and bone erosions were scored quantitatively, while hypoechogenicity, power Doppler signal, calcifications, enthesophytes, bone cortex irregularities, bursal hypertrophy, tenosynovitis and synovitis were score semi-quantitatively.

4.2.6.3.1 Entheseal Thickness

The thickness of each enthesis was measured at its widest point at the insertion point on longitudinal scans. Three measurements were taken per enthesis in an attempt to avoid error due to transducer obliquity and the average of the three recorded.

Where available, normal values for the thickness of each insertion were accepted as reported in the literature and are listed in Table 4.6 (Balint et al., 2002, Gibbon and Long, 1999, de Miguel et al., 2009, Roberts et al., 1999, van Holsbeeck and Introcaso, 1991).

Tendon	Thickness threshold	Reference
Achilles	≥ 5.29mm	van Holsbeeck M, Introcaso J. In: van Holsbeeck M, Introcaso J, eds. Musculoskeletal Ultrasound. St. Louis: Mosby Year Book, 1991:318. Cited by Balint P, Kane D, Wilson H et al. Ann Rheum Dis 2002;61:905-10.
Plantar Aponeurosis	≥ 4.4mm	Gibbon W, Long G. Skeletal Radiol 1999;28:21-6. Cited by Balint P, Kane D, Wilson H et al. Ann Rheum Dis 2002;61:905-10.
Quadriceps	≥ 6.1mm	van Holsbeeck M, Introcaso J. In: van Holsbeeck M, Introcaso J, eds. Musculoskeletal Ultrasound. St. Louis: Mosby Year Book, 1991:318. Cited by Balint P, Kane D, Wilson H et al. Ann Rheum Dis 2002;61:905-10.
Proximal Patellar	≥ 4.0mm	van Holsbeeck M, Introcaso J. In: van Holsbeeck M, Introcaso J, eds. Musculoskeletal Ultrasound. St. Louis: Mosby Year Book, 1991:318. Cited by Balint P, Kane D, Wilson H et al. Ann Rheum Dis 2002;61:905-10.
Distal Patellar	≥ 4.0mm	van Holsbeeck M, Introcaso J. In: van Holsbeeck M, Introcaso J, eds. Musculoskeletal Ultrasound. St. Louis: Mosby Year Book, 1991:318. Cited by Balint P, Kane D, Wilson H et al. Ann Rheum Dis 2002;61:905-10.
Distal Brachial Triceps	≥ 4.3mm	de Miguel E, Cobo T, Munoz-Fernandez S et al. Ann Rheum Dis 2009;68:169-74.

Table 4.6. Published tendon insertion measurement thresholds, above which entheses are deemed thickened.

Normal thickness measurements are not published for the other tendons examined. While several studies have used ultrasound to look at entheseal thickening in patients with psoriasis and included upper limb sites such as the common flexor tendon, no measurement values are provided, with thickening being assessed subjectively by the sonographer. One of the objectives of this pilot study was to determine thresholds for entheseal thickness for those tendons where measurements have not been published be used as a more objective measure in a feasibility study of an investigational medicinal product, by allowing grading of severity and a more comprehensive assessment of change (Chapter 5).

Within the literature providing measurements, only two deliver any methodology as to how the thresholds were reached. de Miguel and colleagues (de Miguel et al., 2009) assessed a number of different entheses during the development of an ultrasound enthesitis score and used those cited by Balint et al (Balint et al., 2002), with the exception of the distal brachial triceps tendon for which no published measurement exists. The value used was based on their own control group mean plus one standard deviation, to which 0.1mm was then added '*to reduce subjectivity*'. An alternative method was used by Gibbon and Long (Gibbon and Long, 1999), who measured the plantar fascia in 48 asymptomatic control subjects (96 heels) and used the upper limit of the range as the cut off when examining a cohort of patients with inferior heel pain. Both methods were applied to the data from the 23 volunteers in the healthy control group and comparisons were made for those tendons where a measurement had been published to determine which was more suited to this data. The results can be found in Chapter 4.4.5.1.

Once determined from the healthy control group, the reference entheseal thickness thresholds were applied to the data from the patients with psoriasis. The published values were used where available, i.e. for the Achilles tendon, plantar aponeurosis, three knee tendons and distal brachial triceps tendon.

The extent of thickening was assessed quantitatively in line with that used in a previous imaging study of peripheral subclinical enthesitis by Ash et al (Ash et al., 2012b).

0 = Less than threshold

1 = Greater than threshold but by less than1mm

2 = ≥1mm above threshold but <2mm

3 = ≥2mm above threshold

4.2.6.3.2 Bone Erosions

Erosions were scored quantitatively based on the diameter of lesions. The largest erosion at any one site was selected for scoring:

0 = absence of erosions

1 = present and <2mm in diameter

2 = present and 2-3mm in diameter

3 = present and ≥ 3mm in diameter

4.2.6.3.3 Other Grey Scale Assessments

The presence and severity of all other grey scale assessments (entheseal hypoechogenicity, calcifications, enthesophytes, bone cortex irregularities, bursal hypertrophy, tenosynovitis and synovial hypertrophy) were scored semi-quantitatively:

0 = absence

1 = mild

2 = moderate

3 = marked/severe

4.2.6.3.4 Power Doppler Assessments

The presence and severity of power Doppler signal at the entheses, tendon sheaths and joint synovium were scored semi-quantitatively:

0 = absence

1 = mild (≤3 isolated signals)
2 = moderate (>3 isolated signals or confluent signal in <50% of the area under examination)
3 = marked (signals in >50% of the area under examination)

4.2.6.3.5 Scoring Systems

Similar to the widely published Glasgow Ultrasound Enthesitis Score (GUESS) score (Balint et al., 2002) and Sonographic Enthesitis Index (SEI) (Alcalde et al., 2007), summative scores were calculated to allow group comparisons of the extent of enthesopathy, although expanded here to include more entheseal sites and parameters (e.g. hypoechogenicity, power Doppler signal, bone cortex irregularities) which are now accepted as relevant since the publication of the GUESS and SEI scores in 2002 and 2007 respectively (D'Agostino et al., 2003, Ash et al., 2012b, Wakefield et al., 2005, de Miguel et al., 2009). The GUESS score involves the calculation of one total score, whereas the SEI is composed of two summative scores; the SEI-A, including those signs of acute injury (thickening, hypoechogenicity, peritendinous oedema and bursitis (where appropriate)), and the SEI-C, which includes chronic changes (tendon tear, loss of

thickness, calcification and bone erosion). Using this as a template, the following scores were calculated:

- ***Enthesopathy Inflammation Score:*** The sum of scores from the assessment of entheseal thickness, hypoechogenicity and power Doppler signal in all tendons, plus any bursal hypertrophy and power Doppler signal where appropriate, at all entheseal sites.
  Maximum score: 294

- ***Enthesopathy Chronicity Score:*** The sum of scores from the assessment of entheseal calcification(s), enthesophytes, bone erosions and bone cortex irregularity, at all entheseal sites.
  Maximum Score: 312

- ***Total Enthesopathy Score:*** The sum of the inflammation and chronicity scores.
  Maximum Score: 606

In addition, scores were calculated for tenosynovitis and synovitis:

- ***Tenosynovitis Score:*** The sum of scores from the grey scale assessment of tendon sheath thickening/hypoechogenicity and power Doppler signal at all examined sites.
  Maximum Score: 264

- ***Synovitis score:*** The sum of the scores from the grey scale assessment of synovial hypertrophy/proliferation and power Doppler signal from all examined joints.
  Maximum Score: 144

Scores were expected to be low as patients were included on the basis of no known rheumatological disease and no persistent symptoms in keeping with a diagnosis of psoriatic arthritis. The full scoring systems used (with parameters and anatomical sites) were as follows:

4.2.6.3.6 Enthesopathy Scoring System

The full enthesopathy scoring system is described in Chapter 4.4.5.1. using the results of the different methods to calculate entheseal thickness.

4.2.6.3.7 Tenosynovitis Scoring System

All scored 0-3, maximum possible 264.

THUMB:

- *Flexor pollicis longus tendon*
    1. GS Tenosynovitis
    2. PD Tenosynovitis
- *Extensor pollicis longus tendon overlying the interphalangeal joint*
    1. GS Tenosynovitis
    2. PD Tenosynovitis
- *Extensor pollicis longus tendon overlying the carpometacarpal joint*
    1. GS Tenosynovitis
    2. PD Tenosynovitis

INDEX FINGER:

- *Flexor digitorum profundus tendon*
    1. GS Tenosynovitis
    2. PD Tenosynovitis
- *Extensor digitorum tendon*
    1. GS Tenosynovitis
    2. PD Tenosynovitis

WRIST:

- *Extensor compartment 1 – Abductor pollicis longus and extensor pollicis brevis tendons*
    1. GS Tenosynovitis
    2. PD Tenosynovitis
- *Extensor compartment 2 – Extensor carpi radialis, longus and brevis tendons*
    1. GS Tenosynovitis
    2. PD Tenosynovitis
- *Extensor compartment 3 – Extensor pollicis longus tendon*
    1. GS Tenosynovitis
    2. PD Tenosynovitis
- *Extensor compartment 4 – Extensor digitorum tendon*
    1. GS Tenosynovitis
    2. PD Tenosynovitis
- *Extensor compartment 5 – Extensor digiti minimi tendon*
    1. GS Tenosynovitis
    2. PD Tenosynovitis
- *Extensor compartment 6 – Extensor carpi ulnaris tendon*
    1. GS Tenosynovitis
    2. PD Tenosynovitis

KNEE:

- *Quadriceps tendon*

1. GS Tenosynovitis
2. PD Tenosynovitis

- *Proximal patellar tendon*
  1. GS Tenosynovitis
  2. PD Tenosynovitis
- *Distal patellar tendon*
  1. GS Tenosynovitis
  2. PD Tenosynovitis

FOOT AND ANKLE:

- *Posterior tibialis tendon*
  1. GS Tenosynovitis
  2. PD Tenosynovitis
- *Flexor digitorum longus tendon*
  1. GS Tenosynovitis
  2. PD Tenosynovitis
- *Flexor hallucis longus tendon*
  1. GS Tenosynovitis
  2. PD Tenosynovitis
- *Anterior tibialis tendon*
  1. GS Tenosynovitis
  2. PD Tenosynovitis
- *Extensor hallucis longus tendon*
  1. GS Tenosynovitis
  2. PD Tenosynovitis
- *Extensor digitorum tendon*
  1. GS Tenosynovitis
  2. PD Tenosynovitis
- *Peroneal longus tendon*
  1. GS Tenosynovitis
  2. PD Tenosynovitis
- *Peroneal brevis tendon*
  1. GS Tenosynovitis
  2. PD Tenosynovitis

4.2.6.3.8 Synovitis Scoring System

All scored 0-3, maximum possible 144.

THUMB:

- *Interphalangeal joint*
  1. GS Synovitis

2. PD Synovitis

- *Carpometacarpal joint*
  1. GS Synovitis
  2. PD Synovitis

INDEX FINGER:

- *Distal interphalangeal joint*
  1. GS Synovitis
  2. PD Synovitis
- *Proximal interphalangeal joint*
  3. GS Synovitis
  4. PD Synovitis
- *Metacarpophalangeal joint*
  5. GS Synovitis
  6. PD Synovitis

WRIST:

- *Wrist joint*
  1. GS Synovitis
  2. PD Synovitis

ELBOW:

- *Lateral elbow joint*
  1. GS Synovitis
  2. PD Synovitis
- *Medial elbow joint*
  1. GS Synovitis
  2. PD Synovitis
- *Posterior elbow joint*
  1. GS Synovitis
  2. PD Synovitis

KNEE:

- *Knee joint*
  1. GS Synovitis
  2. PD Synovitis

ANKLE:

- *Midline ankle joint*
  1. GS Synovitis
  2. PD Synovitis

FOOT:

- *Tarsometatarsal joint (between the base of 5th metatarsal and cuboid bone)*
  1. GS Synovitis
  2. PD Synovitis

4.3 Statistical Analysis

Categorical data are expressed as frequencies, and continuous variables are given as means (standard deviation, s.d.) or medians (interquartile range, IQR), depending on the distribution. Pearson's χ^2 test was used to compare the frequencies of sonographic abnormalities between participant groups, and the Mann-Whitney *U* test was used to compare ultrasound scores, in addition to categorical variables (gender, skin type, smoking history). Comparisons between independent means were analysed using Student's *t* test for continuous variables (age, BMI, alcohol consumption). Linear correlation between ultrasound scores (inflammation, chronic damage, total enthesopathy, tenosynovitis and synovitis) and demographic (gender, age, BMI, smoking history) and clinical covariates (age of psoriasis onset, duration of psoriasis, PASI, BSA, mNAPSI, number of psoriatic sites) were analysed by Spearman rank correlation or rank biserial r_b (Somers *D*) depending on the type of data analysed; absolute rho values >0.3 and d values >0.4 are considered to indicate substantive correlation. *p* values are all two-sided and <0.05 were considered statistically significant. Statistical analysis was performed using IBM© SPSS© version 24.0.

4.4 Results

4.4.1 Participant Characteristics

4.4.1.1 Patients with Psoriasis

36 patients with moderate to severe psoriasis had abnormalities on their initial ultrasound scan consistent with inflammatory subclinical enthesitis. As part of their first clinical assessment (and standard NHS care within Leeds Teaching Hospitals NHS Trust), all patients with moderate to severe psoriasis have a series of serological investigations to ascertain their eligibility for immunosuppressive therapy, including a full blood count (FBC), urea and electrolytes (U&E), liver function tests (LFTs), C-reactive protein (CRP) level, cholesterol and triglycerides, anti-nuclear antibody (ANA) titre, hepatitis B and C serology and a QuantiFERON®-TB Gold test to detect mycobacterium tuberculosis (the cause of tuberculosis). Of these 36 patients, three were found to have abnormalities that precluded them from receiving a biologic drug without further investigation and treatment. One had a positive QuantiFERON-TB Gold test suggestive of latent tuberculosis, another had deranged LFTs secondary to alcohol excess and the third had a high ANA titre (anti-La antibody), requiring further investigation. These patients were therefore ineligible for this study, as recruits to this study were also asked to consider participation in a pilot drug trial investigating the use of a biological medicinal product (Chapter 5), for which an MRI scan was also required. One patient declined participation based on the request to undergo an MRI scan (due to claustrophobia), while another

was ineligible as he was going on prolonged overseas travel and one chose, after careful consideration, to decline any systemic immunosuppressant therapy and requested a prescription for topical therapy only. Another patient was ineligible for inclusion, as when he returned for his clinical assessment and second ultrasound scan three weeks after his first, his psoriasis had virtually cleared (PASI 2.3). He attributed this to the use of oral ginseng from a Chinese Herbalist. Finally, a further patient expressed interest but failed to turn up for the assessment and ultrasound scan, and did not attend any further appointments made for her outside the study within the Department of Dermatology.

28 patients consented to participate in the study after a period of at least seven days to consider the information supplied in the Patient Information Sheet. 15 male and 13 female patients, aged between 20 and 74 years (mean 46.5 years) underwent a more detailed ultrasound scan of their peripheral joints following on from a detailed clinical examination and confirmation of eligibility. One patient was Asian (skin type V), and the remainder were Caucasian (skin types I, II and III). Body mass index (BMI) ranged from 19.6kg/m^2 to 46.0kg/m^2, with a median of 29.6kg/m^2. More than half of the patients (15 out of 28) had a family history of psoriasis, and four had a family member with psoriatic arthritis. Eight had a family history of other rheumatological disorders (six with osteoarthritis, two with rheumatoid arthritis), and two had a family history of autoimmune disease (one with hypothyroidism, one with type I diabetes mellitus). 7 patients were current smokers, smoking between 10 and 20 cigarettes per day (with a median pack year history of 20.5 pack years), 10 patients were ex-smokers and 11 had never smoked. Of the ex-smokers, pack year history ranged from 1-80 pack years (median 26 pack years), and the time since stopped ranged from 1 year to 34 years (median 12 years). Four patients did not drink alcohol, and in the remaining 24, weekly consumption ranged from 2-76 units (median 17.5 units per week). Table 4.7 compares these parameters with those from the healthy volunteer control group.

4.4.1.2 Healthy Control Group Volunteers

25 volunteers were enlisted, from which 23 volunteers (12 male and 11 female) were recruited. Two declined on the basis of the need to undergo an MRI scan (one was claustrophobic, the other had a history of a metal fragment in the eye). The 23 participants were health professionals and researchers within the University of Leeds and their friends and family members. Volunteers ranged in age from 22 to 59 years, with a mean of 39.9 years. BMI ranged from 19.3kg/m^2 to 49.1kg/m^2, with a median of 26.8kg/m^2. All control group participants were Caucasian (skin type I, II or III) with the exception of one volunteer (skin type IV). Ten had a current or previous dermatological diagnosis (Acne vulgaris: 4; infantile eczema: 3; seborrhoeic dermatitis: 1; varicose eczema: 1; plantar eczema: 1), of which four had previously consulted with a dermatologist (three for acne, one for varicose eczema). None of the participants had

ever consulted with a rheumatologist. Two had a family history of psoriasis but no psoriatic arthritis. Eight had a family history of osteoarthritis, one rheumatoid arthritis and one ankylosing spondylitis (the latter in a paternal great uncle). Autoimmune diseases occurred in the family members of six participants (coeliac disease: 2; hypothyroidism: 3 (in one case combined with vitiligo and type I diabetes); Addisons disease: 1). One participant was a current smoker (7.5 pack year history), and four were ex-smokers (mean 8 pack years). Alcohol consumption averaged 12 units per week and two volunteers were tee-total. Table 4.7 compares these parameters with the participants with psoriasis and subclinical enthesitis.

Characteristic		**Healthy Controls (n=23)**	**Psoriasis Patients (n=28)**	**Difference**
Gender [*n (%)*]	Male	12 (52.2%)	15 (53.6%)	*p*=0.920
	Female	11 (47.8%)	13 (46.4%)	
Age (years) [*Mean (s.d.)*]		39.9 (8.34)	46.5 (14.05)	*p*=0.053
Skin Type [*n (%)*]	I	4 (17.4%)	5 (17.9%)	*p*=0.665
	II	14 (60.9%)	12 (42.9%)	
	III	4 (17.4%)	10 (35.7%)	
	IV	1 (4.3%)	0 (0%)	
	V	0 (0%)	1 (3.6%)	
	VI	0 (0%)	0 (0%)	
BMI (kg/m^2) [*Median (IQR)*]		26.8 (24.6, 31.5)	29.6 (28.2, 33.9)	*p*=0.118
Smoking Status [*n (%)*]	Never	18 (78.3%)	11 (39.3%)	*p*=0.007
	Current	1 (4.3%)	7 (25.0%)	
	Previous	4 (17.4%)	10 (35.7%)	
	Ever	5 (21.7%)	17 (60.7%)	
Cigarette pack years in current/ex-smokers [*Median (IQR)*]		7.9 (0,19.8)	7.0 (0, 22.8)	*p*=0.809
Alcohol consumption in drinkers (units/week) [*Median (IQR)*]		12.0 (5.0,25.5)	10.0 (6.25,20.0)	*p*=0.519
Family history of psoriasis [*n (%)*]		2 (8.7%)	15 (53.6%)	***p*=0.0007**
Family history of psoriatic arthritis [*n (%)*]		0 (0%)	4 (14.3%)	*p*=0.136
Family history of other rheumatological disorder [*n (%)*]		10 (43.5%)	8 (28.6%)	*p*=0.268
Family history of autoimmune disease [*n (%)*]		6 (26.1%)	2 (7.1%)	*p*=0.064

Table 4.7. Comparison of demographic characteristics between healthy control group volunteers and psoriasis patients

No significant differences were observed between the groups in terms of gender, age, skin type and BMI. In keeping with previous studies, the patients with psoriasis appeared to lead an unhealthier lifestyle, with more participants smoking, and smoking more heavily than their counterparts in the control group, although these observations failed to meet statistical significance (Naldi et al., 2005). Alcohol consumption was similar in both groups. A family history of psoriasis was found significantly more frequently in those with psoriasis (p=0.0007), although this was not surprising given that 17 patients were positive for HLA-Cw06, a genetic risk allele for the development of psoriasis compared to just three in the healthy control group (p=0.0005).

4.4.2 Clinical Characteristics (psoriasis patients only)

Amongst the 28 patients with moderate to severe psoriasis, median PASI score was 17.1 (range 10-60), and body surface area (BSA) 20% (range 10-50%). Patients had psoriasis symptoms for a median of 18 years, with onset anywhere from age 9 to 54 years (median 22 years of age). 7 patients had type II psoriasis (with onset at the age of 40 or older), the remainder (75.0%) being type I.

20 patients (71.4%) had current nail involvement with a median modified NAPSI score of 9.5 out of possible maximum of 140 (range 0-89). The frequencies of lesions (current and ever present) by anatomical site are listed in Table 4.8. Every patient had a positive DLQI questionnaire, with scores ranging between 3 and 30 out of possible maximum of 30 (median 17.5), suggesting a high impact of psoriasis on quality of life.

Anatomical location	**No. of Patients (%)**		**Anatomical location**	**No. of Patients (%)**	
Nail *n (%)*	Current	21 (75.0%)	Trunk *n (%)*	Current	27 (96.4%)
	Ever	21 (75.0%)		Ever	27 (96.4%)
Scalp *n (%)*	Current	24 (85.7%)	Lower limb *n (%)*	Current	27 (96.4%)
	Ever	28 (100%)		Ever	28 (100%)
Retroauricular *n (%)*	Current	19 (67.9%)	Flexures *n (%)*	Current	14 (50.0%)
	Ever	24 (85.7%)		Ever	18 (64.3%)
Gluteal cleft *n (%)*	Current	17 (60.7%)	Genitals *n (%)*	Current	10 (35.7%)
	Ever	21 (75.0%)		Ever	13 (46.4%)
Umbilicus *n (%)*	Current	11 (39.3%)	Perianal *n (%)*	Current	5 (17.9%)
	Ever	20 (71.4%)		Ever	8 (28.6%)
Face	Current	12 (42.9%)	Palms	Current	5 (17.9%)

Anatomical location	No. of Patients (%)		Anatomical location	No. of Patients (%)	
n (%)	Ever	18 (64.3%)	*n (%)*	Ever	6 (21.4%)
Upper limb *n (%)*	Current	27 (96.4%)	Soles *n (%)*	Current	5 (17.9%)
	Ever	28 (100%)		Ever	8 (28.6%)
Dorsal hand(s) *n (%)*	Current	14 (50.0%)			
	Ever	18 (64.3)			

Table 4.8. Frequency of psoriatic lesions (present on current examination and ever present) by anatomical location.

12 (42.9%) of 28 patients had tender entheseal points clinically despite reporting no clinical symptoms of joint pain, tenderness, stiffness or swelling. The number of sites found to be tender on examination was one in seven patients, two in three patients, four in one patient and twelve in one patient. No healthy volunteers had any significant tender entheseal sites. The presence of clinically detectable entheseal tenderness in the psoriasis group was so low that calculation of clinical entheseal indices was deemed of little value and insufficient for comparison with overall ultrasound scores.

4.4.3 Serological Characteristics

There were very few serological abnormalities in all participants. CRP was normal amongst the healthy control group but elevated above the standard cut off of <5.0mg/l in four psoriasis patients, all of which were most probably attributable to an acute, self-limiting viral or bacterial illness such as an upper respiratory tract infection given the coryzal symptoms described. The highest measurement was marginally elevated at 15.4mg/l, indicative of a very low level of systemic inflammation, as has been previously reported in psoriasis (Rocha-Pereira et al., 2004, Vanizor Kural et al., 2003a, Vanizor Kural et al., 2003b). ANA was negative in all participants, as was rheumatoid factor and anti-CCP antibody. Significantly more patients were positive for the HLA-Cw06 allele in the psoriasis patient group (17 versus 3, p=0.0005). Only one patient was positive for the HLA-B27 allele compared to no volunteers.

4.4.4 Screening Questionnaires

Despite providing a negative history of current or previous joint pain, stiffness and/or swelling to the candidate (LJS) during the initial assessment, only five of 28 patients with psoriasis submitted a negative PEST questionnaire. Using the advised cut off of a score of three or more, 11 of 28 patients screened positive, with eight achieving a score of

three, and three having a score of four. All participants answered ‘no’ to the question ‘Has a doctor ever told you that you have arthritis?’. 18 patients marked that they had previously had a swollen joint or joints, 12 reported heel pain and 8 stated that they had had a swollen toe or finger for no reason. On further questioning, no patient provided a convincing history consistent with inflammatory arthritis or dactylitis (most instances of joint swelling were traumatic and brief) and clinical examination did not identify any current joint swelling or tenderness, or dactylitis. Entheseal tenderness was minimal and found in just over one third of patients at very few sites (Chapter 4.4.2).

Of the 12 psoriasis patients who answered ‘yes’ to the question ‘have you had pain in your heel?’, eight had sonographic evidence of enthesopathy at the Achilles tendon or plantar fascia insertion, and in all, this was inflammatory (hypoechoic change in eight and thickening in five). Tenderness was elicited clinically at the Achilles and/or plantar fascia in four patients, all of which reported heel pain on the PEST questionnaire. Three had corresponding inflammatory entheseal changes at ultrasound whilst the fourth was reported as normal.

15 patients answered ‘yes’ to the question ‘do your fingernails or toenails have holes or pits?’. All of these patients had a mNAPSI score greater than 0 (range 3-89), with the majority (12/15) having a score greater than 10. Six further patients had also had a positive mNAPSI score, although nail changes were mild (mNAPSI score 2-11), and two of these patients had changes other than nail pitting (e.g. onycholysis and/or nail plate crumbling).

All healthy volunteers had a PEST score below three, with seven participants scoring 1 (all answering ‘yes’ to the question ‘have you ever had a swollen joint or joints?’) and one participant scoring 2 (answering ‘yes’ to the same question and ‘yes’ to the question relating to heel pain). On further questioning, all episodes of joint swelling were reported as short lived with a preceding history of acute trauma. No acute inflammatory or chronic sonographic abnormalities were found at either the Achilles tendon or plantar fascia in the participant who reported heel pain.

4.4.5 Ultrasound Characteristics

4.4.5.1 Entheseal Thickness Thresholds

The methods published by de Miguel et al and Gibbon and Long were applied to the data from the healthy control group in this study, and it was found that the first method significantly over estimated the number of psoriasis patients with thickened entheses (Table 4.9). When comparing the values in this cohort (obtained by calculating the mean thickness + one standard deviation + 0.1mm) for a tendon where a published threshold existed, there was a notable difference, with the majority of published values being significantly higher (by up to 0.9mm). For example, this method produced a threshold of

≥3.5mm for the distal brachial triceps tendon entheses, compared with ≥4.3mm in the literature. Similarly, the Achilles tendon and plantar fascia insertion thresholds in this cohort were ≥4.4mm and ≥3.9mm respectively, compared with published thresholds of ≥5.29mm and ≥4.4mm. The same applied to the quadriceps (≥5.6mm versus ≥6.1mm) and distal patellar (≥3.8mm versus ≥4.0mm) tendon insertions, although the values for the proximal patellar tendon insertion were comparable (≥4.0mm in both cohorts).

Using the method published by Gibbon and Long, the thresholds calculated using the upper limit of the range within the control group were more comparable to those in the published literature. For example, here the upper limit of the range for the Achilles tendon insertion thickness was ≥5.1mm, compared to ≥5.29mm, and for the plantar fascia, was ≥4.7mm compared to the published ≥4.4mm. The distal brachial triceps tendon enthesis threshold in this cohort was ≥4.1mm compared with ≥4.3mm, and the knee tendon insertion thicknesses were all within 0.4mm of the published values (quadriceps tendon ≥6.4mm versus ≥6.1mm; proximal patellar tendon ≥4.4mm versus ≥4.0mm; distal patella tendon ≥4.3mm versus ≥4.0mm). Although some of the thresholds in this healthy control cohort are up to 0.4mm higher than the published measurements, they are still closer than those obtained by using the method published by de Miguel and colleagues and it was therefore felt it was better to apply thresholds to the patient data that may underestimate the number of psoriasis patients with entheseal thickening rather than overestimate the incidence of subclinical enthesitis.

Tendon Enthesis	**Maximum Thickness in all Controls (mm)**	**Mean + 1 s.d. + 0.1mm (mm)**	**Threshold using de Miguel et al Method (mm)**	**Threshold using Gibbon & Long Method (mm)**	**Published Threshold (mm)**
Right Thumb FPL	0.9	0.845	≥0.8	≥1.0	N/A
Left Thumb FPL	0.9	0.799			
Mean	0.9	0.800			
Right Thumb EPL	0.7	0.762	≥0.7	≥1.0	N/A
Left Thumb EPL	0.9	0.726			
Mean	0.8	0.700			
Right Index Finger FDP	0.9	0.809	≥0.8	≥1.0	N/A
Left Index Finger FDP	0.9	0.766			
Mean	0.9	0.800			
Right Index Finger ED	0.6	0.589	≥0.6	≥0.9	N/A
Left Index Finger ED	0.8	0.629			
Mean	0.7	0.600			
Right Elbow Common Extensor	4.8	4.509	≥4.5	≥4.9	N/A

Tendon Enthesis	Maximum Thickness in all Controls (mm)	Mean + 1 s.d. + 0.1mm (mm)	Threshold using de Miguel et al Method (mm)	Threshold using Gibbon & Long Method (mm)	Published Threshold (mm)
Left Elbow Common Extensor	4.6	4.474			
Mean	4.7	4.500			
Right Elbow Common Flexor	4.4	3.940			
Left Elbow Common Flexor	4.6	4.062	≥4.0	≥4.7	N/A
Mean	4.5	4.000			
Right Distal Brachial Triceps	4.0	3.619			
Left Distal Brachial Triceps	3.6	3.472	≥3.5	≥4.1	≥4.3
Mean	3.8	3.500			
Right Quadriceps	6.3	5.678			
Left Quadriceps	6.0	5.452	≥5.6	≥6.4	≥6.1
Mean	6.15	5.600			
Right Proximal Patellar	4.3	4.079			
Left Proximal Patellar	4.1	3.825	≥4.0	≥4.4	≥4.0
Mean	4.2	4.000			
Right Distal Patellar	4.2	3.944			
Left Distal Patellar	4.1	3.746	≥3.8	≥4.3	≥4.0
Mean	4.15	3.800			
Right Peroneal Brevis	1.8	1.658			
Left Peroneal Brevis	1.6	1.486	≥1.6	≥1.9	N/A
Mean	1.7	1.600			
Right Achilles	4.5	4.321			
Left Achilles	5.0	4.472	≥4.4	≥5.1	≥5.29
Mean	4.75	4.400			
Right Plantar Fascia	4.6	3.873			
Left Plantar Fascia	4.3	3.684	≥3.8	≥4.7	≥4.4
Mean	4.45	3.800			

Table 4.9. Comparison of the different published methods for calculating tendon thickness thresholds and with published thresholds where available (FPL: Flexor pollicis longus; EPL: Extensor pollicis longus; FDP: Flexor digitorum profundus; ED: Extensor digitorum).

Using these thresholds, the following entheseal scoring system was applied to the data, based on the original GUESS score by Balint et al. (Balint et al., 2002). All lesions were scored 0-3, with a maximum possible total of 606:

- *THUMB: Base of distal phalynx - flexor pollicis longus tendon enthesis*
    1. Flexor pollicis longus enthesis thickness ≥ 1.0mm
    2. Flexor pollicis longus enthesis hypoechogenicity
    3. Flexor pollicis longus enthesis power Doppler signal
    4. Base of distal phalynx calcification
    5. Base of distal phalynx enthesophyte(s)
    6. Base of distal phalynx bony erosion(s)
    7. Base of distal phalynx bony cortex irregularity

- *THUMB: Dorsal base of distal phalynx – extensor pollicis longus tendon enthesis*
    1. Extensor pollicis longus enthesis thickness ≥ 1.0mm
    2. Extensor pollicis longus enthesis hypoechogenicity
    3. Extensor pollicis longus enthesis power Doppler signal
    4. Dorsal base of distal phalynx calcification
    5. Dorsal base of distal phalynx enthesophyte(s)
    6. Dorsal base of distal phalynx bony erosion(s)
    7. Dorsal base of distal phalynx bony cortex irregularity

- *INDEX FINGER: Distal phalynx base - flexor digitorum profundus*
    1. Flexor digitorum profundus/superficialis enthesis thickness ≥ 1.0mm
    2. Flexor digitorum profundus/superficialis enthesis hypoechogenicity
    3. Flexor digitorum profundus/superficialis enthesis power Doppler signal
    4. Middle/distal phalynx base calcification
    5. Middle/distal phalynx base enthesophyte(s)
    6. Middle/distal phalynx base bony erosion(s)
    7. Middle/distal phalynx base bony cortex irregularity

- *INDEX FINGER: Distal phalynx base - extensor digitorum tendon enthesis*
    1. Extensor digitorum enthesis thickness ≥ 0.9mm
    2. Extensor digitorum enthesis hypoechogenicity
    3. Extensor digitorum enthesis power Doppler signal
    4. Distal phalynx base calcification
    5. Distal phalynx base enthesophyte(s)
    6. Distal phalynx base bony erosion(s)
    7. Distal phalynx base bony cortex irregularity

- *ELBOW: Lateral epicondyle of humerus - common extensor tendon enthesis*
    1. Elbow common extensor enthesis thickness ≥ 4.9mm
    2. Elbow common extensor enthesis hypoechogenicity
    3. Elbow common extensor enthesis power Doppler signal
    4. Lateral epicondyle of humerus calcification
    5. Lateral epicondyle of humerus enthesophyte(s)
    6. Lateral epicondyle of humerus bony erosion(s)
    7. Lateral epicondyle of humerus bony cortex irregularity

- *ELBOW: Medial epicondyle of humerus - common flexor tendon enthesis*
    1. Common flexor enthesis thickness ≥ 4.7mm
    2. Common flexor enthesis hypoechogenicity
    3. Common flexor enthesis power Doppler signal
    4. Medial epicondyle of humerus calcification
    5. Medial epicondyle of humerus enthesophyte(s)
    6. Medial epicondyle of humerus bony erosion(s)
    7. Medial epicondyle of humerus bony cortex irregularity

- *ELBOW: Olecranon process of the ulna - distal brachial triceps tendon enthesis*
    1. Elbow distal brachial triceps enthesis thickness ≥ 4.3mm
    2. Elbow distal brachial triceps enthesis hypoechogenicity
    3. Elbow distal brachial triceps enthesis power Doppler signal
    4. Olecranon process of ulna calcification
    5. Olecranon process of ulna enthesophyte(s)
    6. Olecranon process of ulna bony erosion(s)
    7. Olecranon process of ulna bony cortex irregularity
    8. Olecranon bursitis (GS hypertrophy)
    9. Olecranon burseal power Doppler signal

- *KNEE: Superior pole of the patella - quadriceps tendon enthesis*
    1. Quadriceps enthesis thickness ≥ 6.1mm
    2. Quadriceps enthesis hypoechogenicity
    3. Quadriceps enthesis power Doppler signal
    4. Superior pole of patella calcification
    5. Superior pole of patella enthesophyte(s)
    6. Superior pole of patella bony erosion(s)
    7. Superior pole of patella bony cortex irregularity
    8. Suprapatellar bursitis (GS hypertrophy)
    9. Suprapatellar burseal power Doppler signal

- *KNEE: Inferior pole of the patella - proximal patellar tendon enthesis*
    1. Proximal patellar enthesis thickness ≥ 4.0mm
    2. Proximal patellar enthesis hypoechogenicity
    3. Proximal patellar enthesis power Doppler signal
    4. Inferior pole of patella calcification
    5. Inferior pole of patella enthesophyte(s)
    6. Inferior pole of patella bony erosion(s)
    7. Inferior pole of patella bony cortex irregularity
    8. Superficial Infrapatellar bursitis (GS hypertrophy)
    9. Superficial Infrapatellar burseal power Doppler signal

- *KNEE: Tibial tuberosity - distal patellar tendon enthesis*
    1. Distal patellar enthesis thickness ≥ 4.0mm
    2. Distal patellar enthesis hypoechogenicity
    3. Distal patellar enthesis power Doppler signal
    4. Tibial tuberosity calcification
    5. Tibial tuberosity enthesophyte(s)
    6. Tibial tuberosity bony erosion(s)
    7. Tibial tuberosity bony cortex irregularity
    8. Deep Infrapatellar bursitis (GS hypertrophy)
    9. Deep Infrapatellar burseal power Doppler signal

- *FOOT: 5th metatarsal base lateral tuberosity - peroneal brevis tendon enthesis*
    1. Peroneal brevis enthesis thickness ≥ 1.9mm
    2. Peroneal brevis enthesis hypoechogenicity
    3. Peroneal brevis enthesis power Doppler signal
    4. 5th metatarsal base lateral tuberosity calcification
    5. 5th metatarsal base lateral tuberosity enthesophyte(s)
    6. 5th metatarsal base lateral tuberosity bony erosion(s)
    7. 5th metatarsal base lateral tuberosity bony cortex irregularity

- *ANKLE: Superior pole of calcaneus - Achilles tendon enthesis*
    1. Achilles enthesis thickness ≥ 5.29mm
    2. Achilles enthesis hypoechogenicity
    3. Achilles enthesis power Doppler signal
    4. Posterior pole of calcaneus calcification
    5. Posterior pole of calcaneus enthesophyte(s)
    6. Posterior pole of calcaneus bony erosion(s)
    7. Posterior pole of calcaneus bony cortex irregularity
    8. Retrocalcaneal bursitis (GS hypertrophy)

9. Retrocalcaneal bursae power Doppler signal

- *FOOT: Inferior pole of calcaneus - plantar aponeurosis (fascia) enthesis*
  1. Plantar aponeurosis thickness ≥ 4.4mm
  2. Plantar aponeurosis hypoechogenicity
  3. Plantar aponeurosis power Doppler signal
  4. Inferior pole of calcaneus calcification
  5. Inferior pole of calcaneus enthesophyte(s)
  6. Inferior pole of calcaneus bony erosion(s)
  7. Inferior pole of calcaneus bony cortex irregularity

4.4.5.2 Enthesopathy and Bursal Changes

26 entheseal sites (13 per side) were scanned in each participant, totalling 728 entheses in 28 patients with moderate to severe psoriasis and known sonographic evidence of enthesitis and 598 entheses in 23 healthy volunteers. A total of 425 entheseal abnormalities were identified in the psoriasis group, compared with 63 in the healthy control group. Four healthy volunteers had no enthesopathy. Table 4.10 describes these abnormalities at the entheseal and patient level.

Tendon		Parameter	Healthy Control Group				Patients with Psoriasis			
			Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=56)		Patient (max n=28)	
			n	%	n	%	n	%	n	%
Thumb	Flexor pollicis longus	Thickening	0	0.0	0	0.0	9	16.1	7	25.0
		Hypoechogenicity	0	0.0	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	0	0.0	0	0.0
		Enthesophytes	0	0.0	0	0.0	4	7.1	3	10.7
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	1	2.2	1	4.3	15	26.8	11	39.2
	Extensor pollicis longus	Thickening	0	0.0	0	0.0	4	7.1	4	14.3
		Hypoechogenicity	0	0.0	0	0.0	1	1.8	1	3.6
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0
		Calcifications	1	2.2	1	4.3	0	0.0	0	0.0
		Enthesophytes	0	0.0	0	0.0	6	10.7	4	14.3
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	8	14.3	6	21.4

Tendon		Parameter	Healthy Control Group				Patients with Psoriasis			
			Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=56)		Patient (max n=28)	
			n	%	n	%	n	%	n	%
Index Finger	Flexor digitorum profundus	Thickening	0	0.0	0	0.0	5	8.9	5	17.9
		Hypoechogenicity	0	0.0	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	2	3.6	2	7.1
		Enthesophytes	0	0.0	0	0.0	0	0.0	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	1	2.2	1	4.3	5	8.9	4	14.3
	Extensor digitorum	Thickening	0	0.0	0	0.0	1	1.8	1	3.6
		Hypoechogenicity	0	0.0	0	0.0	2	3.6	1	3.6
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	1	1.8	1	3.6
		Enthesophytes	0	0.0	0	0.0	3	5.4	3	10.7
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	1	2.2	1	4.3	7	12.5	4	14.3
Elbow	Common Extensor	Thickening	0	0.0	0	0.0	16	28.6	10	35.7
		Hypoechogenicity	2	4.3	2	8.7	15	26.8	11	39.2
		Power Doppler signal	0	0.0	0	0.0	2	3.6	2	7.1
		Calcifications	0	0.0	0	0.0	0	0.0	0	0.0
		Enthesophytes	0	0.0	0	0.0	3	5.4	2	7.1
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	6	10.7	4	14.3
	Common Flexor	Thickening	0	0.0	0	0.0	15	26.8	8	28.6
		Hypoechogenicity	1	2.2	1	4.3	8	14.3	5	17.9
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	1	1.8	1	3.6
		Enthesophytes	0	0.0	0	0.0	4	7.1	3	10.7
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	4	7.1	3	10.7

Tendon		Parameter	Healthy Control Group				Patients with Psoriasis			
			Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=56)		Patient (max n=28)	
			n	%	n	%	n	%	n	%
	Distal Brachial Triceps	Thickening	0	0.0	0	0.0	4	7.1	4	14.3
		Hypoechogenicity	1	2.2	1	4.3	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0
		Calcifications	1	2.2	1	4.3	5	8.9	4	14.3
		Enthesophytes	0	0.0	0	0.0	6	10.7	4	14.3
		Bony erosions	0	0.0	0	0.0	1	1.8	1	3.6
		Bone cortex irregularities	0	0.0	0	0.0	0	0.0	0	0.0
		Olecranon bursal hypertrophy	0	0.0	0	0.0	0	0.0	0	0.0
		PD within olecranon bursa	0	0.0	0	0.0	0	0.0	0	0.0
Knee	Quadriceps	Thickening	1	2.2	1	4.3	17	30.4	11	39.2
		Hypoechogenicity	2	4.3	2	8.7	18	32.1	13	46.4
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0
		Calcifications	4	8.7	4	17.4	21	37.5	15	53.6
		Enthesophytes	7	15.2	5	21.7	22	39.3	13	46.4
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	2	4.3	2	8.7	5	8.9	3	10.7
		Suprapatellar bursal hypertrophy	0	0.0	0	0.0	0	0.0	0	0.0
		PD within suprapatellar bursa	0	0.0	0	0.0	0	0.0	0	0.0
	Proximal Patellar	Thickening	10	21.7	5	21.7	20	35.7	13	46.4
		Hypoechogenicity	1	2.2	1	4.3	12	21.4	8	28.6
		Power Doppler signal	0	0.0	0	0.0	1	1.8	1	3.6
		Calcifications	0	0.0	0	0.0	5	8.9	3	10.7
		Enthesophytes	1	2.2	1	4.3	6	10.7	4	14.3
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	3	5.4	2	7.1
	Distal Patellar	Thickening	3	7.5	2	8.7	28	50.0	18	67.9
		Hypoechogenicity	2	4.3	2	8.7	7	12.5	7	25.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0
		Calcifications	2	4.3	2	8.7	11	19.6	7	25.0
		Enthesophytes	0	0.0	0	0.0	4	7.1	3	10.7

		Parameter	Healthy Control Group				Patients with Psoriasis			
			Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=56)		Patient (max n=28)	
			n	%	n	%	n	%	n	%
Tendon		Bony erosions	0	0.0	0	0.0	1	1.8	1	3.6
		Bone cortex irregularities	1	2.2	1	4.3	3	5.4	3	10.7
		Superficial infrapatellar bursal hypertrophy	0	0.0	0	0.0	2	3.6	2	7.1
		PD within superficial infrapatellar bursa	0	0.0	0	0.0	1	1.8	1	3.6
		Deep infrapatellar bursal hypertrophy	0	0.0	0	0.0	1	1.8	1	3.6
		PD within deep infrapatellar bursa	0	0.0	0	0.0	0	0.0	0	0.0
Foot and Ankle	Peroneal Brevis	Thickening	0	0.0	0	0.0	7	12.5	5	17.9
		Hypoechogenicity	0	0.0	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	1	1.8	1	3.6
		Enthesophytes	0	0.0	0	0.0	2	3.6	2	7.1
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	3	5.4	3	10.7
	Achilles	Thickening	0	0.0	0	0.0	7	12.5	6	21.4
		Hypoechogenicity	2	4.3	2	8.7	6	10.7	5	17.9
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0
		Calcifications	4	8.7	3	13.0	5	8.9	5	17.9
		Enthesophytes	9	19.6	6	26.1	14	25.0	9	32.1
		Bony erosions	0	0.0	0	0.0	1	1.8	1	3.6
		Bone cortex irregularities	1	2.2	1	4.3	3	5.4	2	7.1
		Retrocalcaneal bursal hypertrophy	1	2.2	1	4.3	0	0.0	0	0.0
		PD within retrocalcaneal bursa	0	0.0	0	0.0	0	0.0	0	0.0
	Plantar Fascia	Thickening	2	4.3	2	8.7	12	21.4	9	32.1
		Hypoechogenicity	0	0.0	0	0.0	11	19.6	9	32.1
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0
		Calcifications	0	0.0	0	0.0	4	7.1	4	14.3
		Enthesophytes	0	0.0	0	0.0	2	3.6	2	7.1
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	0	0.0	0	0.0

Table 4.10. Comparison between patients with psoriasis and healthy volunteers of the number of entheseal and bursal abnormalities by anatomical site and lesion at the entheseal/bursal and patient level

Significantly higher rates of entheseal thickening (p<0.000001), hypoechogenicity (p<0.00001), enthesophytes (p<0.00001), calcifications (p=0.00003) and bone cortex irregularities (p<0.00001) were observed in the group of patients with moderate to severe psoriasis. Bone erosions and power Doppler signal were not found in any healthy volunteers, and only in very low frequencies among patients with psoriasis (both p=0.258).

In patients with psoriasis, the following abnormalities were observed:

- Entheseal thickening in 145 entheses (19.9%)
- Hypoechogenicity in 80 entheses (11.0%)
- Power Doppler signal in 3 entheses (0.4%)
- Enthesophytes in 76 entheses (10.4%)
- Calcifications in 56 entheses (7.7%)
- Bone cortex irregularities in 62 entheses (8.5%)
- Bone erosions in 3 entheses (0.4%)

Among volunteers in the healthy control group, the following abnormalities were observed:

- Entheseal thickening in 16 entheses (2.7%)
- Hypoechogenicity in 11 entheses (1.8%)
- Power Doppler signal in 0 entheses (0%)
- Enthesophytes in 17 entheses (2.8%)
- Calcifications in 12 entheses (2.0%)
- Bone cortex irregularities in 7 entheses (1.2%)
- Bone erosions in 0 entheses (0%)

Inflammatory lesions (thickening, hypoechogenicity and/or power Doppler signal) were identified in 31.3% of entheses scanned in the psoriasis group compared to 4.5% in the healthy control group (p<0.00001). Chronic lesions (enthesophytes, calcifications, bone erosions and/or bone cortex irregularities) were seen in 27.0% of entheses in the disease group compared to 6.0% of healthy volunteers (p<0.00001).

In terms of the location of all lesions, the larger tendons were most frequently involved in both groups, especially the three knee tendons (quadriceps, proximal patellar and distal patellar) and the common extensor and flexor tendons of the elbow (Figure 4.6).

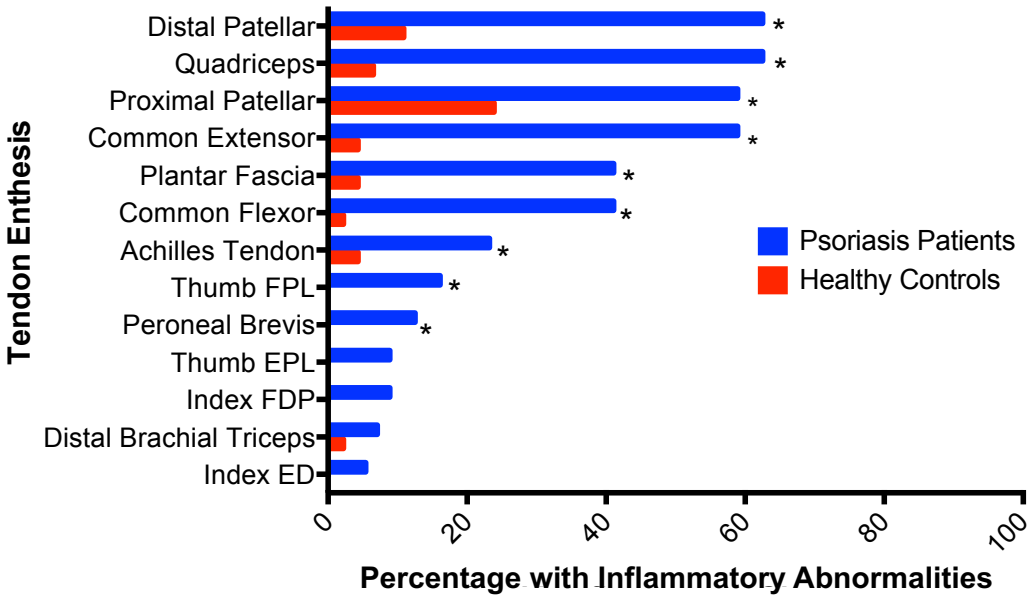

Figure 4.6. Percentages of entheses by location demonstrating inflammatory abnormalities (thickening, hypoechogenicity and/or power Doppler signal) – comparison between psoriasis patients and healthy control group participants. (FPL: Flexor Pollicis Longus; EPL: Extensor Pollicis Longus; ED: Extensor Digitorum; FDP: Flexor Digitorum Profundus). *denotes a significant difference between groups (p<0.05).

Rates of inflammatory lesions were significantly greater in those with psoriasis, with over 40% of entheses being involved (quadriceps 62.5% vs. 6.5%, p<0.00001; distal patellar 62.5% vs. 10.9%, p<0.00001) (Figure 4.7); proximal patellar 58.9% vs. 23.9%, p=0.00038; common extensor 58.9% vs. 4.3%, p<0.00001; common flexor 41.1% vs. 2.2%, p=0.00004; plantar fascia 41.1% vs. 4.3%, p=0.00002). Very few inflammatory lesions were found in the smaller tendons of the digits and ankle (Figure 4.8) in healthy control group participants (Table 4.11).

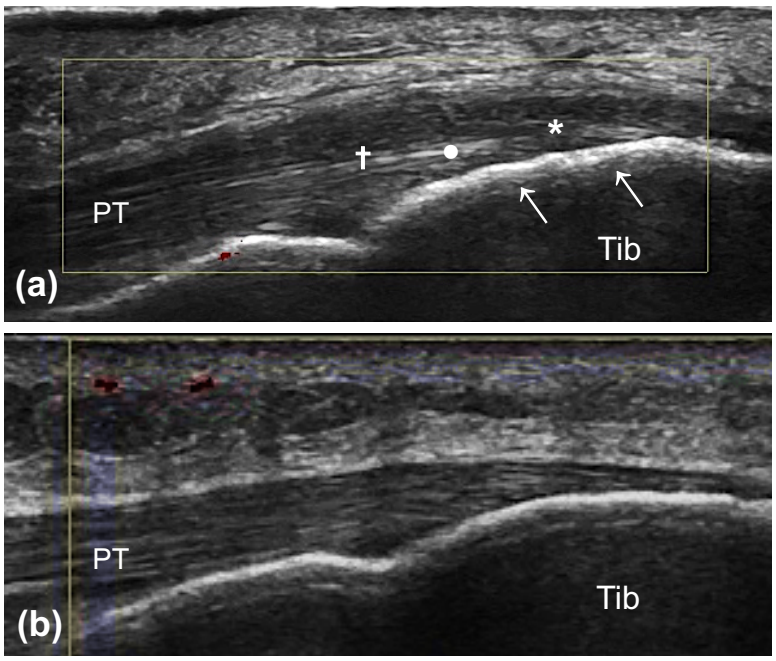

Figure 4.7. Right distal patellar tendon insertion in (a) an asymptomatic patient with moderate to severe psoriasis, demonstrating entheseal thickening (†, grade 2), hypoechogenicity (✶, grade 2), calcification (•, grade 1) and bone cortex irregularities (↑, grade 1) and (b) a healthy volunteer (no abnormalities). PT: Patellar tendon; Tib: Tibia.

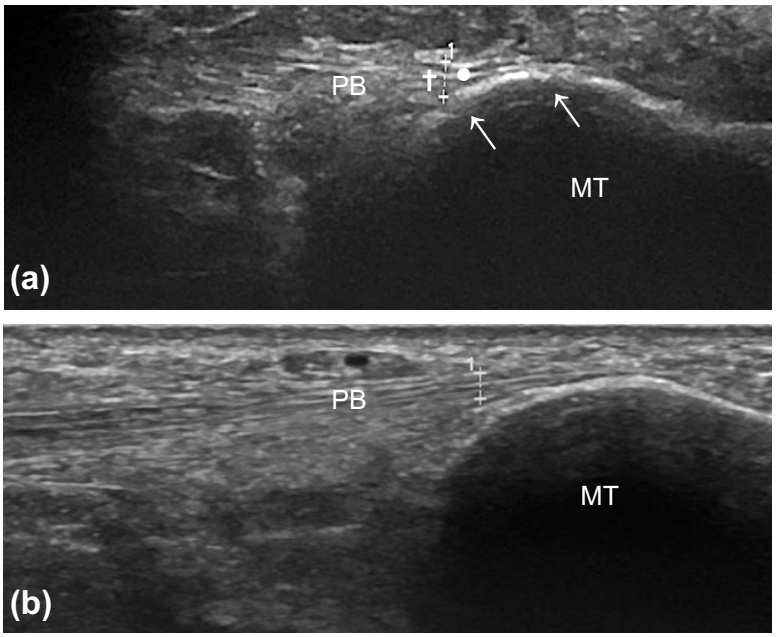

Figure 4.8. Right peroneal brevis tendon insertion in (a) an asymptomatic patient with moderate to severe psoriasis, demonstrating entheseal thickening (†, grade 1), calcification (•, grade 1) and bone cortex irregularities (↑, grade 1) and (b) a healthy volunteer (no abnormalities). PB: Peroneal brevis; MT: Fifth metatarsal.

Of the inflammatory lesions in the non-disease group, the changes were a mixture of thickening (2.7%) and hypoechogenicity (1.8%) (no power Doppler signal), which are most probably attributable to age-related degeneration and/or localised injury. For example, one participant, on further detailed questioning, reported an injury relating to recreational running around the time of the ultrasound scan, which was evident sonographically as unilateral Achilles tendonitis (hypoechoic change). No patients in the psoriasis group reported any sporting injuries or trauma.

Tendon Enthesis	**Percentage frequency of entheses with inflammatory abnormalities**		
	Psoriasis Patient Group	**Healthy Control Group**	**Difference**
Distal patella	62.5	10.9	$p<0.00001$
Quadriceps	62.5	6.5	$p<0.00001$
Proximal patella	58.9	23.9	$p=0.00038$
Common extensor	58.9	4.3	$p<0.00001$
Plantar fascia	41.1	4.3	$p=0.00002$
Common flexor	41.1	2.2	$p=0.00004$
Achilles	23.2	4.3	$p=0.0074$
Thumb flexor pollicis longus	16.1	0.0	$p=0.0111$
Peroneal brevis	12.5	0.0	$p=0.0319$
Thumb extensor pollicis longus	8.9	0.0	$p=0.0896$
Index finger flexor digitorum profundus	8.9	0.0	$p=0.0896$
Distal brachial triceps	7.1	2.2	$p=0.247$
Index finger extensor digitorum	5.4	0.0	$p=0.247$

Table 4.11. Comparison of the percentage of inflammatory lesions by enthesis type between patients with psoriasis and healthy control group participants. Bold denotes significance $p<0.05$.

Inflammatory burseal lesions were observed infrequently, with no hypertrophy or power Doppler signal seen in the olecranon and suprapatellar bursae in either group. Two psoriasis patients had unilateral grey scale superficial infrapatellar bursal hypertrophy, one with additional power Doppler signal, and one patient had unilateral deep infrapatellar bursal hypertrophy (Figure 4.9). Unilateral grey scale retrocalcaneal bursal hypertrophy was seen in only one healthy volunteer, without power Doppler signal.

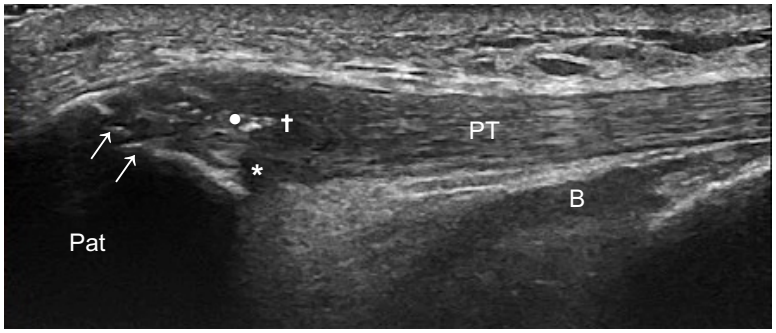

Figure 4.9. Right deep infrapatellar burseal hypertrophy (B) associated with adjacent entheseal thickening (†, grade 2), hypoechogenicity (✶, grade 2), calcification (•, grade 1) and bone cortex irregularities (↑, grade 1) in a patient with moderate to severe psoriasis. B: Bursa; PT: Patella tendon; Pat: Patella.

Lesions indicative of chronic damage and degeneration were again significantly more common in all tendon entheses when compared to healthy control participants (Figure 4.10 and Table 4.12), with the exception of the foot entheses (Achilles tendon p=0.266, plantar fascia insertion p=0.0536, peroneal brevis enthesis p=0.0536), and the flexor digitorum profundus tendon of the index finger (p=0.0536) The majority of chronic lesions identified at the Achilles were enthesophytes, followed by entheseal calcification. The Achilles is perhaps the enthesis that sustains the most amount of microtrauma of all through walking and everyday activity, and it is proposed that the continued damage-repair cycle that takes place may account for the new bone formation resulting in the development of enthesophytes.

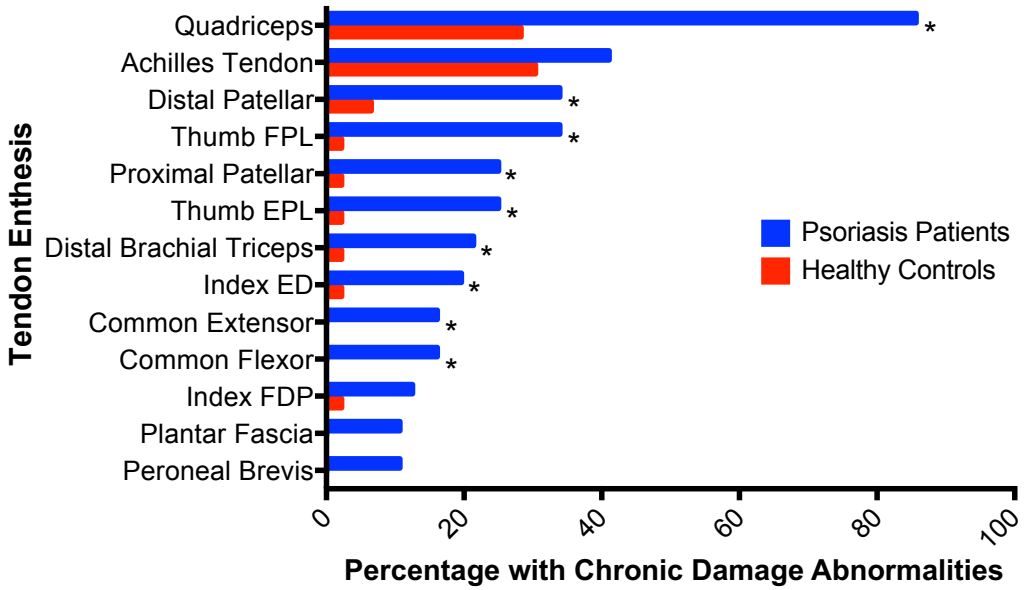

Figure 4.10. Percentages of entheses by location demonstrating chronic damage abnormalities (enthesophytes, calcifications, bone cortex irregularities and bone erosions) – comparison between psoriasis patients and healthy control group participants. (FPL: Flexor Pollicis Longus; EPL: Extensor Pollicis Longus; ED: Extensor Digitorum; FDP: Flexor Digitorum Profundus). *denotes a significant difference between groups (p<0.05).

Tendon Enthesis	Percentage frequency of entheses with chronic damage abnormalities		
	Psoriasis Patient Group	**Healthy Control Group**	**Difference**
Quadriceps	85.7	28.3	p<0.0.0001
Achilles	41.1	30.4	p=0.266
Distal patellar	33.9	6.5	p=0.0008
Thumb flexor pollicis longus	33.9	2.2	p=0.00006
Proximal patella	25.0	2.2	p=0.0012
Thumb extensor pollicis longus	25.0	2.2	p=0.0014
Distal brachial triceps	21.4	2.2	p=0.0037
Index finger extensor digitorum	19.6	2.2	p=0.0064
Common extensor	16.1	0.0	p=0.0111
Common flexor	16.1	0.0	p=0.0111
Index finger flexor digitorum profundus	12.5	2.2	p=0.0536
Plantar fascia	10.7	0.0	p=0.0536
Peroneal brevis	10.7	0.0	p=0.0536

Table 4.12. Comparison of the total number and percentage of chronic damage lesions by enthesis type between patients with psoriasis and healthy control group participants. Bold denotes significance p<0.05.

The quadriceps tendon enthesis demonstrated a disproportionately high degree of chronic damage in both groups (85.7% in the psoriasis group vs. 28.3% in the healthy control group), which again may be accountable to a high degree of stress and microdamage caused at this major enthesis, which is then further attenuated by the pro-inflammatory cascade in those with a genetic predisposition to psoriatic disease. Inflammatory lesions were seen in 62.5% of quadriceps entheses in the psoriasis group compared to 6.5% of healthy control group participants (Figure 4.11).

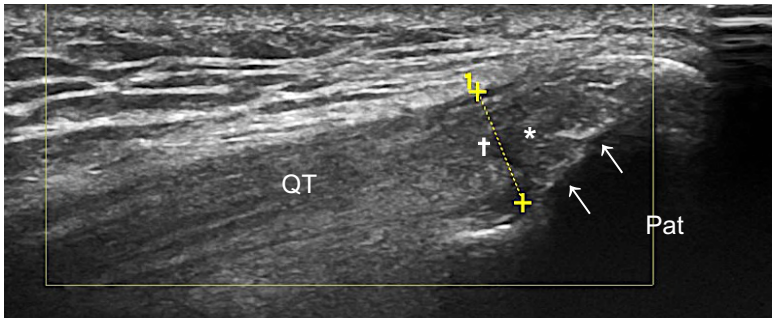

Figure 4.11. Left quadriceps tendon enthesis demonstrating entheseal thickening (†, grade 2), hypoechogenicity (✶, grade 2), bone cortex irregularities and enthesophytes (↑, grade 1) in a patient with moderate to severe psoriasis. QT: Quadriceps tendon; Pat: Patella.

Chronic damage lesions were seen to a lesser degree in the other entheses, which sustain a lesser amount of daily stress and microdamage. However, these lesions were always at a significantly greater frequency than healthy controls, again suggesting that the genetic aberrations in patients with psoriasis leads to an additional inflammatory insult at the enthesis that in turn attenuates the consequences of microdamage and repair.

4.4.5.2.1 Enthesopathy Scores

In terms of the severity of enthesopathy, the majority (81.1%) of abnormalities (both chronic and inflammatory) were mild and scored only as grade 1. 28 (12.1%) of 232 inflammatory lesions observed were of moderate severity (grade 2) and seven (3.0%) were severe (grade 3). 43 (21.8%) of 197 chronic damage lesions were grade 2, and three (1.5%) were grade 3.

Overall mean enthesopathy scores were low, but were still significantly greater in those with psoriasis than healthy volunteers (p<0.0001 for all scores):

- **Enthesopathy Inflammation Score (out of a maximum of 294):**
  - Psoriasis group participants = 10.04 ±7.08
  - Healthy control group participants = 1.09 ±1.38
- **Enthesopathy Chronic Score (out of a maximum of 312):**

- Psoriasis group participants = 9.25 ±7.18
- Healthy control group participants = 1.96 ±1.92

- **Enthesopathy Total Score (out of a maximum of 606):**
  - Psoriasis group participants = 19.29 ±12.68
  - Healthy control group participants = 3.04 ±2.59

4.4.5.2.2 Correlation of Ultrasound Enthesopathy Scores with Clinical Entheseal Tenderness and Screening Questionnaires

In each participant, 14 entheses could be examined both clinically and sonographically (medial and lateral epicondyles of the humerus corresponding to the common flexor and extensor tendon insertions at the elbow, quadriceps insertion at the patella, inferior pole of the patella corresponding to the insertion of the proximal patellar tendon, tibial tubercle corresponding to the distal patellar tendon enthesis, proximal Achilles tendon and plantar fascia insertion at the calcaneus).

12 patients with psoriasis had at least one tender enthesis on clinical examination, involving a total of 30 entheses at 19 different sites. Of these, seven entheses at six sites could not be easily visualised sonographically or were not included in the ultrasound protocol (posterior superior iliac spines bilaterally, left anterior superior iliac spine, left iliac crest, medial femoral condyles bilaterally). Of the remaining 23 clinically tender entheses, 12 had evidence of inflammatory enthesopathy (thickening and/or hypoechogenicity) on ultrasound, one of which also had chronic damage changes (calcifications) and a further site had evidence of chronic damage (enthesophytes) without any inflammation. 47.8% of clinically tender entheses were showed no signs of inflammation on ultrasound. There was no significant difference in overall mean inflammation scores between those patients with clinical enthesitis (9.98 ±7.68, n=12) and those without (10.12 ±7.02, n=16) (p=0.960).

11 of 28 psoriasis patients had a positive PEST screening questionnaire (score of 3 or more). No significant differences were observed between patients with a positive and negative PEST in terms of mean overall ultrasound inflammation score (10.1 ±4.91 vs. 6.88 ±4.72, p=0.095), mean chronic damage scores (8.00 ±4.47 vs. 7.00 ±6.95, p=0.676) and mean total enthesopathy scores (18.09 ±6.72 vs.13.88 ±9.69, p=0.221).

4.4.5.3 Tenosynovitis

Rates of tenosynovitis or peritendonitis were very low in both groups, as demonstrated in Figure 4.12. Only three healthy volunteers (13%) had sonographic evidence of tenosynovitis, two in a single tendon (both posterior tibialis), and one in two adjacent tendons (peroneal longus and brevis). Tenosynovitis was mild (grade 1), unilateral and with no associated power Doppler signal.

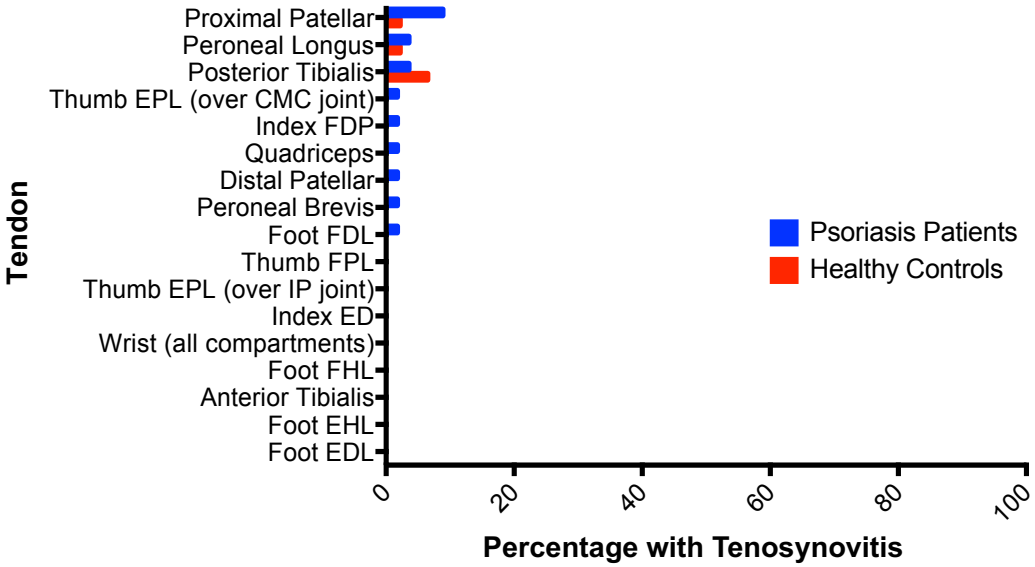

Figure 4.12. Comparison of percentage number of tendons with grey scale synovitis between patients with psoriasis and healthy volunteers (EPL: Extensor pollicis longus; FDP: Flexor digitorum profundus; FPL: Flexor pollicis longus; EPL: Extensor pollicis longus; ED: Extensor digitorum).

Tenosynovitis or peritendonitis was detected in a greater number of tendons in patients with psoriasis than healthy volunteers, although due to the low frequency of tenosynovitis in both groups, no significant differences were observed (p=0.199). 11 of 28 patients (39.3%) had tenosynovitis, in either one (n=6), two (n=2) or three (n=2) tendons, affecting both large and small tendons (Figure 4.13). Knee tendons had the most abnormalities, although rates overall were still low – grey scale peritendonitis of the proximal patellar tendon occurred in 8.9% of tendons (Table 4.13).

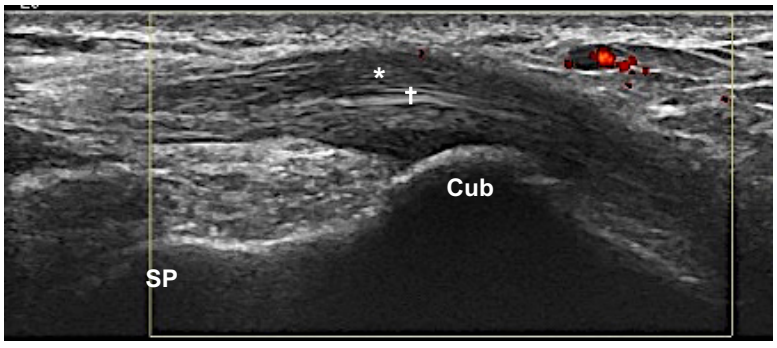

Figure 4.13. Longitudinal view of right peroneus longus tendon demonstrating grey scale tenosynovitis with thickening (†, grade 2) and hypoechogenicity (✶, grade 2) in a patient with moderate to severe psoriasis. SP: Styloid process at base of 5th metatarsal head; Cub: Cuboid.

Peritendoneal power Doppler signal was seen in three psoriasis patients, two unilaterally in a single tendon (thumb extensor pollicis longus tendon/distal patellar tendon) (Figure 4.14) and one bilaterally in the proximal patellar tendons.

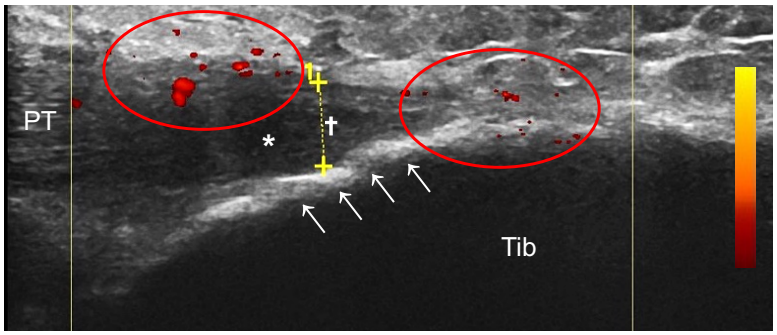

Figure 4.14. Left distal patella tendon demonstrating grey scale and power Doppler peritendonitis (circled, grade 1) in association with adjacent entheseal thickening (†, grade 2), hypoechogenicity (✶, grade 2), power Doppler signal (circled, grade 1), bone cortex irregularities and enthesophytes (↑, grade 2) in a patient with moderate to severe psoriasis. PT: Patellar tendon; Tib: Tibia.

Overall mean tenosynovitis scores were not significantly greater in the psoriasis group (1.04 ±1.774) compared with healthy volunteers (0.26 ±0.619) volunteers (p=0.052).

Tendon		Mode	Healthy Control Group				Patients with Psoriasis			
			Tendon (max n=46)		Patient (max n=23)		Tendon (max n=56)		Patient (max n=28)	
			n	%	n	%	n	%	n	%
Thumb	Flexor pollicis longus	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	EPL overlying the interphalangeal joint	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	EPL overlying the carpometacarpal joint	GS	0	0.0	0	0.0	1	1.8	1	3.5
		PD	0	0.0	0	0.0	1	1.8	1	3.5
Index Finger	Flexor digitorum profundus	GS	0	0.0	0	0.0	1	1.8	1	3.5
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor digitorum	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0
Wrist	Extensor Compartment 1 (APL and EPB)	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0

	Extensor Compartment 2 (ECR, ECL, ECB)	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor Compartment 3 (Extensor pollicis longus)	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor Compartment 4 (Extensor digitorum)	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor Compartment 5 (Extensor digiti minimi)	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor Compartment 6 (Extensor carpi ulnaris)	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0
Knee	Quadriceps	GS	0	0.0	0	0.0	1	1.8	1	3.5
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Proximal Patellar	GS	0	0.0	0	0.0	5	8.9	3	10.7
		PD	0	0.0	0	0.0	3	5.4	2	7.1
	Distal Patellar	GS	0	0.0	0	0.0	1	1.8	1	3.5
		PD	0	0.0	0	0.0	0	0.0	0	0.0
Foot and Ankle	Posterior Tibialis	GS	3	6.5	2	8.7	2	3.6	2	7.1
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Flexor Digitorum Longus	GS	0	0.0	0	0.0	1	1.8	1	3.5
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Flexor Hallucis Longus	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Anterior Tibialis	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor Hallucis Longus	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor Digitorum Longus	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Peroneal Longus	GS	1	2.2	1	4.3	2	3.6	2	7.1
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Peroneal Brevis	GS	1	2.2	1	4.3	1	1.8	1	3.5
		PD	0	0.0	0	0.0	0	0.0	0	0.0

Table 4.13. Comparison of the frequencies of grey scale and power Doppler tenosynovitis/peritendonitis at the patient and tendon level between patients with psoriasis and healthy controls (EPL: Extensor pollicis longus; APL: Abductor pollicis longus; EPB: Extensor pollicis brevis; ECR: Extensor carpi radialis; ECL: Extensor carpi longus; ECB: Extensor carpi brevis).

In terms of correlation with other abnormalities within the synovio-entheseal complex, of the 16 tendons with tenosynovitis identified in patients with psoriasis, only nine had corresponding entheses included in the ultrasound protocol. While the body of a tendon can be easily visualised, not all tendon insertion sites are readily seen on ultrasound, for example, the flexor digitorum longus tendon in the foot. However, a corresponding enthesis organ can be visualised, where then tendon runs over a bony prominence, and is subject to the same mechanical shearing forces during movement as a true enthesis. Of the nine sites with corresponding true entheses examined by ultrasound, seven had associated enthesopathy, all of which had inflammatory thickening and/or hypoechoic changes (five of which also had calcification, enthesophytes and cortical irregularities) (Figure 4.14).

4.4.5.4 Synovitis

Synovitis was common among patients with psoriasis, with 23 of 28 (82.1%) patients having at least one joint affected. Table 4.14 displays the frequencies of grey scale and power Doppler synovial changes by joint. Grey scale abnormalities were most frequently seen in the wrists (46.4% of wrist joints scanned), followed by the thumb carpometacarpal joint (39.3%) and the index metacarpophalangeal joint (21.4%).

Joint		Mode	Healthy Control Group				Patients with Psoriasis			
			Joint (max n=46)		Patient (max n=23)		Joint (max n=56)		Patient (max n=28)	
			n	%	n	%	n	%	n	%
Thumb	Interphalangeal	GS	0	0.0	0	0.0	7	12.5	6	21.4
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Carpometacarpal	GS	3	6.5	3	13.0	22	39.3	14	50.0
		PD	0	0.0	0	0.0	1	1.8	1	3.6
Index Finger	Distal Interphalangeal	GS	0	0.0	0	0.0	8	14.3	8	28.6
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Proximal Interphalangeal	GS	0	0.0	0	0.0	8	14.3	5	17.9
		PD	0	0.0	0	0.0	0	0.0	0	0.0
	Metacarpophalangeal	GS	0	0.0	0	0.0	12	21.4	8	28.6
		PD	0	0.0	0	0.0	3	5.4	2	7.1
Wrist		GS	12	26.1	8	34.8	26	46.4	17	60.7
		PD	0	0.0	0	0.0	4	7.1	4	14.3
Elbow	Lateral Elbow	GS	0	0.0	0	0.0	26	46.4	17	60.7
		PD	0	0.0	0	0.0	4	7.1	4	14.3
	Medial Elbow	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0

	Posterior Elbow	GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0
Knee		GS	3	6.5	2	8.7	0.0	0	0.0	0
		PD	0	0.0	0	0.0	0.0	0	0.0	0
Ankle		GS	2	4.3	1	4.3	1	1.8	1	3.6
		PD	0	0.0	0	0.0	0	0.0	0	0.0
Tarsometatarsal		GS	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0

Table 4.14. Comparison of the frequency of grey scale synovial hypertrophy and synovial power Doppler signal by joint between patients with psoriasis and healthy volunteers.

Grey scale synovitis, while present in healthy volunteers, occurred at significantly lower rates than in patients with psoriasis (wrist joint 46.4% vs. 26.1% in healthy controls, p=0.0345; thumb carpometacarpal joint 39.3% vs. 6.5%, p=0.0001; index metacarpophalangeal joint 21.4% vs. 0%, p=0.0021; knee joint 17.9% vs. 6.5%, p=0.0876; index finger distal interphalangeal joint 14.3% vs 0%, p=0.0188; index finger proximal interphalangeal joint 14.3% vs. 0%, p=0.0188; thumb interphalangeal joint 12.5% vs. 0%, p=0.0319), with the exception of the ankle joint (1.8% vs. 4.3% in healthy controls, p=0.446) (Figure 4.15).

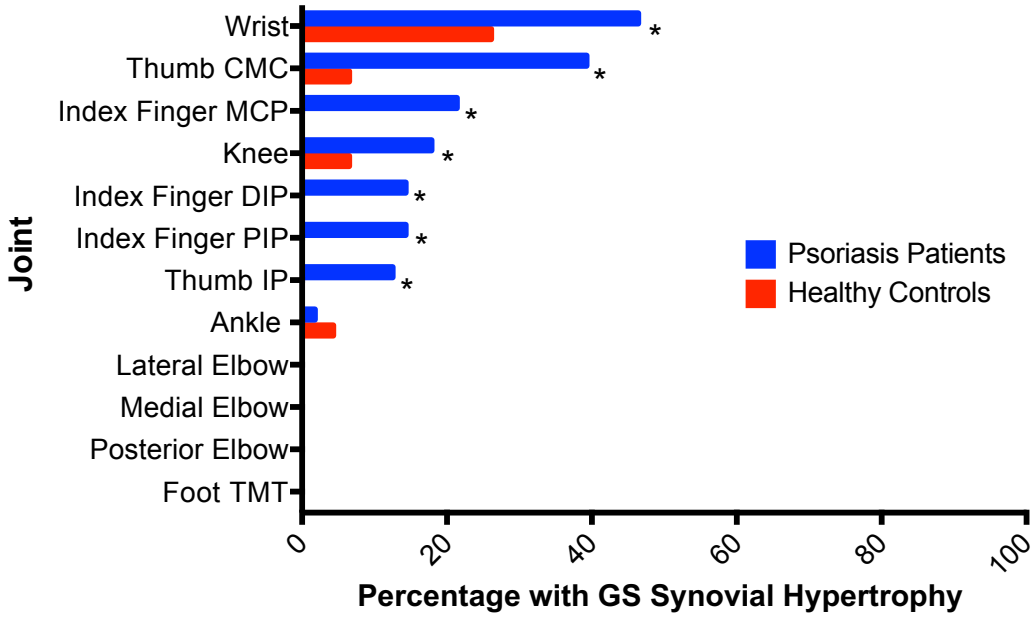

Figure 4.15. Comparison of the frequency of joints with grey scale synovial hypertrophy between patients with psoriasis and healthy volunteers (CMC: Carpometacarpal; MCP: Metacarpophalangeal; DIP: Distal interphalangeal; PIP: Proximal interphalangeal; IP: Interphalangeal; TMT: Tarsometatarsal). *denotes a significant difference between groups (p<0.05).

Power Doppler was identified in a total of eight joints (1.2% of all joins scanned) in the psoriasis patient group and not in any healthy volunteers (Figure 4.16). No significant differences were seen between the groups at any site. No synovitis (grey scale or PD) was seen at the elbow in either group.

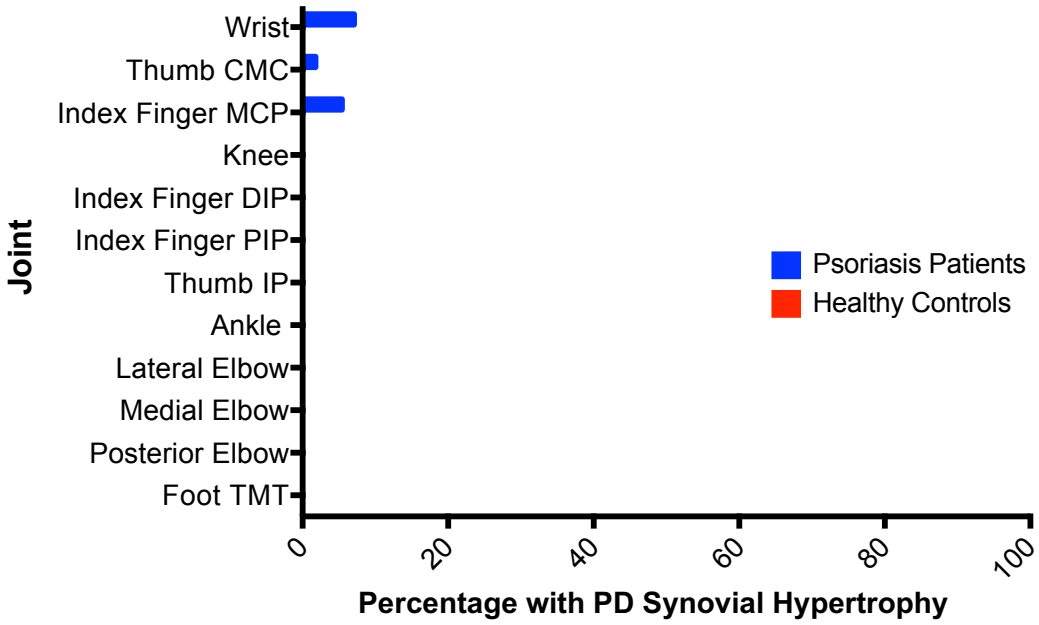

Figure 4.16. Comparison of the frequency of joints with synovial power Doppler signal between patients with psoriasis and healthy volunteers (CMC: Carpometacarpal; MCP: Metacarpophalangeal; DIP: Distal interphalangeal; PIP: Proximal interphalangeal; IP: Interphalangeal; TMT: Tarsometatarsal).

Overall mean synovitis scores were significantly higher in patients with psoriasis (4.46 ±3.97) than healthy volunteers (0.96 ±1.15) (p<0.0001). In the psoriasis group, no significant differences were observed between patients with a positive PEST (score >3) or negative PEST questionnaire and mean overall synovitis score (4.55 ±3.53 vs. 3.18 ±2.96, p=0.278).

4.4.5.5 Associations between clinical assessments and ultrasound findings

Associations between ultrasound scores and a number of clinical and demographic parameters were analysed using Spearman rank correlation, with the exception for ordinal and nominal data correlations, where rank biserial r_b (Somers D) was used. Absolute rho values >0.3 and d>0.4 were considered to indicate substantive correlation.

In the previous chapter, patients with a positive ultrasound (i.e. at least one inflammatory abnormality at screening) were found to be older than those who had a negative ultrasound (p<0.001), and using dichotomous scoring (present/absent) for entheseal

abnormalities, a positive association was found between age and all enthesopathy scores. In this group of 28 patients, this association was further explored taking into account the severity of individual lesions, and increasing age was found to correlate only with greater chronic damage scores (rho=0.66), and therefore total enthesopathy scores (rho=0.51) (Table 4.15). In the healthy volunteer group, age correlated with chronic damage score (rho=0.33) but not inflammation score (rho=0.07), total enthesopathy score (rho=0.28), synovitis score (rho=0.26) or tenosynovitis score (rho=0.05).

BMI was found in the previous chapter to correlate with all enthesopathy scores, but in this cohort a positive association was only found with inflammation score (rho=0.39) and total enthesopathy score (rho=0.33). In the healthy volunteer group, BMI also correlated with the inflammation score (rho=0.41) and total enthesopathy score (rho=0.36), but not chronic damage, synovitis or tenosynovitis scores.

The link between the presence and severity of nail disease in patients with psoriasis (using the mNAPSI score) and severity of subclinical enthesitis has previously been reported (Ash et al., 2012b). In the cohort in this thesis, the mNAPSI score positively correlated with inflammation scores for the entheses (rho=0.32) and synovial joints (rho=0.49). Higher chronic damage scores were seen in those who had had psoriasis for longer (rho=0.44), and who had smoked for longer. No associations were seen in relation to the burden of psoriasis, as assessed by PASI score, BSA involvement and the number of sites involved (currently or ever), PEST score or the number of entheseal points tender on clinical examination and any ultrasound scores.

Correlations	**Inflammation Score**	**Chronic Damage Score**	**Total Enthesopathy Score**	**Total Synovitis Score**	**Total Tenosynovitis Score**
Age	rho=0.08	rho=0.66*	rho=0.51*	rho=0.30	rho=0.16
Gender	d=0.14	d=0.16	d=0.14	d=0.25	d=-0.11
BMI	rho=0.39*	rho=0.21	rho=0.33*	rho=0.25	rho=-0.14
PASI score	rho=-0.26	rho=-0.07	rho=-0.19	rho=0.03	rho=0.30
mNAPSI score	rho=0.32*	rho=0.17	rho=0.26	rho=0.29	rho=-0.02
BSA	rho=-0.16	rho=-0.07	rho=-0.12	rho=0.05	rho=0.26
Duration of Psoriasis	rho=-0.16	rho=0.44*	rho=0.22	rho=015	rho=0.30
Age of Psoriasis Onset	rho=0.17	rho=0.10	rho=0.18	rho=0.00	rho=-0.16
Smoker (ever)	d=0.14	d=0.25	d=0.27	d=0.16	d=-0.10
Smoking pack years	rho=0.21	rho=0.50*	rho=0.49*	rho=0.29	rho=-0.15
No. of PsO sites (current)	rho=-0.006	rho=-0.05	rho=-0.06	rho=0.29	rho=0.05
No. of PsO sites (ever)	rho=-0.001	rho=0.02	rho=-0.008	rho=0.32	rho=-0.07

Correlations	Inflammation Score	Chronic Damage Score	Total Enthesopathy Score	Total Synovitis Score	Total Tenosynovitis Score
No. of clinically tender entheses	rho=0.28	rho=-0.17	rho=0.18	rho=0.11	rho=0.07
PEST Score	rho=0.26	rho=0.19	rho=0.29	rho=0.13	rho=0.02

(Table 4.15. Associations between demographic and clinical parameters, and enthesopathy, tenosynovitis and synovitis scores. rho=Spearman rank correlation coefficient. d=Rank biserial correlation coefficient (Somers *D*). Values in bold represent rho>0.3 and are considered to represent a substantive correlation (PsO: psoriasis). *denotes significance at $p<0.05$ level.

4.5 Discussion

A consensus definition for *enthesitis* remains undetermined within the published literature, with the OMERACT Ultrasound Task Force recently questioning what should be classed as an 'inflammatory' abnormality (Terslev et al., 2014). The main parameter for debate was entheseal thickness, which some experts felt should be included as an inflammatory change, while others attributed this to be a structural damage abnormality. Both arguments have merit; in the acute phase, increased thickness may be present due to inflammation as demonstrated by McGonagle et al, with soft tissue oedema seen at the plantar fascia enthesis on MRI (McGonagle et al., 2002b). However, thickening could also arise as a result of the disorganised repair process in psoriatic disease as a consequence of resolving inflammation. The current published OMERACT definition is for *enthesopathy* and encompasses both inflammatory and chronic damage abnormalities, and this was the basis for the ultrasound protocol used in this cohort study (Wakefield et al., 2005). In keeping with previous studies, thickness was included as part of the inflammation parameters, although the validity of this could be challenged. Further research could include improved imaging and histological analysis. This may, in part, explain why there are so few published reference values for entheseal thickness, and this is the first attempt to provide a means of calculating such measurements to standardise what is meant by the term 'entheseal thickening'.

The most widely published scoring system for sonographic assessments of the entheses is the Glasgow Ultrasound Enthesitis Scoring System (GUESS), but as discussed in the previous chapter, GUESS does not include assessments of hypoechogenicity, an accepted key inflammatory abnormality, nor calcifications or bony cortical irregularities (Balint et al., 2002). GUESS also does not include any assessments of sites outside of the lower limb, and as shown in the previous chapter, the distribution of subclinical entheseal lesions is diverse. This is the first study to assess all aspects of the OMERACT definition of enthesopathy and in a wide variety of upper and lower limb entheses in one

ultrasound protocol, for use in patients with psoriasis and subclinical enthesitis and healthy volunteers.

Total enthesopathy scores were calculated in both groups to encapsulate the overall burden of chronic and inflammatory abnormalities in all participants, to reflect the OMERACT definition in full. However, analyses were also performed on separate inflammation and chronic damage scores as it was expected that healthy volunteers may have a degree of structural abnormality through age-related degeneration, plus understanding the inflammatory burden in psoriasis patients could have future implications on therapeutic choice, if it were shown that inflammatory abnormalities were responsive to skin-directed treatment with immunosuppressive agents.

The use of a scoring system to encompass the severity of abnormalities facilitated a meaningful comparison with a group of healthy volunteers who were broadly matched (as a cohort) in terms of gender, age and BMI. Simply using the presence/absence of lesions is not adequate given the frequency of abnormalities among the normal population. Quantifying the full spectrum of abnormalities showed the severity of subclinical enthesopathy to be generally mild in patients with psoriasis, although the variety of abnormalities and the number of entheses involved were significantly greater than in healthy volunteers, resulting in higher enthesopathy scores in patients with psoriasis. These results are in accordance with those of previous (but more limited) studies that have also compared entheseal imaging abnormalities in psoriatic patients and healthy controls (Ash et al., 2012b, Bandinelli et al., 2013, de Miguel et al., 2009, De Simone et al., 2003, Gisondi et al., 2008, Gutierrez et al., 2011, Naredo et al., 2011, Ozcakar et al., 2005). Gutierrez et al identified grey scale enthesopathy in 8.4% of entheses examined in healthy controls, compared with 10.5% in this cohort (Gutierrez et al., 2011). Of these, 4.5% of abnormalities were inflammatory, which is similar to the rate seen by Naredo and colleagues (5.3%) (Naredo et al., 2011). No power Doppler was seen in any controls in these studies, supporting previous observations that a switch to a vascular phenotype at tendon insertion sites may be the link to arthritis development in genetically predisposed patients with psoriatic disease (Aydin et al., 2013a).

Entheseal thickening was the most frequent inflammatory abnormality amongst healthy volunteers and in similarity to previous studies, predominantly affected the weight-bearing knee entheses (Gisondi et al., 2008, Gutierrez et al., 2011, Naredo et al., 2011). Thickening of the proximal patella enthesis (21.7%) was higher than that reported in other studies (2.2-5.6%), but similar rates were observed at the quadriceps (2.2-7.8%) and distal patella entheses (3.3-6.5%). Limited thickening was observed at the Achilles tendon and plantar fascia as previously shown (Gutierrez et al., 2011) and no abnormalities were seen in the smaller, non-weight bearing entheses in the hand. Increased BMI was related in both groups to higher inflammation scores, which would support the concept of most microtrauma and resultant inflammation occurring at

entheseal sites enduring most mechanical strain (Moshrif et al., 2017). It appears that the initial insult leading to inflammation is the same regardless of the presence of psoriasis, but in genetically-primed individuals, this is sustained and not resolved without leaving lasting structural damage.

Only 6% of entheses in healthy volunteers had any structural damage abnormalities, which are thought to occur as a result of age-related degeneration and normal 'wear and tear'. Healthy volunteers were, on average, six years younger than patients with psoriasis, potentially influencing the degree of age-related degeneration in this group, although the difference in age did not reach statistical significance. Despite this discrepancy, in both groups, increased age was associated with greater chronic damage scores, although scores were significantly higher in psoriasis patients suggesting that the process of developing structural abnormalities is augmented not only as a consequence of age, but also due to a prolonged inflammatory insult at the enthesis. Erosions specifically appear to occur as a consequence of this prolonged inflammation, with no healthy volunteers in this study, or others, exhibiting osseous destructions (Bandinelli et al., 2013, De Simone et al., 2003, Gisondi et al., 2008, Gutierrez et al., 2011). Data regarding the presence of cortical irregularities and calcifications have not been published, and in this cohort, were also rarely observed in healthy volunteers, seen in just 1.2% and 2.0% of entheseal insertions respectively. Enthesophytes were the most frequent chronic damage abnormality, but still seen at low frequency (2.8%), which is comparable to previous findings (Gisondi et al., 2008, Gutierrez et al., 2011). They were seen with the greatest frequency at the Achilles tendon and quadriceps insertions, presumably as a response to mechanical loading at these sites. Chronic damage abnormalities were frequently accompanied by synovitis in healthy volunteers at these sites.

Aside from inflammatory and chronic damage entheseal abnormalities, overall scores were also calculated for tenosynovitis and synovitis for all participants in order to assess the full burden of inflammation within the synovio-entheseal complex. Scores for burseal abnormalities were incorporated into enthesopathy scores. Few previous studies have looked beyond the enthesis in patients with psoriasis to surrounding structures to enable comparison of findings, particularly with regard to the presence/severity synovitis (Naredo et al., 2011) and tenosynovitis (Naredo et al., 2011), with more having included bursitis (Ash et al., 2012b, Bandinelli et al., 2013, De Simone et al., 2003, Gisondi et al., 2008, Gutierrez et al., 2011). However, no previous studies have made a full SEC assessment including all of these structures within the same cohort.

Inflammation within the adjacent bursae has previously been shown to occur with variable frequency in patients with psoriasis and concurrent subclinical enthesopathy. In similarity to this cohort, Acquitter and colleagues identified a very low frequency of bursitis (1.4% of bursae) although the anatomical sites of positivity are not disclosed

(Acquitter et al., 2016). Naredo et al also found low rates of bursitis at the knee (suprapatellar bursitis 1.6%, infrapatellar bursitis 0%) but higher rates at the ankle (retrocalcaneal bursitis 10.0%) (Naredo et al., 2011). Similar rates were found in studies by Gutierrez (retrocalcaneal bursitis 8.9%) and Ash (11%, sites not specified) (Ash et al., 2012b, Gutierrez et al., 2011). In studies of patients with psoriasis and known PsA or musculoskeletal symptoms, rates were much higher in term of retrocalcaneal bursitis (33.9%) (De Simone et al., 2011), and infrapatellar bursitis (10.8-15.2%) (Bandinelli et al., 2013). Despite this early cohort exhibiting low rates of burseal hypertrophy in patients with psoriasis, it does appear from other studies that the frequency and severity of bursitis may progress with time, making it a worthwhile inclusion in a comprehensive ultrasound protocol. Only one healthy volunteer exhibited one area of grey-scale bursitis (out of 230 bursae examined) as a consequence of a sports injury (during marathon training), and previous studies support the absence of bursitis in the healthy, non-psoriatic population (Bandinelli et al., 2013, Gisondi et al., 2008, Naredo et al., 2011).

Only one previous study has examined the presence of tenosynovitis in patients with psoriasis, without PsA (Naredo et al., 2011). Examination was limited to the extensor and flexor tendons of the fingers, and identified peritendinous tissue oedema and tenosynovitis in 0.4% and 0.3% of tendons respectively. In this cohort of psoriasis patients, inflammation of the tendon sheath or peritendinous tissue was also seen with very low frequency (1.5%). Given the infrequent finding of tenosynovitis/peritendinitis, no significant differences were observed between psoriasis patients and healthy volunteers in either cohort, with tenosynovitis/peritendinitis seen in 0.2% of sites in the previous study, and 0.5% in this group of healthy volunteers. Due to the small number of patients with tenosynovitis/peritendinitis, any interpretation should be considered with caution. However, based on these preliminary observations, dissipation of inflammation along the tendon away from the insertion site does not appear to be a major association of subclinical enthesopathy although further larger scale studies would be needed to confirm these findings. However, ‘tendonitis’ has been reported in the Achilles tendon in 40.7% of a cohort of psoriasis patients with symptoms (11 of whom had a diagnosis of PsA), and ‘peritendonitis’ in 7 of 59, suggesting that tenosynovitis and peritendinous tissue oedema should be assessed, albeit as a later event, as part of an ultrasound protocol for patients with psoriasis.

The prominence of synovitis in psoriasis patients with subclinical enthesopathy has been discussed in Chapter 3. In similarity to the only other study to include assessments of the synovial joints in both psoriasis patients and healthy volunteers, grey scale synovial hypertrophy was significantly more frequent in psoriatic patients (32.6%, p=0.005) (Naredo et al., 2011). Amongst healthy volunteers in both cohorts, synovitis was seen most frequently at the wrist (26.1% vs. 9.8%) and knee (6.5% vs. 9.8%) compared to the ankle (4.5% vs. 0%), and no synovitis was seen in the proximal interphalangeal, distal

interphalangeal or metacarpophalangeal joints of the finger(s). Ultrasound findings suggestive of synovial inflammation have been shown to occur frequently in the healthy population (Millot et al., 2011, Ellegaard et al., 2007, Terslev et al., 2003), although most data are from studies of rheumatoid arthritis and relate to the small joints of the hands.

The patients with psoriasis in the present cohort were selected as they were known to have at least one inflammatory entheseal abnormality on ultrasound, and many had inflammatory abnormalities at other sites within the synovio-entheseal complex. Interestingly, despite being deemed to be currently asymptomatic and have had no prior persistent musculoskeletal complaints consistent with inflammatory arthritis, 11 of 28 patients had a positive PEST screening questionnaire (score ≥3/5) for a diagnosis of PsA. At first glance, this appears encouraging, in that screening questionnaires may be helpful in detecting patients with subclinical musculoskeletal disease, especially as no healthy volunteers had a score ≥3. However, on reviewing the questions to which patients gave a positive answer, the most frequent question was 'Have you ever had a swollen joint or joints?' and it was the use of the word '*ever*' that prompted respondents to tick 'yes'. Many patients, like healthy volunteers, responded 'yes' as they had sustained an injury following a fall or sporting injury that had resolved within days to weeks. Also, patients were aware that they had subclinical enthesitis on their screening ultrasound and were taking part in a clinical trial looking for further musculoskeletal abnormalities. This may have imposed a positive bias on their decision to report <u>any</u> previous minor and self-limiting musculoskeletal problem. No participants in either group reported recurrent or sustained symptoms or signs of joint effusion consistent with inflammatory arthritis, as would be detected in the real world setting in the dermatology clinic. Indeed, PsA screening questionnaires are considered to have resulted in an influx of patients without inflammatory arthritis being referred to rheumatology services in the UK, and as such a PEST score ≥3 in isolation is not used as a solitary trigger for referral in many centres.

While no healthy volunteers had a PEST score ≥3, 30.4% of healthy participants gave one or two positive responses, again mostly to the question relating to ever having had a swollen joint. Most of these participants had no abnormalities on their ultrasound scan, but had they had psoriasis and nail involvement, they too would have had a score ≥3 and a falsely positive PEST questionnaire.

17 of 28 psoriasis patients with subclinical enthesopathy did not screen positive on the PEST questionnaire, demonstrating that the use of the PEST questionnaire is inadequate to detect patients with the very earliest stages of PsA and cannot be used as a guide to target ultrasound screening. It only becomes a sensitive tool once patients have sustained symptoms of inflammation (Tinazzi et al., 2012, Haroon et al., 2013), by which time patients are likely to have developed irreversible osseous lesions and

structural damage. No differences in the burden of enthesitis were seen between those with and without a positive PEST score in terms of enthesopathy scores.

Clinical entheseal examination was also not sufficiently sensitive to reflect the ultrasound findings in this cohort of patients with psoriasis and sonographic enthesitis. Of the 392 entheses assessed both sonographically and clinically, only 5.3% of those with at least one inflammatory ultrasound abnormality were also tender. No differences were observed in enthesopathy scores between those with and without clinically tender entheses to suggest that those with more subclinical disease were more likely to have signs on clinical examination. van der Ven and colleagues examined the lateral epicondyle of the elbow, quadriceps tendon and Achilles tendon bilaterally both clinically and with ultrasound in 111 patients in primary care. In agreement with the findings in this cohort, they identified clinical tenderness at 145 of 666 sites, but found corresponding sonographic inflammatory abnormalities in only 38 tendons (5.7%) (van der Ven et al., 2016).

In this study, 47.8% of clinically tender entheseal points were normal on ultrasound. van der Ven et al found an even greater discrepancy, with 63.8% (lateral epicondyle), 76.4% (quadriceps tendon) and 87.5% (Achilles tendon) of tender sites having no corresponding inflammatory abnormality on ultrasound. These data confirm the need for imaging in patients with psoriasis to correctly identify early entheseal pathology, especially with the increasing recognition of the need to intervene therapeutically at the earliest juncture before significant structural damage occurs.

The ultrasound protocol described in this chapter took significantly longer than that in the previous chapter, averaging around 45-50 minutes per patient. Reasons for this were that, despite no longer including the third, fourth and fifth digits of the hand, extended time was needed to score each structure, in addition to scanning for signs of burseal hypertrophy and tenosynovitis. This protocol is too long for routine use in the clinical setting in every patient with psoriasis, especially in the absence of any clinical or demographic ‘biomarkers’ to help target screening. One limitation in this study was the small sample size, which prohibited the comparison of enthesopathy scores at different anatomical sites (only one or two patients had no disease at a particular anatomical location making the group size too small). In a much larger cohort, it would be useful to compare scores to see if disease at a particular anatomic location could be predictive for a greater burden of subclinical enthesopathy, given that Wilson et al observed that patients with disease at the gluteal cleft, nail and scalp had a greater hazard ratio for PsA than those without (Wilson et al., 2009). In this cohort, an association was observed between mNAPSI score and inflammation score, which warrants further investigation in larger studies.

In terms of reducing scanning time, there are certain abnormalities that were not observed at particular sites, such as synovitis at the elbow joint. However, the elbow

entheses warrant inclusion as other abnormalities occur not infrequently in psoriasis patients, and to view the joint while scanning three tendon insertions adds very little time. Similarly, no tenosynovitis was observed in the wrist, but with high rates of synovitis, the wrist should not be removed from the protocol. This protocol has however, shown significant differences in the burden of subclinical musculoskeletal abnormalities between patients with psoriasis and healthy volunteers, and is therefore recommended for use in the research setting. It now needs to be tested in a cohort of psoriasis patients to observe if it is able to detect subtle changes in abnormalities following immunosuppressive therapy.

4.6 Conclusion

The development of a scoring system that encompasses the severity of abnormalities in an extensive number of entheseal sites and the surrounding synovio-entheseal complex, and includes all components of the OMERACT definition of enthesopathy, facilitated a meaningful comparison of subclinical musculoskeletal disease between patients with psoriasis and healthy volunteers, who were broadly matched in terms of age, body mass index and gender. Quantifying the full spectrum of abnormalities demonstrated the severity of subclinical enthesitis to be generally mild amongst patients, although the range of abnormalities and number of entheseal sites involved were significantly greater than in healthy volunteers. Aside from synovitis, few abnormalities were seen outside the enthesis in both groups although bursitis and tenosynovitis are commonly reported in studies of established PsA and so there may be value in continuing to include these parameters for longitudinal assessments.

As in previous studies, no power Doppler was seen in the control group, supporting the concept that a switch to a vascular phenotype at tendon insertion sites may be linked with arthritis development and is likely to be a valuable tool in the assessment of disease progression. Among patients with psoriasis, entheseal inflammation scores showed weak positive correlation with body mass index and nail disease severity, while higher chronic damage scores were associated with increasing age and duration of psoriasis. High discordance between clinical and ultrasound assessments was observed, with only 5.3% of clinically accessible, sonographically inflamed entheses being tender on clinical examination suggesting that clinical examination is of little value in the dermatology setting. No relationship was observed between ultrasound entheseal and synovial inflammation scores and PEST score, although the question relating to heel pain appeared discriminatory with 8/12 patients reporting symptoms of possible plantar fasciitis having sonographic inflammation at that site.

Chapter 5
Response in Ultrasound Appearances of Peripheral Subclinical Enthesopathy to Anti-IL-12/23p40 Therapy for Moderate to Severe Psoriasis

5.1 Introduction

In recent years, the IL-23/17 axis have emerged as a key pathway in the pathogenesis of several immune inflammatory diseases including psoriasis and psoriatic arthritis (PsA). Murine models have demonstrated the essential role IL-17, IL-22 and IL-23 play in bone homeostasis (Quinn et al., 2008, Adamopoulos et al., 2011, Sherlock et al., 2012). IL-23 regulates bone homeostasis by inducing osteoclastogenesis (Adamopoulos et al., 2011) and altering the differentiation of IL-17 and IL-22 secreting innate and adaptive immune cells. IL-17, IL-22 and IL-23 also increase bone resorption (Ritchlin et al., 2003). Sherlock and colleagues further added credence to the pathogenic role of IL-23 at the enthesis through the identification of a resident entheseal population of innate-like T cells in mice with early psoriatic-like spondyloarthropathy (Sherlock et al., 2012). This novel population of cells expressed the IL-23 receptor, RORγt and CD3 (but not CD4 and CD8), and produced IL-17 and IL-22 in response to stimulation with IL-23. More recently, the human enthesis has been shown to harbour a resident population of innate lymphoid cells (ILC3s) characterised by the expression of RORγt, which when activated by local or systemic IL-1β and IL-23, produce IL-17 and IL-22 (Cuthbert et al., 2017). ILC3s have also been shown to be comparatively abundant in synovial fluid (Ciccia et al., 2015, Leijten et al., 2015) and psoriatic skin (Villanova et al., 2014) and are likely to play a key role in the pathogenesis of psoriatic disease. In addition, genome-wide association studies (GWAS) have identified a substantial number of candidate genes of significance in both psoriasis and PsA, including those involved in adaptive immune responses involving IL-23/IL-17 *(HLA-C, IL12B, IL23R, IL23A, TRAF3IP2, ERAP1).*

Given the clear role of IL-23 in the development of spondyloarthropathy-based, entheseal-driven pathology, and the acceptance of enthesitis as the primary lesion in PsA, a therapeutic strategy aimed at blocking the IL-23/Th17 axis would therefore pose a logical option for the treatment subclinical enthesopathy in early PsA.

To date, only one anti-IL-23 monoclonal antibody, ustekinumab (CNTO 1275, Stelara®; Janssen Cilag®) has marketing authority for use in psoriasis and more latterly, PsA. Ustekinumab is a potent inhibitor of IL-12 and IL-23 through high affinity binding to their shared p40 subunit. Such has been the success of ustekinumab that several other

inhibitors of IL-23 are in development for use in psoriasis and other autoinflammatory disorders (Guselkumab (CNTO-1959), Janssen-Cilag®; Tildrakizumab (MK-3222; SCH 900222), Sun Pharmaceutical®; Risankizumab (BI 655066), AbbVie®), although each of these specifically target the IL-23 specific p19 subunit, rather than p40.

In terms of enthesitis, the P-SUMMIT I and II trials examined the response to ustekinumab therapy and the results appear promising (Chapter 1.7.3.3.) (McInnes et al., 2013, Ritchlin et al., 2014). However, these trials only investigated patients with established PsA and enthesitis was included as a secondary outcome measure. Assessments of enthesitis were clinical, with no imaging evaluations made of the tendon insertion sites. The ECLIPSA trial is the only study to date using clinical enthesitis measures (SPARCC) as a primary outcome measure to assess the reponse to therapy either with ustekinumab or a TNF inhibitor at six months. These data showed ustekinumab to be superior in resolving the enthesitis component of disease in PsA patients with active entheseal disease. The authors conclude by recommending more stratified treatment approaches where enthesitis-driven patients are targeted by IL-23/IL-17 pathway inhibitors (Araujo et al., 2017).

The sonographic response in subclinical enthesopathy to biologic drugs used in both psoriasis and established PsA is not well studied. One small observational study has reported a decrease in morphological sonographic abnormalities in a psoriasis patients with enthesitis treated with methotrexate with or without a TNF inhibitor for six months, although a proportion of these patients fulfilled the CASPAR criteria for PsA (Acquacalda et al., 2015). To date, there have been no studies to assess the response to ustekinumab in early subclinical disease in patients with psoriasis. Given that in excess of 70% of patients who develop PsA will have precedent psoriasis, and ustekinumab provides superior PASI responses, it is therefore timely to determine if skin-directed treatment with ustekinumab can reduce subclinical enthesopathy and ultimately prevent the evolution of PsA in patients with psoriasis.

The aims and objectives of this chapter were as follows:

- To assess if any of the ultrasound abnormalities of subclinical enthesopathy (and surrounding synovio-entheseal complex changes) alter in response to therapy with anti-IL-12-23 p40 (Ustekinumab), a licensed product for the treatment of moderate to severe psoriasis, assessed at 12, 24 and 52 weeks.
- To test the feasibility of a full randomised controlled trial comparing ustekinumab with other treatment modalities for the management of subclinical psoriatic joint disease in patients with psoriasis.
- To observe if any change in clinical entheseal assessments relate to the change in subclinical enthesopathy seen on ultrasound.

- To determine if changes in entheseal scores are related to skin outcomes or improvements in nail disease.
- To establish if there is a relationship between skin outcomes, ultrasound responses and the presence of genetic risk alleles (HLA-Cw06 and HLA-B27).
- To assess whether age, gender, BMI and smoking status impact on sonographic enthesopathy scores in response to ustekinumab therapy.

5.2 Methods

Ethical approval was obtained from the National Research Ethics Committee (Reference YH/12/0483) for a phase IV, prospective, single-centre, open-label feasibility study investigating the response of subclinical enthesitis to ustekinumab, an interleukin(IL)-12/23p40 antagonist. An amendment was subsequently approved to extend the study beyond 24 weeks. Relevant approvals were also granted by the Medicines and Healthcare Products Regulatory Authority (MHRA) and the Research and Development Unit within Leeds Teaching Hospitals NHS Trust. The University of Leeds accepted the duties of Sponsor under The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amendment (No.2) Regulations 2006.

5.2.1 Sample Size

This was an exploratory proof-of-concept study and therefore no formal power calculations were performed. Published rules of thumb for such studies suggest that between 12 and 30 patients should be recruited to provide a good trade-off between feasibility and accuracy of effect size estimation (Julious, 2005, Lancaster et al., 2004). It was difficult to accurately estimate the recruitment rate to the study given that the inclusion criteria include subclinical pathology on which no prior data were available. To maximize the accuracy of the effect size estimates, the aim was to recruit 30 patients. However, it was decided prior to commencement that should recruitment prove to be difficult, a minimum of 12 patients would be deemed acceptable.

5.2.2 Participant Identification and Recruitment

The study was conducted in one tertiary centre in the United Kingdom within Leeds Teaching Hospitals NHS Trust. Patients were recruited from the Leeds Centre for Dermatology, and imaging took place within the Leeds Musculoskeletal Biomedical Research Unit (LMBRU), both at Chapel Allerton Hospital.

Recruitment took place over a two-year period (May 2013 to May 2015), which allowed for seasonal variation in psoriasis severity. Recruitment was slower in the summer

months due to patients presenting to their new patient appointment with less severe psoriasis (PASI score less than 10) and vacations.

Twenty-three adult patients (aged 18 and over) with moderate to severe chronic plaque psoriasis and signs of inflammatory subclinical enthesitis at ultrasound (but without clinically diagnosed psoriatic arthritis) were consented for participation.

These patients were recruited from a cohort of 28 patients who consented to a short screening ultrasound (to identify whether they had subclinical enthesitis) followed by a more detailed ultrasound scan (to quantify the extent of abnormalities within the synovio-entheseal complex). They were all new patients who had been referred by their General Practitioner (GP) for treatment of moderate to severe chronic plaque psoriasis (defined as a Psoriasis Area and Severity Index (PASI) score of 10 or more) and were systemic and biologic treatment naïve. They all failed to meet the CASPAR classification for psoriatic arthritis on the basis of no definitive symptoms of inflammatory arthritis, defined clinically as early morning stiffness (15 minutes or more duration) and/or prolonged and non-traumatic joint swelling. Inflammatory subclinical enthesitis was defined as entheseal thickening, hypoechogenicity and/or power Doppler signal in at least one peripheral tendon insertion site. All participants were rheumatoid factor and anti-citrullinated peptide (anti-CCP) antibody negative. Chapter 4.2.1.1. provides more detail on recruitment into the cohort of 28 patients.

At the initial new patient consultation, in preparation for starting therapy at the next appointment, a series of standard investigations were performed. These form part of ‘routine’ care for any patient being considered for any form of systemic immunosuppressive therapy and feature in the BAD and NICE guidelines for moderate to severe psoriasis:

- Blood tests: Full blood count, urea and electrolytes, liver function tests, C-reactive protein, fasting glucose, cholesterol (total, HDL and LDL), triglycerides, anti-nuclear antibody
- Hepatitis B and C serology: Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody
- Human immunodeficiency virus (HIV) testing
- QuantiFERON® Gold serology (to test for tuberculosis)
- Chest x-ray (to exclude infection, malignancy and latent tuberculosis)
- Electrocardiogram

At their initial consultation, patients were provided with impartial information sheets written by the British Association of Dermatologists (BAD) for the different treatment options that would be potentially available to them (e.g. narrowband phototherapy (with or without acitretin), fumaric acid esters and systemic immunosuppressants including methotrexate and ciclosporin) if their screening investigations were normal. In addition,

those patients with inflammatory subclinical enthesitis on the initial ultrasound scan were also given written information about the investigational medicinal product (IMP), ustekinumab, an IL-12/23 antagonist and a Patient Information Sheet about the study. Patients were asked to contemplate their treatment preferences and consider their participation in the trial in the interval between scans, which was between one and three weeks depending on sonographer availability. No screening abnormalities or contraindications to any therapy were found in the cohort of 28 patients who returned for the second, more detailed ultrasound scan.

Potential participants were made aware that outside of the research setting, biologic therapy would not have been available to them at this stage in their therapeutic journey, as the National Institute of Health and Care Excellence (NICE) guidelines require patients within the NHS to have been treated with at least two non-biologic systemic immunosuppressant therapies first. This restriction is based purely on economic grounds, and in no way reflects the efficacy or safety of the drug in treatment naïve patients.

At the time of recruitment, ustekinumab was licensed for the treatment of psoriasis, but not psoriatic arthritis. Promising musculoskeletal data were emerging and part way through the study, ustekinumab was granted marketing authority for the treatment of active psoriatic arthritis. Figure 5.1 details the therapeutic indications that ustekinumab is licensed for in the United Kingdom:

> **PLAQUE PSORIASIS:** *Ustekinumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and psoralen ultraviolet A (PUVA).*
>
> **PSORIATIC ARTHRITIS:** *Ustekinumab, either alone or in combination with methotrexate is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic (DMARD) therapy has been inadequate.*

Figure 5.1. Licensed therapeutic indications for ustekinumab

At the second scan appointment, five patients declined participation and chose standard therapy (narrowband UVB phototherapy) and 23 chose to enter the study and receive ustekinumab. The five who declined participation in the study did consent to undergo the second, more detailed ultrasound scan for comparison with the results from volunteers in the healthy control group (Chapter 4).

5.2.3 Inclusion/Exclusion Criteria

5.2.3.1 Inclusion Criteria

- Male and female patients aged 18 years and older
- Diagnosis of chronic plaque psoriasis, confirmed by a dermatologist (the candidate, LS)
- Duration of psoriasis symptoms greater than twelve months
- Moderate or severe disease (classified as a PASI score >10)
- No prior treatment with systemic immunosuppressant or biologic agents
- Failure to meet the CASPAR classification for psoriatic arthritis on the basis of no symptoms of inflammatory arthritis (early morning stiffness lasting 15 minutes or more in duration, joint pain and/or prolonged and non-traumatic joint swelling)
- Evidence of inflammatory subclinical enthesitis on ultrasound in at least one peripheral enthesis

In addition, all male and female subjects biologically capable of having children must have agreed to use at least one reliable method of contraception for the duration of the study and for 24 weeks after the end of the study. Acceptable methods of contraception were surgical sterilization, oral, implantable or injectable hormonal methods, intrauterine devices or barrier contraceptives.

5.2.3.2 Exclusion Criteria

- Psoriasis of mild to moderate severity (PASI<10)
- Previous treatment with any systemic immunosuppressant or biologic agent (for psoriasis or any other indication)
- Patients unable or not willing to attend all imaging, serological and clinical assessments
- Any contraindication to magnetic resonance imaging (MRI) scanning (e.g. pacemaker, aneurysm coil, history of metal in the eye) (Appendix 10).
- Patients not willing to use adequate methods of contraception
- Pregnancy or lactation
- Any contraindication to systemic or biologic therapy:
    - Active infection, including open leg ulcers, human immunodeficiency virus (HIV), hepatitis B or C carriers
    - Active or latent tuberculosis
    - Malignancy – current, or previous within the last ten years (except basal cell carcinoma)
    - Severe heart failure (NYHA grade III or more)
    - Demyelinating disorders

    - Uncontrolled diabetes
    - Chronic lung disease (pulmonary fibrosis or bronchiectasis)
    - Previous PUVA phototherapy (>1000 joules)
- History of other significant medical conditions, including:
    - Severe pulmonary disease (defined as requiring previous hospital admission or supplemental oxygen)
    - Active or severe cardiovascular disorders: uncontrolled hypertension, myocardial infarction within the previous twelve months, unstable angina within the previous six months)
    - Any immunodeficiency disorder
    - Connective tissue diseases (e.g. primary Sjogrens syndrome, systemic sclerosis, systemic lupus erythematosus, polymyositis)
    - Renal impairment (creatinine clearance <45ml/min)
    - Abnormal liver function tests (alanine transferase >3x upper limit of normal)
    - Blood disorders, i.e. neutropenia (neutrophils $<2.0x10^9$/l), thrombocytopenia (platelets $<125x10^9$/l) or anaemia (haemoglobin <8g/dl).
- Any forthcoming event that may interrupt participation (e.g. a holiday, elective hospital admission) lasting longer than 14 days.

5.2.4 Drug Therapy

5.2.4.1 Ustekinumab

Ustekinumab (experimental name CNTO1275) is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23p40, produced in a murine myeloma cell line using recombinant DNA technology. It is under patent (until 2024) with holders Janssen Biotech (the pharmaceutical arm of Johnson & Johnson) with the proprietary commercial name Stelara®. It is supplied in a pre-filled syringe, with each vial containing 45mg ustekinumab in 0.5ml solution and is available on prescription in the United Kingdom in secondary care centres only. Ustekinumab was prescribed by the candidate (LS), a dermatologist experienced in the diagnosis and treatment of plaque psoriasis.

Ustekinumab is administered subcutaneously at a dose dependant on body weight. In adults, the standard dose is 45mg, but for patients who weigh in excess of 100kg, 90mg is licensed. The recommended posology of ustekinumab is an initial dose followed by a second dose four weeks later, and then every 12 weeks thereafter. Every dose was administered by the candidate (LS) at a patient's appointment to ensure compliance and

reduce the need for patient training and consumables at home (e.g. burn bins for needles). No dose adjustment is needed for elderly patients.

Known adverse reactions to ustekinumab are listed in Table 5.1.

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Common	Dental infections, upper respiratory tract infections, nasopharyngitis
	Uncommon	Cellulitis, viral upper respiratory tract infections, herpes zoster
Immune system disorders	Uncommon	Hypersensitivity reactions (e.g. rash, urticarial)
	Rare	Serious hypersensitivity reactions (e.g. anaphylaxis, angioedema)
Psychiatric disorders	Uncommon	Depression
Nervous system disorders	Common	Dizziness, fatigue
	Uncommon	Facial palsy
Respiratory, thoracic and mediastinal disorders	Common	Oropharyngeal pain
	Uncommon	Nasal congestion
Gastrointestinal disorders	Common	Nausea and diarrhoea
Skin and subcutaneous tissue disorders	Common	Pruritus
	Uncommon	Pustular psoriasis, skin exfoliation
	Rare	Exfoliative dermatitis
Musculoskeletal and connective tissue disorders	Common	Back pain, myalgia, arthralgia
General disorders and administration site reactions	Common	Injection site erythema, injection site pain, fatigue
	Uncommon	Injection site reactions (e.g. haematoma, haemorrhage, induration, swelling, pruritus)

Table 5.1. List of known adverse reactions to ustekinumab

Further information on ustekinumab can be found in the Summary of Medical Characteristics (www.medicines.org.uk/emc/medicine/32569).

5.2.4.2 Permitted and Prohibited Concomitant Treatments

All treatments taken (prescribed or otherwise) by participants in addition to the investigational product, on entry to the study or at any time during the study, were regarded as concomitant treatments and were documented.

Concomitant medications were kept to a minimum during the study. However, if they were considered necessary for the participants' welfare, and were unlikely to interfere with the investigational products, they were permitted at the discretion of the candidate (LS) and recorded.

Permitted concomitant medications:

- Topical psoriasis therapies, including:
    - Emollients
    - Vitamin D analogues
    - Topical corticosteroids
    - Coal tar preparations
    - Dithranol
    - Tazarotene
    - Eosin
- Analgesic medications, including paracetamol, codeine, tramadol and morphine. As required use of non-steroidal anti-inflammatory drug (NSAID) medications was permitted as long as it was not in excess of two standard doses (e.g. ibuprofen 400mg) per week.

Prohibited concomitant medications:

- Oral or intravenous steroids
- Regular NSAIDs
- Any other systemic, DMARD or biologic agent (regardless of indication, e.g. leflunomide for rheumatoid arthritis)
- Any alkylating agents (e.g. cyclophosphamide)
- Any experimental drug
- Vaccination with live vaccines

Surgical Procedures

Planned surgery within the study period (which was expected to require omission of any study medication for 14 days or more) was an exclusion criterion. However, unplanned surgical treatments could be performed; each must have been documented as a

separate adverse event. Patients undergoing general anaesthesia were permitted to interrupt study medication. In total, a single dosing interruption of 14 days was allowed. Patients requiring surgical procedures involving local or regional anaesthesia could continue with study medication.

5.2.5 Participant Visit Schedule

After their initial new patient consultation, patients consenting to take part in the trial attended for a total of six study visits at weeks 0, 4, 12, 16, 24 and 52. Baseline (week 0) was taken as the date of first injection, which occurred immediately following written consent, the second ultrasound scan and clinical assessment. Ustekinumab was administered at week 0, week 4 and week 16 by the candidate (LS). After the primary end point of 24 weeks, the administration of therapy was passed to the BUPA™ Healthcare at Home team, a free nurse-led service provided by the drug manufacturer (Janssen Pharmaceuticals) to the NHS. The drug is delivered to the patient's home at a mutually convenient time, and a nurse then arranges a visit to administer the drug. Standardised reporting procedures are in place should the nurse have any concerns about the patient or their therapy. Between weeks 24 and 52, patients were asked to attend for a brief review in the general psoriasis clinic within the Leeds Centre for Dermatology. Patients were reviewed by either the candidate (LS) or the candidate's supervisor, a Consultant Dermatologist (MDG). No research assessments were made but any adverse events were recorded. Patients provided written consent a second time at the week 52 visit to continue in the study beyond week 24.

Ultrasound scans were performed at weeks 0, 12, 24 and 52. The full study schedule can be found in Table 5.2. All visits happened within seven days of the scheduled date.

Study Week	Weeks -3 to -1	Week 0	Week 4	Week 12	Week 16	Week 24	Week 52
Study Phase	**New patient appointment**	**Baseline**	**Monitor**	**Midpoint**	**Dosing Visit**	**Primary Endpoint**	**Secondary Endpoint**
Study Visit No.	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Demographics, past medical history, social history, family history	X	X					
Medication history	X	X	X	X		X	X
Assessment for PsA/Application of CASPAR classification	X	X					
Physical examination of skin, joints and entheses	X	X	X	X		X	X
PASI, BSA and assessment of involved sites	X	X	X	X		X	X
DLQI questionnaire	X	X		X		X	X
mNAPSI	X	X		X		X	X
PEST questionnaire	X	X					
Blood pressure and heart rate	X	X	X	X		X	X
Assessment of suitability for systemic/biologic	X	X					
Serology: FBC, U&E, LFT, CRP, PV, glucose, cholesterol, triglycerides	X		X	X		X	X

Study Week	Weeks -3 to -1	Week 0	Week 4	Week 12	Week 16	Week 24	Week 52
Study Phase	**New patient appointment**	**Baseline**	**Monitor**	**Midpoint**	**Dosing Visit**	**Primary Endpoint**	**Secondary Endpoint**
Study Visit No.	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Serology: ANA	X					X	X
Serology: Hepatitis B and C, HIV	X						X
Serology: QuantiFERON Gold	X						X
Chest X-ray	X						X
12 lead electrocardiogram	X			X			X
Review of inclusion/exclusion criteria	X	X				X	
Screening ultrasound (peripheral joints) with written consent	X						
Provision of treatment and study information sheets	X						
Informed written consent for study participation		X					X
General Practitioner Information Sheet posted		X					X
Adverse Events			X	X	X	X	X

Study Week	Weeks -3 to -1	Week 0	Week 4	Week 12	Week 16	Week 24	Week 52
Study Phase	**New patient appointment**	**Baseline**	**Monitor**	**Midpoint**	**Dosing Visit**	**Primary Endpoint**	**Secondary Endpoint**
Study Visit No.	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Concomitant medications/illnesses		X	X	X		X	X
Compliance assessment			X	X		X	X
Review blood results (monitoring)		X	X	X		X	X
GS and PD Ultrasound (peripheral entheses)		X		X		X	X
Whole body MRI Scan (Chapter 7)		X				X	X
Drug administration (S/C Injection) by candidate (LS)		X	X		X		
Drug administration switched to NHS/BUPA (standard care)						X	

Table 5.2. Study schedule for participants

5.2.6 Data Collection

With written consent, three types of data (participant-reported data, clinical examination data and imaging data) were collected from participants for research purposes and entered into an encrypted, password-protected database by the candidate (LS).

Participant-reported and clinical examination data collections were carried out solely by the candidate (LS) and immediately onto a case report form (CRF). Ultrasounds were performed by one of two experienced musculoskeletal sonographers (LH and AJ), who recorded the imaging data on a separate CRF (Appendix 9) at the time of the scan. All data was transposed into encrypted password-protected databases on the University of Leeds server for analysis within seven days. Care was taken to ensure the check integrity of the dataset at upload. Paper record forms are stored in a locked filing cabinet within a locked room within LIRMM, in accordance with the University's Information Security Policy.

Participant-reported data included all elements of the medical history at baseline (demographics, skin type, social history (smoking, alcohol and employment), past medical and surgical history, history of skin and joint disease, family history, medications (current prescribed, over-the-counter, alternative and psoriasis-specific medications, and any previous psoriasis therapies), age of psoriasis symptom onset, areas ever affected by psoriasis, areas currently affected by psoriasis and current or previous musculoskeletal symptoms). Adverse events, medication history, areas of psoriasis involvement and musculoskeletal symptoms were recorded at week 4, 12, 24 and 52. Patients also self-completed the DLQI at baseline, week 4, week 12, week 24 and week 52.

Clinical examination data included assessment of the severity, extent and anatomical location of psoriatic plaques, blood pressure and heart rate, height and weight, and assessment of any signs of psoriatic arthritis (joint swelling and/or tenderness, entheseal tenderness or dactylitis). Clinical examination was performed at baseline, then weeks 4, 12, 24 and 52.

5.2.7 Clinical Assessment

5.2.7.1 Psoriasis Severity and Impact

At week 0, 4, 12, 24 and 52, patients were fully exposed (to their underwear) and unblinded assessments made of their psoriasis (distribution, extent, plaque thickness, erythema and scale) and nails (onycholysis, pitting, crumbling, red spots in the lunula, leuconychia, oil spot dyschromia, nail bed hyperkeratosis) by the candidate (LS). From

these assessments, scores were calculated for the PASI (Appendix X), BSA and mNAPSI (Appendix X). The assessor did not look at previous scores prior to each clinic visit. Skin responses to ustekinumab were calculated as the number of patients achieving a 75%, 90% and 100% improvement in PASI score from week 0 (termed PASI 75, PASI 90 and PASI 100, respectively) at week 4, 12, 24 and 52.

Quality of life was assessed using the patient-completed DLQI questionnaire at weeks 0, 4 (DLQI only), 12 (DLQI only), 24 and 52.

5.2.7.2 Psoriatic Arthritis

All accessible peripheral joints were visually examined for gross evidence of swelling, and where a patient reported any discomfort, a closer examination was made to identify tenderness. Several entheseal points were also examined for tenderness – direct pressure was applied to the following sites, with sufficient force to just blanche the thumbnail of the examiner:

- 1st and 7th costochondral joints
- Supraspinatus insertion
- Medial and lateral epicondyles of the humerus
- Anterior and posterior superior iliac spines
- Iliac crest
- 5th lumbar process
- Greater trochanter
- Medial condyle of the femur
- Quadriceps insertion at the patella
- Inferior pole of the patella
- Tibial tubercle
- Proximal Achilles
- Plantar fascia insertion

In addition, the fingers and toes were examined for any fusiform swelling (with or without tenderness) consistent with dactylitis. Examinations for joint swelling (and tenderness), enthesitis and dactylitis were performed at weeks 0, 4, 12, 24 and 52.

5.2.8 Laboratory Assessment

Safety monitoring was undertaken in line with standard NHS care procedures for any patient taking a biologic therapy. A full blood count, urea and electrolytes, liver function tests, C-reactive protein, cholesterol (total, HDL and LDL), triglycerides, fasting glucose and anti-nuclear antibody, in addition to urinalysis, were done at the initial new patient consultation, then repeated at weeks 4, 12, 24 and 52. Samples were processed in the

relevant NHS laboratories within Leeds Teaching Hospitals NHS Trust under the terms of their standard operating procedures and patients were informed within 24 hours of any abnormalities.

In terms of study procedures, anti-CCP antibody and rheumatoid factor were sampled at week 0 and repeated at week 24 and 52, to ensure that patients did not have, or develop, any other rheumatological disorders such as rheumatoid arthritis. All participants were negative at baseline. Rheumatoid Factor was measured by nephelometry (IU/ml) and anti-CCP antibody was measured by multiplex bead technology (bioplex) (U/ml).

Patients were also tested at baseline for two genetic risk alleles for psoriatic arthritis in patients with psoriasis – HLA-Cw06 and HLA-B27. The former is shown to be associated with skin responses to ustekinumab, but any association with subclinical enthesitis is not known. HLA-Cw06 and HLA-B27 were both measured by single antigen bead testing (median fluorescent intensity, MFI).

5.2.9 Ultrasonography

5.2.9.1 Ultrasound Equipment and Protocol

Ultrasonography was undertaken by two dedicated musculoskeletal research sonographers (AJ and LH) in the Leeds Musculoskeletal Biomedical Research Unit (LMBRU). Scans were performed at baseline (week 0), week 12, week 24 and week 52. Details about the equipment and scanning technique can be found in Chapter 3.1.6. It was not possible to blind the sonographers to the study visit due to the same sonographers performing the scans and the small number of participants in the trial. They were not aware of their response to therapy in the later scans, and participants were asked not to disclose any details of their medical consultation to the sonographer. Scans were performed in a darkened room reducing the sonographer's ability to inspect the patients' skin if they wished to do so.

Tables 4.2., 4.3., 4.4., and 4.5. (Chapter 4) summarise the tendon entheses and corresponding bone insertion sites, associated bursa and sites for tenosynovitis and synovitis scanned. Chapter 3.1.6. describes the procedure followed by the sonographers to incorporate all of these structures in the scan.

5.2.9.2 Ultrasound Image Interpretation

Images were evaluated and scored at the time of the scan by the sonographer and when possible, the candidate (LS). Enthesopathy, bone erosions, tenosynovitis and synovial hypertrophy were identified according to the definitions provided by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Special Interest Group for

Musculoskeletal Ultrasound in Rheumatology (Figures 4.1., 4.2., 4.3. and 4.4., Chapter 4) (Wakefield et al., 2005). Bursitis was defined as a well circumscribed, localised anechoic or hypoechoic area at the site of an anatomical bursa which was compressible by the transducer with bursal wall thickening, with or without periburseal or intraburseal power Doppler signal (Schmidt et al., 2004).

5.2.9.3 Ultrasound Scoring

Ultrasound parameters were scored either quantitatively or semi-quantitatively:

Quantitative measurements:

- Entheseal thickness*:

  0 = Less than threshold
  1 = Greater than threshold but by less than1mm
  2 = ≥1mm above threshold but <2mm
  3 = ≥2mm above threshold
  *Measured at its widest point at the insertion on longitudinal scans. Published thresholds used where available. See Chapter 4.2.6.3.1. for details of how the other thresholds were determined.

- Bone erosions**:

  0 = absence of erosions
  1 = present and <2mm in diameter
  2 = present and 2-3mm in diameter
  3 = present and ≥ 3mm in diameter
  **Largest erosion measured at each site.

Semi-quantitative assessments:

- Hypoechogenicity*
- Entheseal power Doppler signal**
- Calcifications*
- Enthesophytes*
- Bone cortex irregularities*
- Bursal hypertrophy*
- Bursal power Doppler signal**
- Tenosynovitis (grey scale* and power Doppler**)
- Synovitis (grey scale* and power Doppler**)

  *All scored as:

  0 = absence
  1 = mild

2 = moderate

3 = marked/severe

**Power Doppler scored as:

0 = absence

1 = mild (≤3 isolated signals)

2 = moderate (>3 isolated signals or confluent signal in <50% of the area under examination)

3 = marked (signals in >50% of the area under examination)

5.2.9.4 Ultrasound Scoring System

Summative scores were calculated to allow comparisons of the extent of enthesopathy over time at a patient level. Based on the Glasgow Ultrasound Enthesitis Score (GUESS) score (Appendix 11) (Balint et al., 2002) and Sonographic Enthesitis Index (SEI) (Alcalde et al., 2007) (Appendix 12), a more comprehensive enthesopathy score was created which encompassed all of the sites and parameters assessed. Like the SEI, this was divided into an inflammation score, a chronic damage score and a total overall score (the sum of the two). Scores were also calculated for tenosynovitis and synovitis.

- ***Enthesopathy Inflammation Score:*** The sum of scores from the assessment of entheseal thickness, hypoechogenicity and power Doppler signal in all tendons, plus any bursal hypertrophy and power Doppler signal where appropriate, at all entheseal sites.
  Maximum score: 294

- ***Enthesopathy Chronicity Score:*** The sum of scores from the assessment of entheseal calcification(s), enthesophytes, bone erosions and bone cortex irregularity, at all entheseal sites.
  Maximum Score: 312

- ***Total Enthesopathy Score:*** The sum of the inflammation and chronicity scores.
  Maximum Score: 606

- ***Tenosynovitis Score:*** The sum of scores from the grey scale assessment of tendon sheath thickening/hypoechogenicity and power Doppler signal at all examined sites.
  Maximum Score: 264

- ***Synovitis score:*** The sum of the scores from the grey scale assessment of synovial hypertrophy/proliferation and power Doppler signal from all examined joints.
  Maximum Score: 144

5.2.9.4.1 Enthesopathy Score

26 entheses (13 per side) were scanned in each participant, and each parameter scored 0-3, with a maximum possible score of 606:

- *THUMB: Base of distal phalynx - flexor pollicis longus tendon enthesis*
  8. Flexor pollicis longus enthesis thickness ≥ 1.0mm
  9. Flexor pollicis longus enthesis hypoechogenicity
  10. Flexor pollicis longus enthesis power Doppler signal
  11. Base of distal phalynx calcification
  12. Base of distal phalynx enthesophyte(s)
  13. Base of distal phalynx bony erosion(s)
  14. Base of distal phalynx bony cortex irregularity

- *THUMB: Dorsal base of distal phalynx – extensor pollicis longus tendon enthesis*
  8. Extensor pollicis longus enthesis thickness ≥ 1.0mm
  9. Extensor pollicis longus enthesis hypoechogenicity
  10. Extensor pollicis longus enthesis power Doppler signal
  11. Dorsal base of distal phalynx calcification
  12. Dorsal base of distal phalynx enthesophyte(s)
  13. Dorsal base of distal phalynx bony erosion(s)
  14. Dorsal base of distal phalynx bony cortex irregularity

- *INDEX FINGER: Distal phalynx base - flexor digitorum profundus*
  8. Flexor digitorum profundus/superficialis enthesis thickness ≥ 1.0mm
  9. Flexor digitorum profundus/superficialis enthesis hypoechogenicity
  10. Flexor digitorum profundus/superficialis enthesis power Doppler signal
  11. Middle/distal phalynx base calcification
  12. Middle/distal phalynx base enthesophyte(s)
  13. Middle/distal phalynx base bony erosion(s)
  14. Middle/distal phalynx base bony cortex irregularity

- *INDEX FINGER: Distal phalynx base - extensor digitorum tendon enthesis*
  8. Extensor digitorum enthesis thickness ≥ 0.9mm
  9. Extensor digitorum enthesis hypoechogenicity

10. Extensor digitorum enthesis power Doppler signal
11. Distal phalynx base calcification
12. Distal phalynx base enthesophyte(s)
13. Distal phalynx base bony erosion(s)
14. Distal phalynx base bony cortex irregularity

- *ELBOW: Lateral epicondyle of humerus - common extensor tendon enthesis*
  8. Elbow common extensor enthesis thickness ≥ 4.9mm
  9. Elbow common extensor enthesis hypoechogenicity
  10. Elbow common extensor enthesis power Doppler signal
  11. Lateral epicondyle of humerus calcification
  12. Lateral epicondyle of humerus enthesophyte(s)
  13. Lateral epicondyle of humerus bony erosion(s)
  14. Lateral epicondyle of humerus bony cortex irregularity

- *ELBOW: Medial epicondyle of humerus - common flexor tendon enthesis*
  8. Common flexor enthesis thickness ≥ 4.7mm
  9. Common flexor enthesis hypoechogenicity
  10. Common flexor enthesis power Doppler signal
  11. Medial epicondyle of humerus calcification
  12. Medial epicondyle of humerus enthesophyte(s)
  13. Medial epicondyle of humerus bony erosion(s)
  14. Medial epicondyle of humerus bony cortex irregularity

- *ELBOW: Olecranon process of the ulna - distal brachial triceps tendon enthesis*
  10. Elbow distal brachial triceps enthesis thickness ≥ 4.3mm
  11. Elbow distal brachial triceps enthesis hypoechogenicity
  12. Elbow distal brachial triceps enthesis power Doppler signal
  13. Olecranon process of ulna calcification
  14. Olecranon process of ulna enthesophyte(s)
  15. Olecranon process of ulna bony erosion(s)
  16. Olecranon process of ulna bony cortex irregularity
  17. Olecranon bursitis (GS hypertrophy)
  18. Olecranon burseal power Doppler signal

- *KNEE: Superior pole of the patella - quadriceps tendon enthesis*
  10. Quadriceps enthesis thickness ≥ 6.1mm
  11. Quadriceps enthesis hypoechogenicity
  12. Quadriceps enthesis power Doppler signal

13. Superior pole of patella calcification
14. Superior pole of patella enthesophyte(s)
15. Superior pole of patella bony erosion(s)
16. Superior pole of patella bony cortex irregularity
17. Suprapatellar bursitis (GS hypertrophy)
18. Suprapatellar burseal power Doppler signal

- *KNEE: Inferior pole of the patella - proximal patellar tendon enthesis*
  10. Proximal patellar enthesis thickness ≥ 4.0mm
  11. Proximal patellar enthesis hypoechogenicity
  12. Proximal patellar enthesis power Doppler signal
  13. Inferior pole of patella calcification
  14. Inferior pole of patella enthesophyte(s)
  15. Inferior pole of patella bony erosion(s)
  16. Inferior pole of patella bony cortex irregularity
  17. Superficial Infrapatellar bursitis (GS hypertrophy)
  18. Superficial Infrapatellar burseal power Doppler signal

- *KNEE: Tibial tuberosity - distal patellar tendon enthesis*
  10. Distal patellar enthesis thickness ≥ 4.0mm
  11. Distal patellar enthesis hypoechogenicity
  12. Distal patellar enthesis power Doppler signal
  13. Tibial tuberosity calcification
  14. Tibial tuberosity enthesophyte(s)
  15. Tibial tuberosity bony erosion(s)
  16. Tibial tuberosity bony cortex irregularity
  17. Deep Infrapatellar bursitis (GS hypertrophy)
  18. Deep Infrapatellar burseal power Doppler signal

- *FOOT: 5th metatarsal base lateral tuberosity - peroneal brevis tendon enthesis*
  8. Peroneal brevis enthesis thickness ≥ 1.9mm
  9. Peroneal brevis enthesis hypoechogenicity
  10. Peroneal brevis enthesis power Doppler signal
  11. 5th metatarsal base lateral tuberosity calcification
  12. 5th metatarsal base lateral tuberosity enthesophyte(s)
  13. 5th metatarsal base lateral tuberosity bony erosion(s)
  14. 5th metatarsal base lateral tuberosity bony cortex irregularity

- *ANKLE: Superior pole of calcaneus - Achilles tendon enthesis*

10. Achilles enthesis thickness ≥ 5.29mm
11. Achilles enthesis hypoechogenicity
12. Achilles enthesis power Doppler signal
13. Posterior pole of calcaneus calcification
14. Posterior pole of calcaneus enthesophyte(s)
15. Posterior pole of calcaneus bony erosion(s)
16. Posterior pole of calcaneus bony cortex irregularity
17. Retrocalcaneal bursitis (GS hypertrophy)
18. Retrocalcaneal bursae power Doppler signal

- *FOOT: Inferior pole of calcaneus - plantar aponeurosis (fascia) enthesis*
  8. Plantar aponeurosis thickness ≥ 4.4mm
  9. Plantar aponeurosis hypoechogenicity
  10. Plantar aponeurosis power Doppler signal
  11. Inferior pole of calcaneus calcification
  12. Inferior pole of calcaneus enthesophyte(s)
  13. Inferior pole of calcaneus bony erosion(s)
  14. Inferior pole of calcaneus bony cortex irregularity

5.2.9.4.2 Tenosynovitis Score

44 tendon sheaths (22 per side) were scanned in each participant, and each parameter scored 0-3, with a maximum possible score of 264:

THUMB:

- *Flexor pollicis longus tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Extensor pollicis longus tendon overlying the interphalangeal joint*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Extensor pollicis longus tendon overlying the carpometacarpal joint*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis

INDEX FINGER:

- *Flexor digitorum profundus tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Extensor digitorum tendon*
  3. Grey scale Tenosynovitis

4. Power Doppler Tenosynovitis

WRIST:

- *Extensor compartment 1 – Abductor pollicis longus and extensor pollicis brevis tendons*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Extensor compartment 2 – Extensor carpi radialis, longus and brevis tendons*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Extensor compartment 3 – Extensor pollicis longus tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Extensor compartment 4 – Extensor digitorum tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Extensor compartment 5 – Extensor digiti minimi tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Extensor compartment 6 – Extensor carpi ulnaris tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis

KNEE:

- *Quadriceps tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Proximal patellar tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Distal patellar tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis

FOOT AND ANKLE:

- *Posterior tibialis tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Flexor digitorum longus tendon*

3. Grey scale Tenosynovitis
4. Power Doppler Tenosynovitis

- *Flexor hallucis longus tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Anterior tibialis tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Extensor hallucis longus tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Extensor digitorum tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Peroneal longus tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis
- *Peroneal brevis tendon*
  3. Grey scale Tenosynovitis
  4. Power Doppler Tenosynovitis

5.2.9.4.3 Synovitis Score

24 joints (12 per side) were scanned in each participant, and each parameter scored 0-3, with a maximum possible score of 144:

THUMB:

- *Interphalangeal joint*
  3. Grey scale Synovitis
  4. Power Doppler Synovitis
- *Carpometacarpal joint*
  3. Grey scale Synovitis
  4. Power Doppler Synovitis

INDEX FINGER:

- *Distal interphalangeal joint*
  7. Grey scale Synovitis
  8. Power Doppler Synovitis
- *Proximal interphalangeal joint*
  9. Grey scale Synovitis
  10. Power Doppler Synovitis

- *Metacarpophalangeal joint*
  11. Grey scale Synovitis
  12. Power Doppler Synovitis

WRIST:

- *Wrist joint*
  3. Grey scale Synovitis
  4. Power Doppler Synovitis

ELBOW:

- *Lateral elbow joint*
  3. Grey scale Synovitis
  4. Power Doppler Synovitis
- *Medial elbow joint*
  3. Grey scale Synovitis
  4. Power Doppler Synovitis
- *Posterior elbow joint*
  3. Grey scale Synovitis
  4. Power Doppler Synovitis

KNEE:

- *Knee joint*
  3. Grey scale Synovitis
  4. Power Doppler Synovitis

ANKLE:

- *Midline ankle joint*
  3. Grey scale Synovitis
  4. Power Doppler Synovitis

FOOT:

- *Tarsometatarsal joint (between the base of 5th metatarsal and cuboid bone)*
  3. Grey scale Synovitis
  4. Power Doppler Synovitis

5.2.10 Primary and Secondary Endpoints

5.2.10.1 Primary Endpoint

- Change in enthesopathy inflammation score (as assessed by ultrasound of the upper and lower limb entheses) from baseline after 24 weeks of treatment with ustekinumab (open-label) prescribed to treat moderate to severe psoriasis.

5.2.10.2 Secondary Endpoints

- Change in enthesopathy inflammation scores (as assessed by ultrasound of the upper and lower limb entheses) to treatment with ustekinumab (open-label) prescribed to treat moderate to severe psoriasis, from baseline to week 12 and baseline to week 52.
- Change in enthesopathy chronic damage scores (as assessed by ultrasound of the upper and lower limb entheses) to treatment with ustekinumab (open-label) prescribed to treat moderate to severe psoriasis, from baseline to week 12, week 24 and week 52.
- Change in total enthesopathy scores (as assessed by ultrasound of the upper and lower limb entheses) to treatment with ustekinumab (open-label) prescribed to treat moderate to severe psoriasis, from baseline to week 12, week 24 and week 52.
- Demonstrable improvement in enthesopathy scores between baseline and week 24 (and maintenance/improvement through to week 52) to potentially enable an accurate power calculation for a larger randomised controlled trial against systemic immunosuppressants and/or other biologic molecules.
- Comparison of new enthesopathy scores with the total modified GUESS score (the most widely cited published ultrasound enthesitis score) at all ultrasound time points (weeks 0, 12, 24 and 52), to see if the new, more extensive system is significantly different (better) in terms of detecting change in subclinical enthesitis over time, and can justify the additional time needed to scan more entheses in a larger randomised controlled trial.
- Change in tenosynovitis and synovitis scores (as assessed by ultrasound of the upper and lower limb entheses) to treatment with ustekinumab (open-label) prescribed to treat moderate to severe psoriasis, from baseline to week 12, week 24 and week 52.
- Change in severity of skin psoriasis (as assessed by PASI and BSA) after treatment with ustekinumab for 12, 24 and 52 weeks, and correlation with change in ultrasound enthesopathy scores and HLA-Cw06 status.

- Correlation of anatomical locations of psoriasis (e.g. nail, scalp etc.) and response to ustekinumab therapy over time (week 24 and 52).
- Change in severity of nail psoriasis (as assessed by mNAPSI) after treatment with ustekinumab for 12, 24 and 52 weeks and correlation with change in ultrasound enthesopathy scores and HLA-Cw06 status.
- Change in quality of life measure (as assessed by DLQI) after treatment with ustekinumab for 12, 24 and 52 weeks and correlation with change in skin disease, nail disease and ultrasound enthesopathy scores.
- Correlation between ultrasound enthesopathy scores and clinical enthesitis scores over time, from baseline to weeks 12, 24 and 52.

5.3 Statistical Analysis

As appropriate for an unpowered pilot study, primary emphasis is placed on descriptive statistics throughout. Results for categorical data are expressed as frequencies, and continuous variables are given as means (standard deviation) or medians (inter-quartile range), depending on the distribution. Inferential tests are presented for guidance only and have not been corrected for multiple comparisons; the results of these tests will be considered exploratory rather than confirmatory. Changes from baseline in the primary outcome (enthesopathy scores) were assessed using Student's paired t-tests. Correlations between demographic (age, skin type, BMI, smoking history, alcohol consumption) and clinical parameters (age of psoriasis onset, duration of psoriasis, PASI, BSA, mNAPSI, DLQI) were analysed by Spearman rank correlation; absolute rho values >0.3 are considered to indicate weak correlation. For categorical variables (gender, family history of psoriasis, anatomical location of psoriasis plaques, presence/absence of ultrasound inflammation) associations were evaluated according to the extent of descriptive differences between groups. For associations with change in enthesopathy score, both unadjusted differences and differences adjusted for baseline enthesopathy score have been provided. Effect sizes for within-group changes are presented as Cohen's d, calculated as (mean change/standard deviation of change)*$\sqrt{2}$. For adjusted between group comparisons, partial Eta squared is presented. Statistical analysis was performed using IBM© SPSS© version 24.0.

5.4 Results

23 patients were recruited to the trial. All patients completed 24 weeks of treatment and assessment (primary endpoint). 20 patients completed 52 weeks of treatment and assessment, with three lost to follow-up.

5.4.1 Participant Characteristics

23 patients, 12 males and 11 females, with moderate to severe psoriasis and at least one lesion consistent with subclinical inflammatory enthesitis on ultrasound consented to participation. Three patients did not continue beyond week 24; the first patient in the trial was not approached to continue as the decision was only made to extend the study beyond the primary endpoint of 24 weeks after he had been discharged, and two were lost to follow up.

Patients were aged between 20 and 74 years, with a median (interquartile range) of 45 (33-55) years. All patients were Caucasian (skin types I-III) with the exception of one patient with skin type V. Median BMI was 29.6 (27.6-35.3) kg/m^2, with 10 patients (43.5%) being classed as obese (BMI greater than $30kg/m^2$). 15 patients (65.2%) were current or ex-smokers, with a smoking pack year history ranging from 1-64 years, median 20 (7-32) years. Four patients did not drink alcohol, with the remainder drinking between 4 and 76 units of alcohol per week. Average (median) consumption was 10 (10-20) units per week, but four patients were drinking excessive amounts at 30 or more units per week.

Psoriasis onset varied from 9 to 54 years of age, with a median duration of disease of 11 (7-25) years. All had chronic plaque disease. 13 patients had at least one family member with psoriasis and two had a family history of psoriatic arthritis. Four had a family member with another musculoskeletal diagnosis (all osteoarthritis) and two had a family member with autoimmune disease (hypothyroidism, type I diabetes mellitus).

Patient comorbidities included autoimmune disease (vitiligo, type I diabetes mellitus), mild asthma, type II diabetes mellitus (tablet controlled), epilepsy, hypertension, gastroesophageal reflux disease, factor V Leiden deficiency (with recent pulmonary embolus) and anxiety and depression. At baseline, four patients were taking analgesic medications, three of which were taking non-steroidal anti-inflammatory drugs (NSAIDs). All three were asked to discontinue their NSAIDs and did so at least one week prior to their baseline ultrasound scan. They were permitted to take other forms of analgesia if required.

5.4.2 Laboratory Assessment

Blood parameters were generally within normal limits, and all patients were deemed safe to be prescribed the investigational medicinal product, ustekinumab. At baseline, one patient had an elevated CRP at 15.4mg/l (upper limit of normal <10.0mg/l), and coincided with coryzal symptoms suggestive of an upper respiratory tract infection. Plasma viscosity (PV) was elevated in five patients (upper limit of normal 1.72m.Pa.s, range of abnormalities 1.76-1.84mPa.s). Eight patients had an abnormal alanine transferase

(ALT) level (upper limit of normal <40iu/l), although none had a level of three times the upper limit of normal, a contraindication to ustekinumab (range of abnormalities 41-72iu/l). Only one of these patients had abnormalities in their other liver function tests, and the elevations in bilirubin and alkaline phosphatase were mild. Total cholesterol was recorded above 5mmol/l in eight patients, and four had elevated triglycerides (upper limit of normal <2.3mmol/l, range of abnormalities 2.4-3.0mmol/l). Such elevations are expected in patients with psoriasis, especially in those who are overweight and obese, who often have a degree of metabolic syndrome associated with their psoriatic disease. These patients were offered lifestyle advice and advised to discuss statin therapy with their general practitioner if their levels did not reduce. All remaining blood parameters were all within normal limits.

All patients were negative for rheumatoid factor, anti-CCP antibody and ANA, and remained so throughout the study. One patient was positive for the HLA-B27 allele, and 15 patients (65.2%) were positive for HLA-Cw06.

CRP was entirely normal in all patients at weeks 24 and 52. Most other blood parameters also improved over time, with the exception of ALT in one patient, which rose from 72iu/l at baseline to 76iu/l at week 24 and 109iu/l by week 52. Bilirubin remained mildly elevated in this patient at 34umol/l, but ALP normalised. This patient was referred for an ultrasound scan of the liver, which was reported as normal. Total cholesterol also remained elevated above 5.0mmol/l in eight patients (as baseline, maximum level 7.2mmol/l) and patients were advised again to seek advice from their general practitioner if they had not done so already. Triglyceride levels were elevated in six patients, with a maximum level of 3.8mmol/l by week 24 and 3.6mmol/l by week 52. Plasma viscosity reduced in all but three patients, remaining elevated in these patients at week 52 (maximum level 1.80mPa.s).

5.4.3 Adverse Events

Adverse events were minimal in the study, and most were mild and self-limiting.

- Three patients developed an upper respiratory tract infection (all around week 12) for which they consulted with their General Practitioner, for which two received a short course of oral antibiotics.
- Three patients reported tiredness, beginning between week 4 and 12.
- One patient developed gastroenteritis around week 22. This was self-limiting and did not require any treatment other than rest and oral hydration.
- Two patients reported follicular abnormalities at week 12 – one developed facial acne for which a topical retinoid/benzoyl peroxide product was prescribed, and

the second developed small areas of folliculitis on the abdominal wall, away from the injection site, which resolved without treatment.

- One patient sustained accidental trauma to the left shoulder at the gymnasium around week 2 and chose to wear a sling for a couple of weeks but did not seek medical advice. He was symptom free and had a full range of movement at his next review at week 4.

Serious adverse events (SAE) occurred in two patients and were reported to the Sponsor (University of Leeds) and the manufacturer (Janssen Pharmaceuticals):

- One patient was involved in a road traffic accident while riding her scooter just before her week 16 visit and sustained a severe fracture of her left femur. She underwent surgical pinning and was hospitalised for several weeks. Her ustekinumab therapy continued as normal. This SAE was not attributed to the investigational medicinal product
- A different patient developed an abdominal pericolic gutter abscess around week 37 of treatment. This developed spontaneously, nine weeks after her previous dose of ustekinumab. She required hospitalisation and intravenous antibiotics for seven days, but made a full recovery. After discussion with the patient and the patient's dermatologist (MDG, the Candidate's supervisor), ustekinumab was continued, at the correct time point. This SAE may have been related to the investigational medicinal product and was therefore reported to the MHRA through the yellow card scheme.

5.4.4 Clinical Outcomes

5.4.4.1 Skin Disease

All patients at baseline had a diagnosis of moderate to severe chronic plaque psoriasis and PASI scores at baseline ranged from 10.4 to 38.4, with a median PASI score of 18.0 (13.4, 28.4). Body surface area ranged from 10-60%, with a median of 30 (15,40)%. At the primary outcome of 24 weeks, median PASI had reduced to 0.6 (0,2.5), and body surface area to 1 (0,3)%. Response to ustekinumab therapy was rapid, with every patient experiencing a noticeable reduction in PASI score by week 4. Median PASI scores and BSA percentages at each time point, and the respective percentage reduction from baseline are listed in Table 5.3.

	Week 0	Week 4	Week 12	Week 24	Week 52
Median (IQR) PASI score	18 (13.4, 28.4)	7.2 (4.3, 12.4)	2.3 (0.9, 3.9)	0.6 (0, 2.5)	0.1 (0, 2.93)
Median (IQR) % reduction from baseline	N/A	61% (49%, 77%)	88% (84%, 94%)	97% (87%, 100%)	99% (82%, 100%)
Median (IQR) BSA (%)	30 (15, 40)	15 (10, 25)	5 (1, 10)	1 (0, 3)	0.5 (0, 2.75)
Median (IQR) % reduction from baseline	N/A	50% (33%, 50%)	83% (67%, 97%)	98% (90%, 100%)	99% (90%, 100%)

Table 5.3. Median PASI and BSA scores at each time point, and the percentage reduction from baseline. PASI: Psoriasis Area and Severity Index, BSA: Body Surface Area; IQR: Interquartile Range; N/A: Not applicable.

At the primary endpoint of week 24, 21 patients (91.3%) achieved a PASI 75 response, 17 patients (73.9%) achieved a PASI 90 response and 11 patients (47.8%) achieved a PASI 100 response. Responses were generally maintained out to week 52. Two of the patients who failed to achieve PASI 90 at week 24 did so by week 52. Two different patients who did make PASI 90 at week 24 lost some efficacy but still maintained a PASI75 response.

In terms of distribution of lesions, the frequency at which these were involved at different time points is listed in Table 5.4.

Location	**Ever** (n=23)	**Week 0** (n=23)	**Week 4** (n=23)	**Week 12** (n=23)	**Week 24** (n=23)	**Week 52** (n=20)
Nail *n (%)*	17 (73.9%)	17 (73.9%)	15 (65.2%)	13 (56.5%)	10 (43.5%)	12 (60.0%)
Scalp *n (%)*	23 (100%)	20 (87.0%)	14 (60.9%)	6 (26.1%)	2 (8.7%)	3 (15.0%)
Retroauricular *n (%)*	21 (91.3%)	17 (73.9%)	7 (30.4%)	1 (4.3%)	0 (0%)	3 (15.0%)
Gluteal cleft *n (%)*	19 (82.6%)	14 (60.9%)	9 (39.1%)	5 (21.7%)	2 (8.7%)	1 (5.0%)
Umbilicus *n (%)*	15 (65.2%)	11 (47.8%)	8 (34.8%)	2 (8.7%)	1 (4.3%)	1 (5.0%)
Face *n (%)*	16 (69.6%)	13 (56.5%)	4 (17.4%)	2 (8.7%)	0 (0%)	0 (0%)
Upper limb *n (%)*	23 (100%)	23 (100%)	23 (100%)	16 (69.6%)	10 (43.5%)	8 (40.0%)
Dorsal hand(s) *n (%)*	15 (65.2%)	14 (60.9%)	8 (34.8%)	3 (13.0%)	0 (0%)	1 (5.0%)
Trunk *n (%)*	22 (95.7%)	21 (91.3%)	21 (91.3%)	10 (43.5%)	7 (30.4%)	7 (35.0%)
Lower limb *n (%)*	23 (100%)	23 (100%)	22 (95.7%)	17 (73.9%)	8 (34.8%)	6 (30.0%)
Flexures *n (%)*	15 (65.2%)	11 (47.8%)	2 (8.7%)	2 (8.7%)	0 (0%)	1 (5.0%)
Genitals *n (%)*	11 (47.8%)	7 (30.4%)	1 (4.3%)	1 (4.3%)	0 (0%)	0 (0%)
Perianal *n (%)*	8 (34.8%)	6 (26.1%)	0 (0%)	1 (4.3%)	0 (0%)	1 (5.0%)
Palms *n (%)*	5 (21.7%)	4 (17.4%)	1 (4.3%)	0 (0%)	0 (0%)	0 (0%)
Soles *n (%)*	7 (30.4%)	3 (13.0%)	2 (8.7%)	1 (4.3%)	0 (0%)	1 (5.0%)

Table 5.4. Frequency of clinically involved anatomical sites at each time point.

The upper and lower limbs had the slowest cutaneous lesions to resolve, followed by the trunk. This most probably reflects those areas that have the greatest body surface area coverage and are usually the most severe in terms of induration and erythema. These data also show a slight worsening or re-emergence of lesions at week 52 compared with week 24, but this is likely due to the timing of assessment in relation to the timing of the last injection. It is not uncommon for patients to experience a dip in control in the few weeks leading up to their next injection. Patients were typically seven or eight weeks post their last injection at the week 24 visit and were therefore in the period where their therapy was providing maximal disease suppression, compared to the week 52 visit, where patients were 12 weeks post their last injection and due their next dose imminently.

5.4.4.2 Nail Disease

17 patients (73.9%) had nail disease at baseline, with a mNAPSI score between 2 and 89 (out of a maximum possible score of 140). Pitting was the most frequent abnormality in 15 patients (65.2%), closely followed by onycholysis in 13 (56.5%) and crumbling in 13 (56.5%). 7 of 17 patients (41.2%) with nail disease at baseline had complete resolution of their nail psoriasis by week 24, with a further five having at least a 75% improvement. Improvement in mNAPSI from baseline to week 24 ranged from 22.2% to 100%, with a median reduction of 15 points (91.2%), and from baseline to week 52 ranged from 55.6% to 100%, with a median reduction of 22 points (86.4%). The most notable improvements occurred in nail bed psoriasis, leading to a greater reduction in onycholysis and nail bed hyperkeratosis than in nail plate changes such as pitting.

5.4.4.3 Entheseal tenderness and Dactylitis

Clinically detectable entheseal tenderness in asymptomatic patients was not infrequent but of a low level, with 11 of 23 (47.8%) patients having evidence of at least one tender enthesis, with a median of 1.5 (1.0-2.5) sites per patient at baseline. With treatment, this number reduced, with 7 of 23 (30.4%) patients having clinical entheseal tenderness at week 12, 4 of 23 (17.4%) at week 24 and 8 of 23 (34.8%) at week 52. The most common clinically tender enthesis was the medial humeral epicondyle, with five entheses (in four patients) being tender at baseline. No swollen entheses were found.

In total, 29 tender entheseal sites were identified from 736 examined in all 23 patients at baseline (3.9%). Tenderness resolved in 23 entheseal sites; 17 by week 12, a further four by week 24 and a further two by week 52. Tenderness persisted throughout in six entheses and new tenderness developed at 12 new entheseal sites (in seven patients) over the course of the study to 52 weeks.

Dactylitis was evident in four patients at baseline, in one digit in three and in four digits in one. These had resolved by week 12. One further patient developed dactylitis later in the study (in two digits at week 12), but this resolved by week 24.

5.4.5 Sonographic Outcomes

5.4.5.1 Enthesopathy and Bursitis

26 entheseal sites (13 per side) were scanned in 23 patients at baseline, week 12 and week 24, and in 20 patients at week 52. This equates to 598 entheses in all participants at week 0, 12 and 24, and 520 entheses in all participants at week 52.

Frequency of Entheseal and Bursal Abnormalities

325 entheseal abnormalities were identified at baseline, with the number of abnormalities ranging from two to 28 per patient. The quadriceps tendon was the most frequently involved site for both inflammatory and chronic damage lesions at baseline. Inflammatory lesions principally involved the large tendon entheses of the knee, elbow and ankle (Figure 5.1), whereas there was no correlation with tendon size and the presence of structural damage (Figure 5.2)

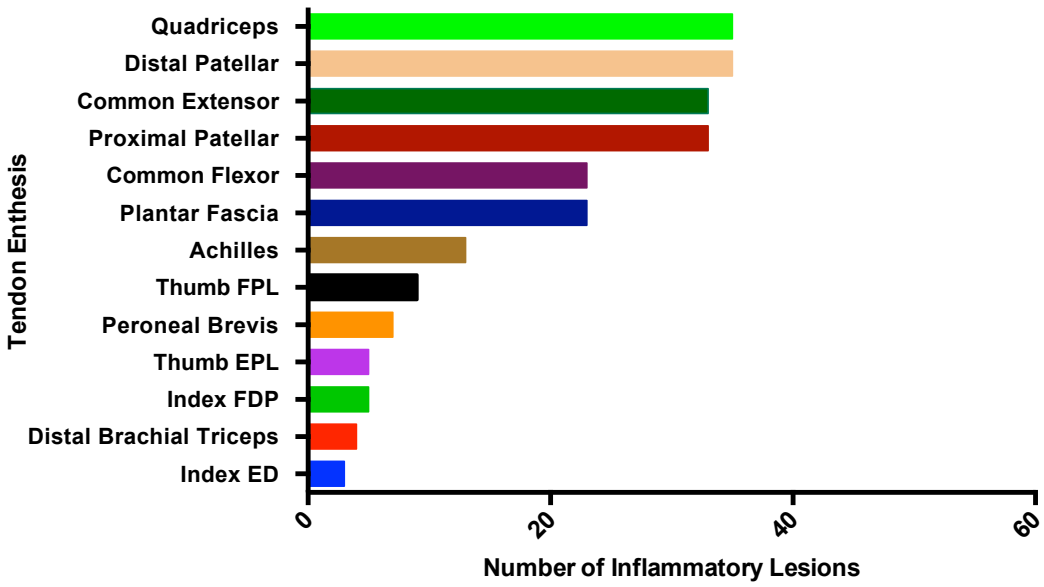

Figure 5.1. Pre-treatment distribution of inflammatory entheseal lesions by enthesis. (Common flexor and common flexor tendons at the elbow).

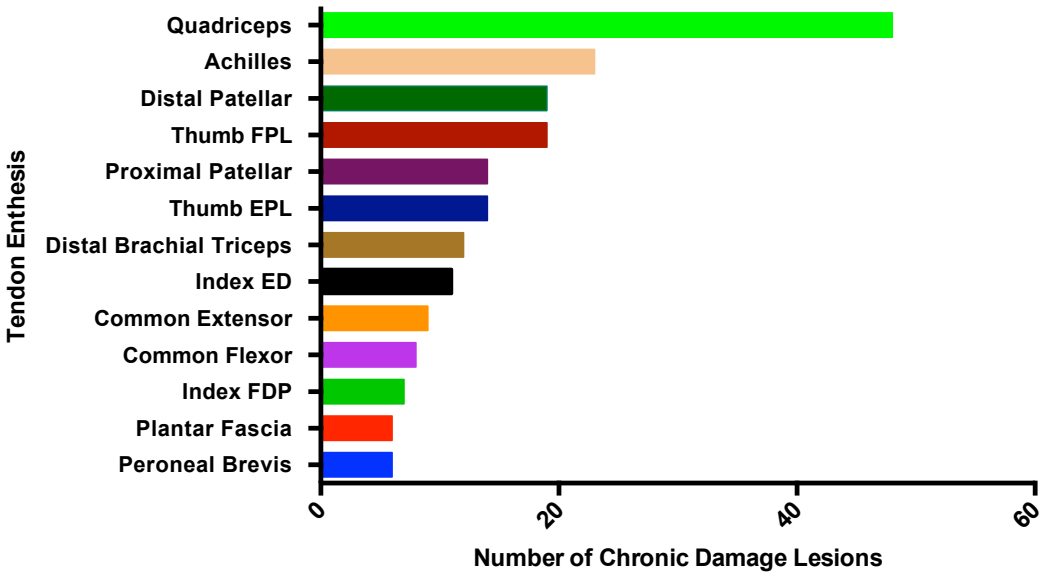

Figure 5.2. Pre-treatment distribution of chronic damage entheseal lesions by enthesis. (Common flexor and common flexor tendons at the elbow).

The total number of abnormalities (inflammatory and chronic damage) and the range of total number of abnormalities per patient at each time point are displayed in Table 5.5.

All abnormalities	**Week 0**	**Week 12**	**Week 24**	**Week 52**
Number of patients	23	23	23	20
Maximum number of entheseal abnormalities possible per patient[§]	182	182	182	182
Maximum total number of entheseal abnormalities possible[§]	4186	4186	4186	3640
Total number of entheseal abnormalities found in all patients	324	259	279	222
Range of total number of abnormalities per patient	2-28	0-28	0-34	0-28
Mean (± s.d.) total number of abnormalities per patient	14.1 ± 7.8	11.3 ± 7.5	12.1 ± 8.7	11.1 ± 7.3
Mean (95% CI) change in total number of abnormalities per patient	N/A	-2.8 (-4.4, -1.2)	-2.0 (-4.2, -0.3)	-3.1 (-6.1, -0.11)

Effect size (Cohen's d*)	N/A	1.1	0.5	0.7
Median (IQR) number of entheses involved per patient	9 (4, 12)	6 (3, 9)	7 (4, 9)	6 (5, 9)
Median (IQR) change in number of entheses involved per patient	N/A	-2 (-4, 0)	-1 (-4, 0)	-1 (-4, 1)

Calculated as (|mean change|/SD change)√2

Table 5.5. Total number of entheseal abnormalities at each time point ([§]based on 13 entheses bilaterally, seven parameters per enthesis)

Figure 5.3 demonstrates the mean total number of all entheseal abnormalities in all patients at each time point. With treatment, the mean number of entheseal abnormalities appears to reduce compared to baseline, although such differences failed to reach statistical significance at all time points.

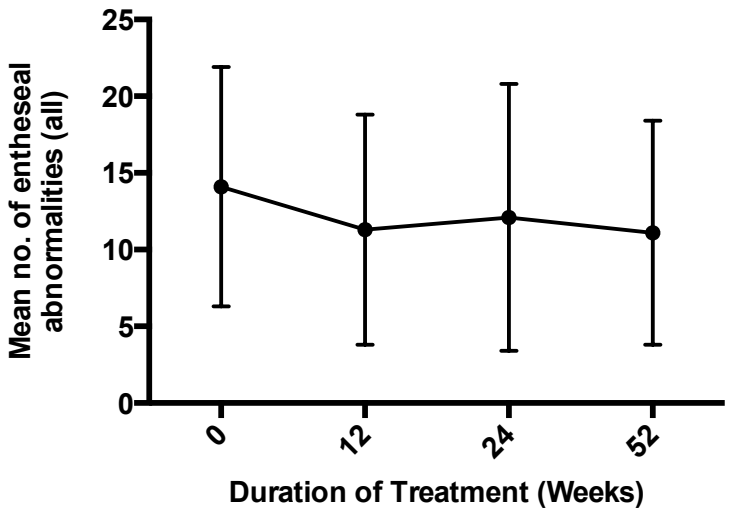

Figure 5.3. Change in mean total number of all entheseal abnormalities for all patients over time.

However, when separated into inflammatory and chronic damage entheseal abnormalities, there are clear differences in way different lesion types appear to respond to therapy over time (Figure 5.4).

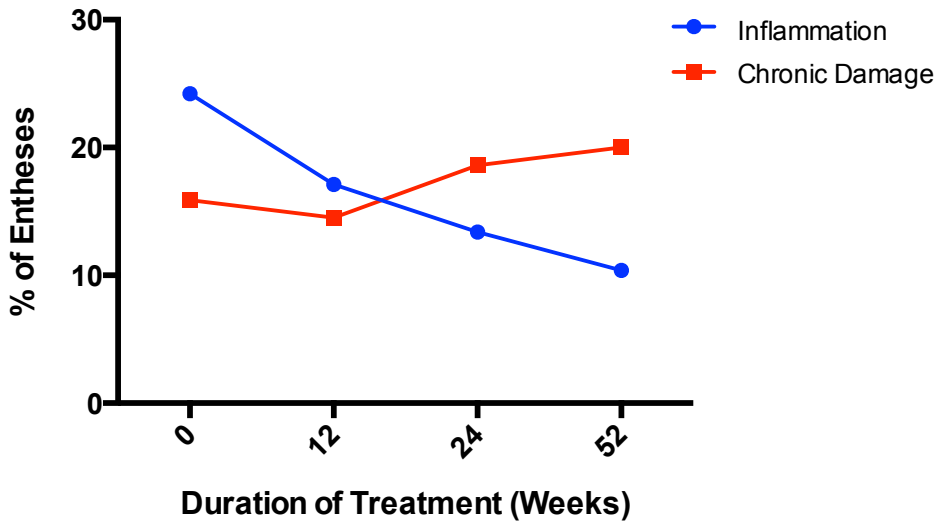

Figure 5.4. Percentage of entheses with inflammatory (blue line) and chronic damage (red line) lesions over time in all patients.

Enthesopathy: Active Inflammation

At baseline, 145 of 598 (24.2%) entheses scanned in 23 psoriasis patients (median (IQR) 6 (4, 9) out of 26 per patient) had at least one inflammatory entheseal abnormality (thickening, hypoechogenicity and/or power Doppler signal), defined as a grey scale or power Doppler signal score in these parameters >0.

The frequency of inflammatory parameters at the entheseal/bursal and patient level over time can be found in Table 5.6.

In total, 187 inflammatory entheseal abnormalities were identified at baseline, with a mean (±s.d.) of 9.8 (±6.7) abnormalities per patient (out of a total possible of 78). The number of entheses with an inflammatory abnormality and the total number of inflammatory abnormalities per patient declined at each visit (Table 5.7 and Figure 5.5). By week 52, the mean number of inflammatory abnormalities per patient had reduced by more than half compared to baseline.

Tendon		Parameter	Week 0				Week 12				Week 24				Week 52			
			Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=56)		Patient (max n=28)		Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=40)		Patient (max n=20)	
			n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%
Thumb	Flexor pollicis longus	Thickening	9	19.6	7	30.4	8	17.4	6	26.1	9	19.6	6	26.1	3	7.5	3	15.0
		Hypoechogenicity	0	0.0	0	0.0	0	0.0	0	0.0	1	2.2	1	4.3	1	2.5	1	5.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor pollicis	Thickening	4	8.7	4	17.4	3	6.5	3	13.0	2	4.3	2	8.7	0	0.0	0	0.0
		Hypoechogenicity	1	2.2	1	4.3	1	2.2	1	4.3	1	2.2	1	4.3	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Index Finger	Flexor digitorum	Thickening	5	10.9	5	21.7	6	13.0	4	17.4	5	10.9	4	17.4	1	2.5	1	5.0
		Hypoechogenicity	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor digitorum	Thickening	1	2.2	1	4.3	3	6.5	3	13.0	1	2.2	1	4.3	0	0.0	0	0.0
		Hypoechogenicity	2	4.3	1	4.3	2	4.3	1	4.3	1	2.2	1	4.3	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Elbow	Common Extensor	Thickening	13	28.3	8	34.9	5	10.9	4	17.4	5	10.9	4	17.4	2	5.0	2	10.0
		Hypoechogenicity	10	21.7	8	34.9	8	17.4	7	30.4	6	13.0	5	21.7	4	10.0	4	20.0
		Power Doppler signal	1	2.2	1	4.3	1	2.2	1	4.3	1	2.2	1	4.3	1	2.5	1	5.0

Tendon		Parameter	Week 0				Week 12				Week 24				Week 52			
			Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=56)		Patient (max n=28)		Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=40)		Patient (max n=20)	
			n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%
	Common Flexor	Thickening	13	28.3	7	30.4	4	8.7	2	8.7	2	4.3	1	4.3	1	2.5	1	5.0
		Hypoechogenicity	5	10.9	3	13.0	4	8.7	3	13.0	4	8.7	3	13.0	4	10.0	2	10.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Distal Brachial Triceps	Thickening	3	6.5	3	13.0	0	0.0	0	0.0	1	2.2	1	4.3	1	2.5	1	5.0
		Hypoechogenicity	2	4.3	2	8.7	2	4.3	2	8.7	1	2.2	1	4.3	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Olecranon bursal hypertrophy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD within olecranon bursa	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Knee	Quadriceps	Thickening	15	32.6	10	43.5	8	17.4	6	26.1	5	10.9	4	17.4	5	12.5	3	15.0
		Hypoechogenicity	16	34.8	11	47.8	13	28.3	9	39.1	12	26.1	9	39.1	7	17.5	4	20.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Suprapatellar bursal hypertrophy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0.0	0	0.0
		PD within suprapatellar bursa	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0.0	0	0.0
	Proximal Patellar	Thickening	14	30.4	9	39.1	12	26.1	8	34.9	14	30.4	8	34.9	7	17.5	5	25.0
		Hypoechogenicity	10	43.5	7	15.2	9	19.6	5	21.7	9	19.6	5	21.7	6	15.0	4	20.0
		Power Doppler signal	1	2.2	1	4.3	1	2.2	1	4.3	3	6.5	2	8.7	1	2.5	1	5.0

Tendon		Parameter	Week 0				Week 12				Week 24				Week 52			
			Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=56)		Patient (max n=28)		Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=40)		Patient (max n=20)	
			n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%
	Distal Patellar	Thickening	25	54.3	16	69.6	20	43.5	13	56.5	11	23.9	8	34.9	9	22.5	7	35.0
		Hypoechogenicity	4	8.7	4	17.4	4	8.7	4	17.4	6	13.0	6	26.1	6	15.0	4	20.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0	1	2.2	1	4.3	1	2.5	1	5.0
		Superficial infrapatellar bursal hypertrophy	1	2.2	1	4.3	1	2.2	1	4.3	0	0.0	0	0.0	0	0.0	0	0.0
		PD within superficial infrapatellar bursa	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Deep infrapatellar bursal hypertrophy	1	2.2	1	4.3	1	2.2	1	4.3	1	2.2	1	4.3	0	0.0	0	0.0
		PD within deep infrapatellar bursa	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Foot and Ankle	Peroneal Brevis	Thickening	6	13.0	4	17.4	0	0.0	0	0.0	1	2.2	1	4.3	0	0.0	0	0.0
		Hypoechogenicity	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Achilles	Thickening	6	13.0	5	21.7	1	2.2	1	4.3	0	0.0	0	0.0	0	0	0	0.0
		Hypoechogenicity	5	10.9	4	17.4	3	6.5	3	13.0	1	2.2	1	4.3	0	0.0	0	0.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Retrocalcaneal bursal hypertrophy	0	0.0	0	0.0	0	0.0	0	0.0	1	2.2	1	4.3	0	0.0	0	0.0
		PD within retrocalcaneal bursa	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Tendon		Parameter	Week 0				Week 12				Week 24				Week 52			
			Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=56)		Patient (max n=28)		Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=40)		Patient (max n=20)	
			n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%
	Plantar Fascia	Thickening	9	19.6	7	30.4	6	13.0	5	21.7	4	8.7	3	13.0	5	12.5	4	20.0
		Hypoechogenicity	8	17.4	7	30.4	6	13.0	6	26.1	3	6.5	3	13.0	5	12.5	4	20.0
		Power Doppler signal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 5.6. Frequency of active inflammatory parameters at the entheseal/bursal and patient level over time

Inflammatory abnormalities	Week 0	Week 12	Week 24	Week 52
Number of patients	23	23	23	20
Maximum number of entheseal abnormalities possible per patient§	78	78	78	78
Maximum total number of entheseal abnormalities possible§	1794	1794	1794	1560
Total number of entheseal abnormalities found in all patients	187	130	109	70
Range of total number of abnormalities per patient	1-17	0-16	0-15	0-15
Mean (± s.d.) total number of abnormalities per patient	8.1 (4.7)	5.7 (3.8)	4.7 (4.2)	3.5 (2.7)
Mean (95% CI) change in total number of abnormalities per patient	N/A	-2.5 (-3.6, -1.3)	-3.4 (-4.9, -1.9)	-4.7 (-6.6, -2.7)
Effect size (Cohen's d*)	N/A	1.3	1.4	1.6
Total number of entheses involved	145	102	84	54
Median (IQR) number of entheses involved per patient	6 (4, 9)	4 (2, 6)	3 (2, 5)	3 (1, 4)
Median (IQR) change in number of entheses involved per patient	N/A	-2 (-3, 0)	-2 (-5, -1)	-3 (-6, -1)

Calculated as (|mean change|/SD change)$\sqrt{2}$

Table 5.7. lists the frequency of inflammatory entheseal abnormalities by enthesis at each time point (§based on 13 entheses bilaterally, three parameters per enthesis).

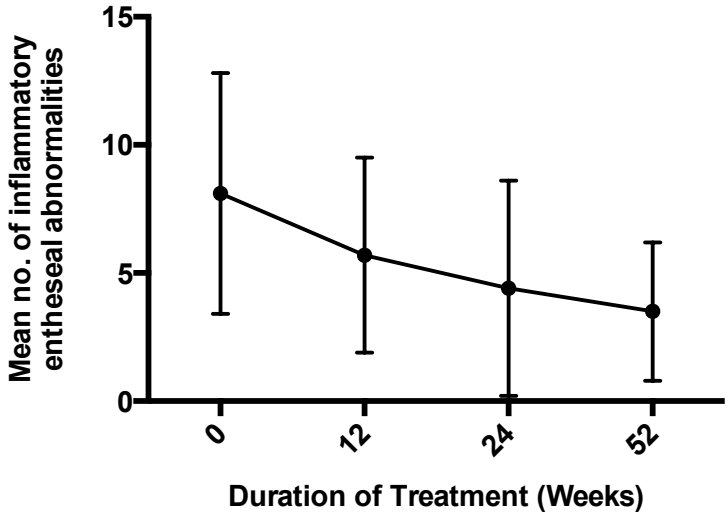

Figure 5.5. Change in mean number of inflammatory entheseal abnormalities for all patients over time. Statistically significant differences were found at week 12 and 24 compared with baseline (where $p<0.1$).

These data suggest that treatment with ustekinumab may have a positive impact on active (inflammatory) subclinical enthesitis within as little as 12 weeks, and the trend in this improvement appears to continue with therapy out to a year.

Enthesopathy: Chronic Damage

In contrast to active inflammation, structural changes (entheseal calcification, enthesophytes, bone erosions and bone cortex irregularities) did not improve with ustekinumab therapy over time. The frequency of chronic damage parameters at the entheseal/bursal and patient level over time can be found in Table 5.8.

95 of 598 (15.9%) entheses scanned in 23 patients at baseline (mean ± s.d. 4.1 (3.7) out of 26 per patient) had at least one chronic damage abnormality, defined as a grey scale or power Doppler signal score in the above parameters >0. In total, 137 chronic damage changes were identified at baseline in 23 patients, with a mean ± s.d. of 6.0 ± 4.7 abnormalities per patient. Over time, the number of entheses with chronic abnormalities fluctuated, whilst the total number of chronic abnormalities tended to increase slightly (Table 5.9 and Figure 5.6). The majority of abnormalities were entheseal calcifications and enthesophytes

.

Tendon		Parameter	Week 0				Week 12				Week 24				Week 52			
			Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=56)		Patient (max n=28)		Enthesis (max n=46)		Patient (max n=23)		Enthesis (max n=40)		Patient (max n=20)	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Thumb	Flexor pollicis longus	Calcifications	0	0.0	0	0.0	0	0.0	0	0.0	7	15.2	7	30.4	6	15.0	5	25.0
		Enthesophytes	4	8.7	3	13.0	2	4.3	1	4.3	2	4.3	1	4.3	3	7.5	2	10.0
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	14	30.4	10	43.5	9	19.6	7	30.4	9	19.6	8	34.8	5	12.5	5	25.0
	Extensor pollicis longus	Calcifications	0	0.0	0	0.0	0	0.0	0	0.0	3	6.5	3	13.0	2	5.0	2	10.0
		Enthesophytes	4	8.7	3	13.0	3	6.5	2	8.7	3	6.5	2	8.7	1	2.5	1	5.0
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	6	13.0	5	21.7	7	15.2	5	21.7	5	10.8	3	13.0	7	17.5	4	20.0
Index Finger	Flexor digitorum profundus	Calcifications	2	4.3	2	8.7	1	2.2	1	4.3	3	6.5	3	13.0	1	2.5	1	5.0
		Enthesophytes	0	0.0	0	0.0	0	0.0	0	0.0	2	4.3	2	8.7	3	7.5	2	10.0
		Bony erosions	1	2.2	1	4.3	1	2.2	1	4.3	1	2.2	1	4.3	1	2.5	1	5.0
		Bone cortex irregularities	4	8.7	3	13.0	4	8.7	3	13.0	3	6.5	2	8.7	2	5.0	2	10.0

	Extensor digitorum	Calcifications	1	2.2	1	4.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Enthesophytes	3	6.5	3	13.0	2	4.3	2	8.7	3	6.5	3	13.0	3	7.5	3	15.0
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	5	10.9	3	13.0	6	13.0	4	17.4	6	13.0	4	17.4	7	17.5	5	25.0
Elbow	Common Extensor	Calcifications	0	0.0	0	0.0	0	0.0	0	0.0	1	2.2	1	4.3	4	10.0	4	20.0
		Enthesophytes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0	1	2.2	1	4.3	1	2.5	1	5.0
		Bone cortex irregularities	4	8.7	3	13.0	5	10.9	4	17.4	6	13.0	4	17.4	5	12.5	3	15.0
	Common Flexor	Calcifications	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Enthesophytes	0	0.0	0	0.0	0	0.0	0	0.0	1	2.2	1	4.3	3	7.5	2	10.0
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0.0
		Bone cortex irregularities	2	4.3	2	8.7	2	4.3	2	8.7	2	4.3	2	8.7	2	5.0	1	5.0
	Distal Brachial Triceps	Calcifications	1	2.2	1	4.3	1	2.2	1	4.3	4	8.7	4	17.4	3	7.5	3	15.0
		Enthesophytes	5	10.9	3	13.0	5	10.9	3	13.0	7	15.2	4	17.4	7	17.5	4	20.0
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	1	2.2	1	4.3	1	2.2	1	4.3	0	0.0	0	0.0

Knee	Quadriceps	Calcifications	16	34.8	11	47.8	16	34.8	11	47.8	20	43.5	13	56.5	16	40.0	10	50.0
		Enthesophytes	16	34.8	10	43.5	18	39.1	10	43.5	19	41.3	12	52.2	16	40.0	11	55.0
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	5	10.9	3	13.0	8	17.4	5	21.7	12	26.1	8	34.8	7	17.5	5	25.0
	Proximal Patellar	Calcifications	4	8.7	2	8.7	3	6.5	2	8.7	3	6.5	2	8.7	4	10.0	2	10.0
		Enthesophytes	4	8.7	3	13.0	4	8.7	3	13.0	3	6.5	2	8.7	4	10.0	2	10.0
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0.0	0	0.0
		Bone cortex irregularities	3	6.5	2	8.7	5	10.9	3	13.0	5	10.9	3	13.0	6	15.0	3	15.0
	Distal Patellar	Calcifications	11	23.9	7	30.4	8	17.4	6	26.1	11	23.9	8	34.9	7	17.5	5	25.0
		Enthesophytes	2	4.3	2	8.7	3	6.5	3	13.0	2	4.3	2	8.7	2	5.0	2	10.0
		Bony erosions	1	2.2	1	4.3	1	2.2	1	4.3	1	2.2	1	4.3	0	0.0	0	0.0
		Bone cortex irregularities	3	6.5	3	13.0	4	8.7	3	13.0	4	8.7	3	13.0	2	5.0	1	5.0
Foot and Ankle	Peroneal Brevis	Calcifications	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.5	1	5.0
		Enthesophytes	0	0.0	0	0.0	0	0.0	0	0.0	1	2.2	1	4.3	1	2.5	1	5.0
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	1	2.2	1	4.3	1	2.2	1	4.3	1	2.2	1	4.3	1	2.5	1	5.0

	Achilles	Calcifications	4	8.7	4	17.4	4	8.7	4	17.4	8	17.4	5	21.7	7	17.5	5	25.0
		Enthesophytes	6	13.0	4	17.4	5	10.9	3	13.0	8	17.4	6	26.1	10	25.0	7	35.0
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	2	4.3	1	4.3	0	0.0	0	0.0	1	2.2	1	4.3	1	2.5	1	5.0
	Plantar Fascia	Calcifications	2	4.3	2	8.7	0	0.0	0	0.0	1	2.2	1	4.3	0	0.0	0	0.0
		Enthesophytes	1	2.2	1	4.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Bony erosions	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Bone cortex irregularities	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.5	1	4.3

Table 5.8. Frequency of chronic damage parameters at the entheseal/bursal and patient level over time

Chronic abnormalities	Week 0	Week 12	Week 24	Week 52
Number of patients	23	23	23	20
Maximum number of entheseal abnormalities possible per patient§	104	104	104	104
Maximum total number of entheseal abnormalities possible§	2392	2392	2392	2080
Total number of entheseal abnormalities found in all patients	137	129	170	152
Range of total number of abnormalities per patient	0 to 17	0 to 18	0 to 24	0 to 19
Mean ± s.d. total number of abnormalities per patient	6.0 ± 4.7	5.6 ± 5.0	7.4 ± 5.7	7.6 ± 6.1
Mean (95% CI) change in total number of abnormalities per patient	N/A	-0.3 (-1.2, 0.6)	1.4 (0.2, 2.7)	1.6 (-0.3, 3.4)
Effect size (Cohen's d*)	N/A	0.2	0.7	0.6
Total number of entheses involved	95	87	111	104
Median (IQR) number of entheses involved per patient	3 (2, 6)	2 (1, 5)	4 (2, 7)	4 (2, 8)
Median (IQR) change in number of entheses involved per patient	N/A	0 (0, 0)	1 (0, 2)	1 (-2, 3)

Calculated as (|mean change|/SD change)√2

Table 5.9. The frequency of chronic damage/structural entheseal abnormalities by enthesis at each time point. (§based on 13 entheses bilaterally, four parameters per enthesis).

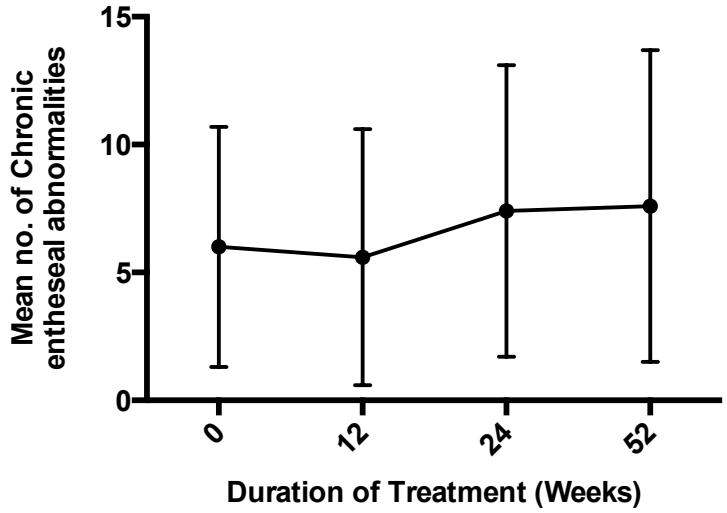

Figure 5.6. Change in mean number of chronic damage entheseal abnormalities for all patients over time.

The trend in these data suggest that treatment with ustekinumab has minimal impact on those structural damage lesions associated with enthesopathy and that there may be slow progression in damage over time. However, it may be that progression is slowed with ustekinumab, but without a group of patients with psoriasis and subclinical enthesitis receiving no treatment, this remains unknown.

Bursitis

Bursitis was minimal in this cohort, with only four patients having unilateral grey scale synovial hypertrophy throughout the study. One patient had bursitis at two locations at baseline (deep infrapatellar bursa and contralateral superficial infrapatellar bursa), both of which resolved after 24 weeks of treatment. Bursitis appeared in the deep infrapatellar bursa in two patients, one at week 12 and the other at week 24, but both had resolved by the next ultrasound scan. A fourth patient developed retrocalcaneal bursitis at week 24, but this had resolved by week 52. No bursal power Doppler signal was seen throughout.

5.4.5.1.1 Severity of Entheseal/Bursal Abnormalities

The majority of abnormalities, both inflammatory and structural, were mild (grade 1). The overall severity of lesions lessened a little with time. Of the 4186 entheseal inflammatory and chronic damage scores at baseline, 60 (1.43%) were of grade 2 or 3. At weeks 12, 24 and 52, 37/4186 (0.88%), 43/4186 (1.03%) and 33/3640 (0.91%) of the total number of abnormality scores were of grade 2 or more, respectively. Bursal synovial hypertrophy, where present, was always scored as mild (grade 1).

By the primary endpoint of 24 weeks, the severity of inflammatory lesions overall improved from baseline, with a reduction from 32/1794 (1.78%) to 16/1794 (0.89%) of all inflammatory abnormality scores being of grade 2 or 3. Figure 5.7, Figure 5.8 and Figure 5.9 provide examples of the reduction in inflammatory abnormalities seen with ustekinumab therapy within both small and large entheses of upper and lower limbs.

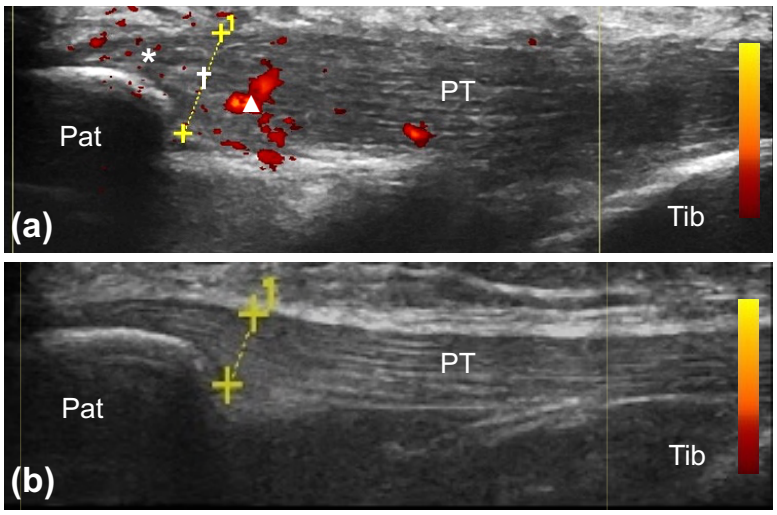

Figure 5.7. Reduction in entheseal thickness (†, grade 2 to 0), hypoechogenicity (✶, grade 1 to 0) and power doppler signal (▲, grade 3 to 0) within the left proximal patellar tendon enthesis between week 0 (a) and week 52 of ustekinumab therapy (b). PT: Patellar tendon; Pat: Patella; Tib: Tibia.

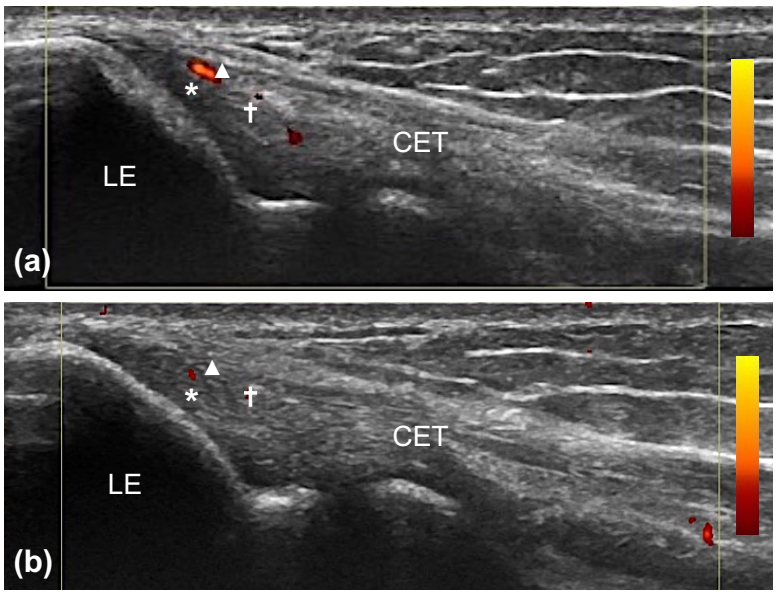

Figure 5.8. Reduction in entheseal thickness (†, grade 1 to 0), hypoechogenicity (✶, grade 2 to 0) and power doppler signal (▲, grade 2 to 1) within the right common extensor tendon enthesis between week 0 (a) and week 52 of ustekinumab therapy (b). CET: Common extensor tendon; LE: Lateral epicondyle.

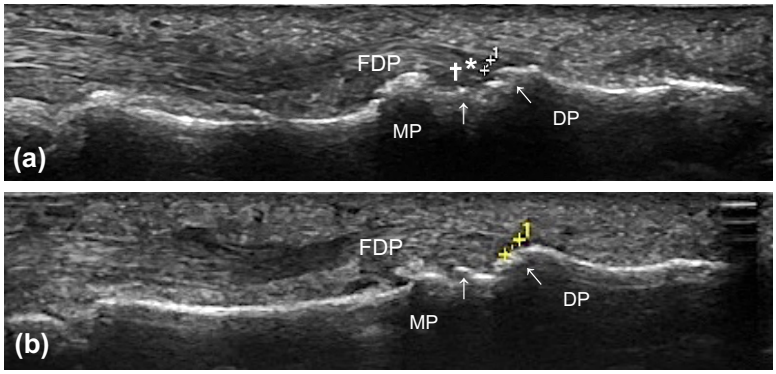

Figure 5.9. Normalisation of entheseal thickness (†, grade 2 to 0) and hypoechogenicity (✶, grade 2 to 0) within the left index finger flexor digitorum tendon enthesis between week 0 (a) and week 52 of ustekinumab therapy (b). Chronic damage abnormalities (↑) (bone cortex irregularities and enthesophytes) remained unchanged. FDP: Flexor digitorum profundus; MP: Middle phalynx; DP: Distal phalynx.

For chronic damage lesions, there was little change, with 28/2392 (1.17%) of all chronic abnormality scores being of grade 2 or 3 at baseline compared to 27/2392 (1.13%) at week 24. However, these totals mask the fact that at the patient level some lesions improved or resolved completely (Figure 5.10 and Figure 5.11), while in others new lesions appeared.

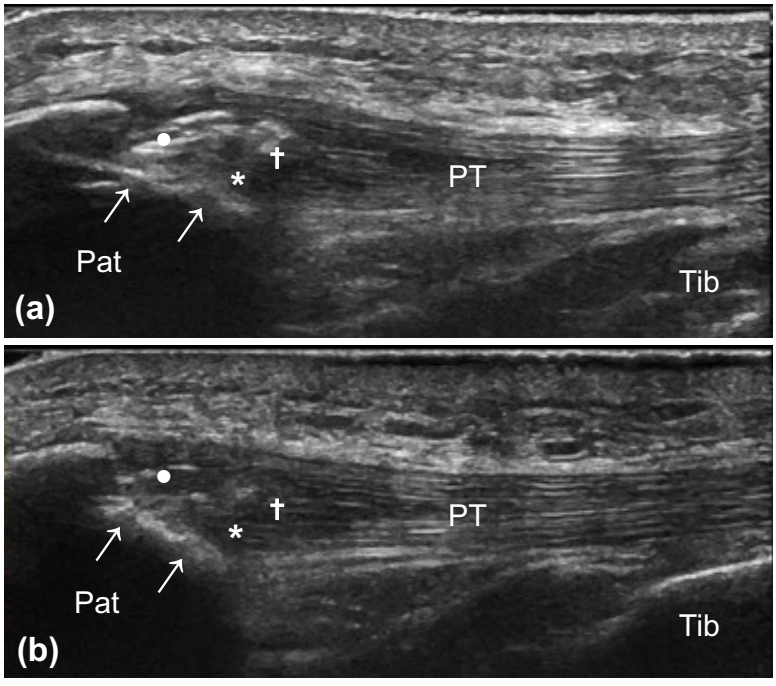

Figure 5.10. Reduction in entheseal calcification (•, grade 2 to 1), accompanied by a reduction in entheseal thickness (†, grade 1 to 0) and hypoechogenicity (✶, grade 2 to 0) within the right proximal patellar tendon enthesis between week 0 (a) and week 24 of ustekinumab therapy (b). PT: Patellar tendon; Pat: Patella; Tib: Tibia.

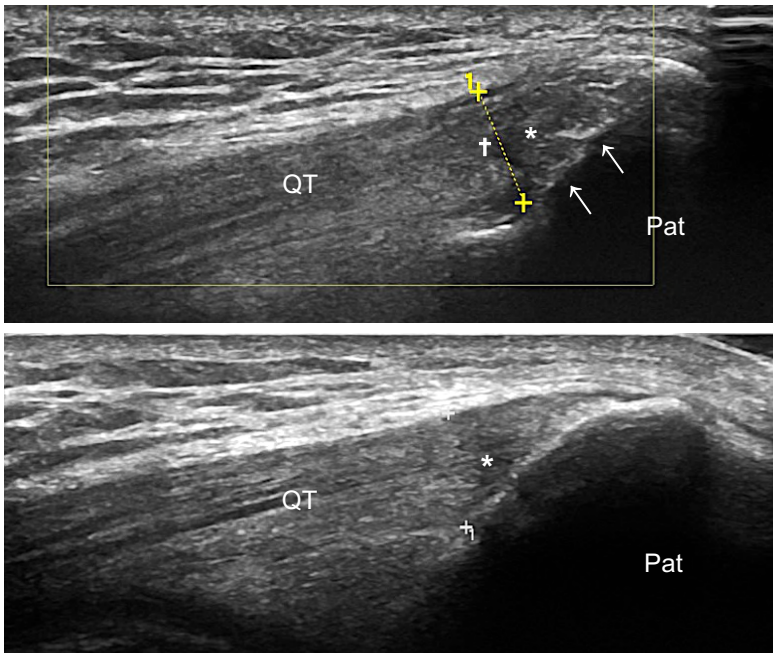

Figure 5.11. Reduction in bone cortex irregularities and enthesophytes (↑, grade 2 to 1), accompanied by a reduction in entheseal thickness (†, grade 1 to 0) and hypoechogenicity (✶, grade 2 to 1) within the left quadriceps tendon enthesis between week 0 (a) and week 24 of ustekinumab therapy (b). QT: Quadriceps tendon; Pat: Patella.

Table 5.10 shows the changes in entheseal scores between week 0 and week 24. The majority of inflammatory lesions (130/187) scoring 1 or more at baseline either resolved or improved, although 2 worsened and 38 inflammatory new inflammatory lesions developed while on therapy.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Total (Inflammation + Chronic)	All	151	28	3886	15	106
	0			3756		106
	1	137		113	14	
	2	14	22	13	1	
	3	0	6	4		
Inflammation	All	116	14	1624	2	38
	0			1569		38
	1	106		48	1	
	2	10	10	4	1	
	3	0	4	3		
Chronic	All	35	14	2262	13	68
	0			2187		68
	1	31		65	13	
	2	4	12	9	0	
		0	2	1		

Table 5.10. Changes in entheseal abnormality scores between baseline and week 24. ‘New’ lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had ‘resolved’. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Table 5.11 below repeats the same analyses, restricted to patients who were scanned by the same sonographer on both occasions. There were still a handful of chronic scores that improved or resolved from baseline.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Combined	All	90	13	1648	10	59
	0			1569		59
	1	83		71	9	
	2	7	13	7	1	
	3	0	0	1		
Inflammatory	All	70	4	685	1	20
	0			649		20
	1	65		31	0	
	2	5	4	4	1	
	3	0	0	1		
Chronic	All	20	9	963	9	39
	0			920		39
	1	18		40	9	
	2	2	9	3	0	
	3	-	-	-		

Table 5.11. Changes in entheseal abnormality scores between baseline and week 24, restricted to patients who were scanned by the same sonographer at both time points. 'New' lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had 'resolved'. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

5.4.5.1.2 Enthesopathy Scores

As expected, all enthesopathy scores were low, reflecting the very early stage of disease, with only mild abnormalities in a handful of entheses seen in each patient (Table 5.12). There was a wide variance in the number of abnormal parameters at each time point between patients, with some having only one active inflammatory lesion at baseline, compared to others with as many as 17 different abnormalities. Chronic damage lesions ranged in frequency from 0 to 24 and were maximal at week 24.

	Week 0 n=23	Week 12 n=23	Week 24 n=23	Week 52 n=20
Inflammation Score				
Range	1-29	0-20	0-19	0-16
Mean ± s.d.	9.9 ± 6.6	6.8 ± 4.9	5.7 ± 5.3	4.8 ± 4.6
Mean change ± s.d.	N/A	-3.1 ± 3.8	-4.2 ± 4.9	-4.7 ± 5.2
Confidence interval for change	N/A	(-4.8, -1.5)	(-6.3, -2.1)	(-7.1, -2.3)
Paired Student's *t* value, *p* value	N/A	t=-4.0, p=.001	t=-4.1, p<.001	t=-4.0, p=.001
Effect size (Cohen's d*)	N/A	1.2	1.2	1.3
Chronic Damage Score				
Range	0-21	0-20	0-25	0-26
Mean ± s.d.	7.9 ± 5.7	7.0 ± 5.7	9.1 ± 6.5	8.6 ± 7.0
Mean change ± s.d.	N/A	-0.8 ±2.6	1.3 ± 3.3	0.8 ± 5.0
Confidence interval for change	N/A	(-1.9, 0.3)	(-0.2, 2.7)	(-1.6, 3.1)
Paired Student's *t* value, *p* value	N/A	t=-1.5, p=.137	t=1.8, p=.082	t=0.7, p=.512
Effect size (Cohen's d*)	N/A	0.5	0.5	0.2
Total Score				
Range	2-42	0-32	0-38	0-42
Mean ± s.d.	17.8 ± 10.4	13.8 ± 9.1	14.8 ± 10.6	13.6 ± 9.9
Mean change ± s.d.	N/A	-4.0 ± 4.7	-3.0 ± 6.3	-4.0 ± 8.3
Confidence interval for change	N/A	(-6.0, -1.9)	(-5.7, -0.2)	(-7.8, -0.1)
Paired Student's *t* value, *p* value	N/A	t=-4.1, p=.001	t=-2.3, p=.034	t=-2.1, p=.047
Effect size (Cohen's d*)	N/A	1.2	0.7	0.7

Calculated as (|mean change|/SD change)√2

Table 5.12. Range in enthesopathy scores (including bursa) over time.

The trends in mean inflammation, chronic damage and total enthesopathy scores with treatment over time are shown in Figure 5.12, Figure 5.13 and Figure 5.14. Large decreases in inflammation scores were seen between week 0 and weeks 24 and 52; *p* values for these changes were both <0.1 (Table 5.12).

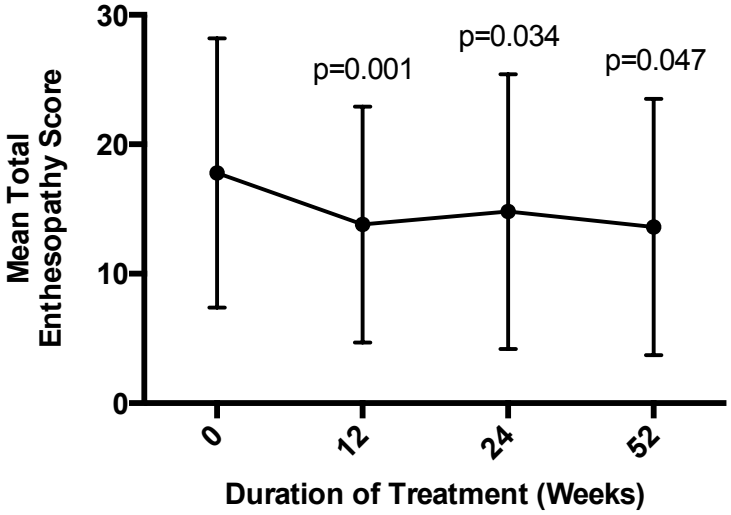

Figure 5.12. Mean change in total enthesopathy score with treatment over time

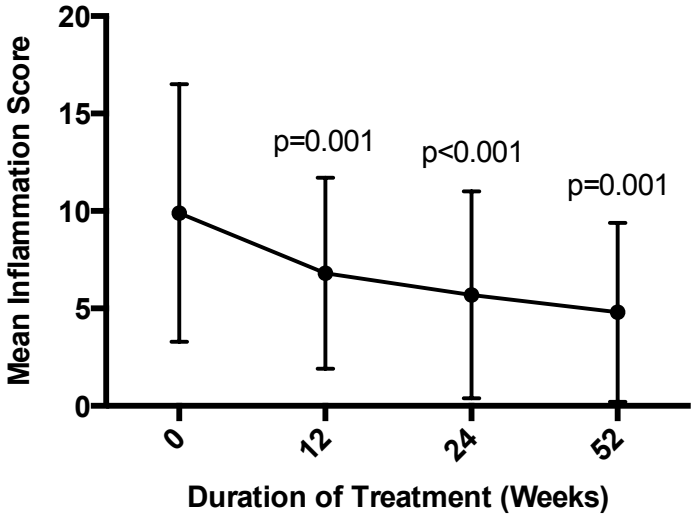

Figure 5.13. Mean change in inflammation score with treatment over time

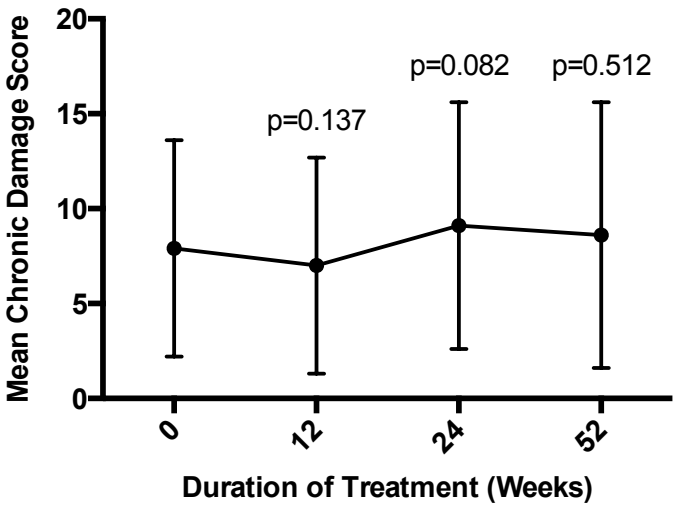

Figure 5.14. Mean change in chronic damage score with treatment over time

5.4.5.2 Tenosynovitis

13 of 23 patients (56.5%) had sonographic evidence of grey scale tenosynovitis at some stage during the study (Table 5.13).

At baseline, 14 tendon sheaths in nine patients were abnormal, with a maximum of three abnormalities in any one patient. Power Doppler signal was seen in four tendon sheaths in three patients - two unilaterally in a single tendon (thumb extensor pollicis longus tendon/proximal patellar tendon) and one bilaterally in the proximal patellar tendons. Knee and ankle tendons most frequently exhibited tenosynovitis, with very little seen in the digits of the hands. Tenosynovitis scores (out of a possible maximum of 264) ranged from 0-7.

With treatment, the majority of abnormalities resolved by the primary endpoint of 24 weeks with the exception of one lesion in two patients. However, six patients developed new areas of tenosynovitis during the study – in four patients at week 24, and in two different patients at week 52. Power Doppler signal resolved in all but two tendon sheaths (one distal and one proximal patellar tendons) in two patients. Tenosynovitis scores ranged from 0-2 at week 12, 0-6 at week 24 and 0-6 at week 52.

Of the 14 tendons identified at baseline with grey scale tenosynovitis, only eight had corresponding entheses included the ultrasound protocol, seven of which had an associated inflammatory enthesopathy. The remainder occurred at sites where the tendon crosses a bony prominence and acts as an enthesis organ, still subject to the same mechanical shearing forces but with no true bone insertion site to visualise with ultrasound. Of the twelve sites after baseline with tenosynovitis and corresponding true entheses (four at week 12, three at week 24 and five at week 52), six had an associated inflammatory enthesopathy and only one had chronic damage (grade 1 bone erosions).

Tendon		Mode	Week 0				Week 12				Week 24				Week 52			
			Tendon (max n=46)		Patient (max n=23)		Tendon (max n=46)		Patient (max n=23)		Tendon (max n=46)		Patient (max n=23)		Tendon (max n=40)		Patient (max n=20)	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Thumb	Flexor pollicis longus	GS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	EPL overlying the interphalangeal joint	GS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	EPL overlying the carpometacarpal joint	GS	1	2.2	1	4.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	1	2.2	1	4.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Index Finger	Flexor digitorum profundus	GS	1	2.2	1	4.3	1	2.2	1	4.3	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor digitorum	GS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Wrist	Extensor Compartment 1 (APL and EPB)	GS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor Compartment 2 (ECR, ECL, ECB)	GS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

	Extensor Compartment 3 (Extensor pollicis longus)	GS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor Compartment 4 (Extensor digitorum)	GS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor Compartment 5 (Extensor digiti minimi)	GS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor Compartment 6 (Extensor carpi ulnaris)	GS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Knee	Quadriceps	GS	1	2.2	1	4.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Proximal Patellar	GS	5	10.9	3	13.0	2	4.3	1	4.3	1	2.2	1	4.3	1	2.5	1	5.0
		PD	3	6.5	2	8.7	0	0.0	0	0.0	1	2.2	1	4.3	1	2.5	1	5.0
	Distal Patellar	GS	0	0.0	0	0.0	0	0.0	0	0.0	1	2.2	1	4.3	1	2.5	1	5.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	1	2.2	1	4.3	1	2.5	1	5.0
Foot and Ankle	Posterior Tibialis	GS	2	4.3	2	8.7	2	4.3	2	8.7	4	8.7	4	17.4	2	2.5	2	5.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Flexor Digitorum Longus	GS	1	2.2	1	4.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

	Flexor Hallucis Longus	GS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Anterior Tibialis	GS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor Hallucis Longus	GS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Extensor Digitorum Longus	GS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Peroneal Longus	GS	2	4.3	2	8.7	0	0.0	0	0.0	1	2.2	1	4.3	0	0.0	0	0.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Peroneal Brevis	GS	1	2.2	1	4.3	1	2.2	1	4.3	0	0.0	0	0.0	2	5.0	2	10.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 5.13. Frequencies of grey scale and power Doppler tenosynovitis at the patient and tendon level at baseline and after 12, 24 and 52 weeks of treatment (EPL: Extensor pollicis longus; APL: Abductor pollicis longus; EPB: Extensor pollicis brevis; ECR: Extensor carpi radialis; ECL: Extensor carpi longus; ECB: Extensor carpi brevis)

5.4.5.3 Synovitis

Low grade synovitis was a common finding, with 22 of 23 (95.7%) patients having at least one area of grey scale synovitis during the study. At baseline, 18 of 23 (78.3%) patients had a total of 79 joints with grey scale synovitis (defined as a score >0), seven of which (in four patients) also had power Doppler signal. The number of joints per patient with grey scale synovitis ranged from 0-12, with a median (IQR) of 3 (0-6). Median total synovitis score was 4 (IQR 0-8) out of a possible 264.

By week 12, 18 of 23 (78.3%) patients had a total of 68 joints with grey scale synovitis. Three of these (in three patients) had persistent power Doppler signal from baseline, with the remainder having resolved. Two of the 18 patients with grey scale synovitis were different to baseline. The number of joints per patient with grey scale synovitis ranged from 0-10, with a median (IQR) of 2 (1-4). Median total synovitis score was 2 (IQR 1-6) out of a possible 264.

By week 24, the number of patients with grey scale synovitis had increased to 21 of 23 (91.3%), involving a total of 89 joints, three of which (in three patients) also had power Doppler signal. These three lesions were new, with the seven from baseline having now resolved. The number of joints per patient with grey scale synovitis ranged from 0-11, with a median (IQR) of 3 (0-6). Median total synovitis score was 3 (IQR 2-6) out of a possible 264.

By week 52, the number of patients with grey scale synovitis reduced to 14 of 23 (60.9%), involving a total of 47 joints, one of which also had power Doppler signal. This was a new area of signal, with all previous areas having resolved. The number of joints per patient with grey scale synovitis ranged from 0-10, with a median (IQR) of 1 (0-3). Median total synovitis score was 1.5 (IQR 1-4) out of a possible 264 (Table 5.14).

In terms of numbers of joints, by the primary endpoint of week 24 the burden of synovitis worsened from baseline in eight patients, and new synovitis appeared in a further seven. A reduction of number of joints involved occurred in six and resolved altogether in another one patient. One patient remained static with the same number of areas of synovitis at baseline and week 24.

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Joint		Mode	Week 0				Week 12				Week 24				Week 52			
			Joint (max n=46)		Patient (max n=23)		Joint (max n=46)		Patient (max n=23)		Joint (max n=46)		Patient (max n=23)		Joint (max n=40)		Patient (max n=20)	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Thumb	Interphalangeal	GS	6	13.0	5	21.7	5	10.9	4	17.4	5	10.9	5	21.7	3	7.5	2	10.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Carpometacarpal	GS	18	39.1	12	52.2	17	37.0	11	47.8	28	60.9	16	69.6	7	17.5	4	20.0
		PD	1	2.2	1	4.3	0	0.0	0	0.0	1	2.2	1	4.3	0	0.0	0	0.0
Index Finger	Distal Interphalangeal	GS	8	17.4	8	34.8	3	6.5	3	13.0	4	8.7	3	13.0	3	7.5	3	15.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Proximal Interphalangeal	GS	8	17.4	5	21.7	6	13.0	4	17.4	8	17.4	5	21.7	5	12.5	3	15.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Metacarpophalangeal	GS	12	26.1	8	34.8	6	13.0	4	17.4	5	10.9	3	13.0	2	5.0	1	5.0
		PD	3	6.5	2	8.7	2	4.3	2	8.7	0	0.0	0	0.0	0	0.0	0	0.0
Wrist		GS	17	37.0	12	52.2	16	34.8	12	52.2	26	56.5	18	78.2	15	37.5	11	55.0
		PD	3	6.5	3	13.0	1	2.2	1	4.3	2	4.3	2	8.7	1	2.5	1	5.0

Elbow	Lateral Elbow	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
		0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
	Medial Elbow	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
		0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
	Posterior Elbow	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
		0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
Knee		GS	9	19.6	7	30.4	11	23.9	8	34.8	8	17.4	6	26.1	10	25.0	6	30.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Ankle		GS	1	2.2	1	4.3	1	2.2	1	4.3	2	4.3	1	4.3	1	2.5	1	5.0
		PD	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 5.14. Frequencies of grey scale and power Doppler synovitis at the patient and tendon level at baseline and after 12, 24 and 52 weeks of treatment.

In terms of the grade of synovitis, grey scale synovitis resolved in 42 (79.5%), improved in 6 (7.6%), remained unchanged in 28 (35.4%) and worsened in 3 (3.8%) from week 0 to week 24. New synovial inflammation appeared in 49 joints (Table 5.15).

Synovitis score	Score at baseline	Resolved	Improved	Unchanged	Worse	New
GS	All	42	6	406	3	49
	0			378		49
	1	34		28	3	
	2	8	5	0	0	
	3	0	1	0		
PD	All	7	0	496	0	3
	0			496		3
	1	6		0	0	
	2	1	0	0	0	
	3	-	-	-		

Table 5.15. Changes in synovitis scores between baseline and week 24. ‘New’ lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had ‘resolved’. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Table 5.16 below repeats the same analyses, restricted to patients who were scanned by the same sonographer on both occasions.

Synovitis score	Score at baseline	Resolved	Improved	Unchanged	Worse	New
GS	All	20	5	174	2	19
	0			152		19
	1	16		22	2	
	2	4	4	0	0	
	3	0	1	0		
PD	All	4	0	215	0	1
	0			215		1
	1	3		0	0	
	2	1	0	0	0	
	3	-	-	-		

Table 5.16. Changes in synovitis scores between baseline and week 24. ‘New’ lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had ‘resolved’. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved

The carpometacarpal joints of the thumb most frequently exhibited sonographic grey scale changes in keeping with synovitis, closely followed by the wrist joints and the index finger metacarpophalangeal joints. No synovitis was seen throughout the study in the

elbow joints or tarsometatarsal joints (between the base of the fifth metatarsal and cuboid bone) and was uncommon at the ankle (Figure 5.15).

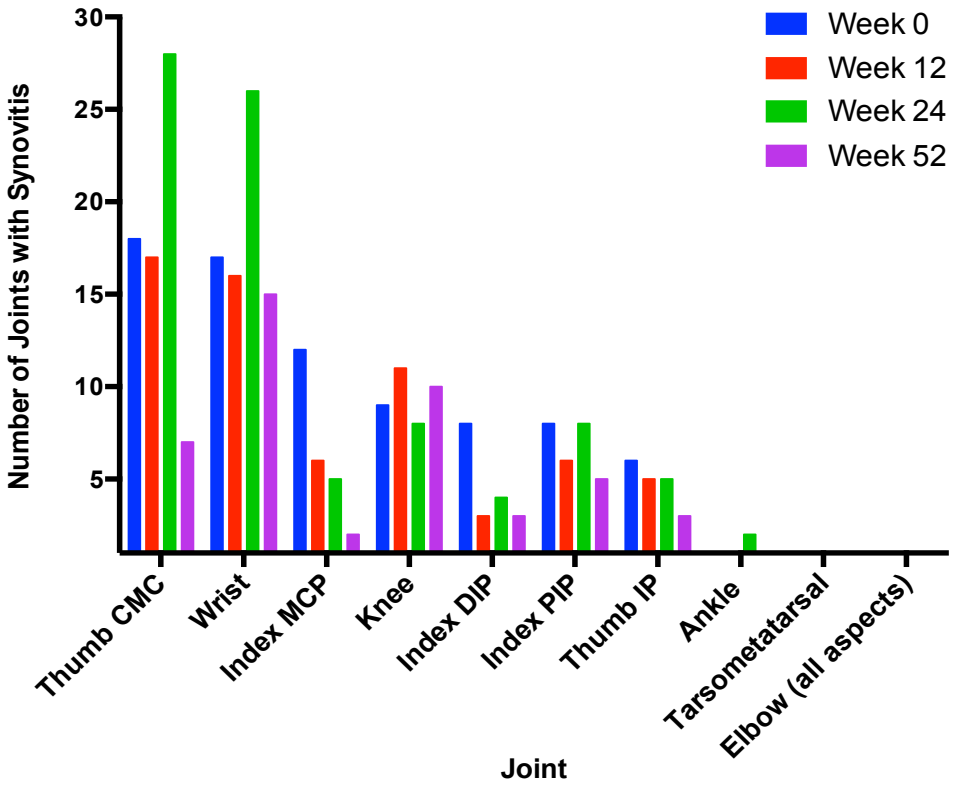


Figure 5.15.. Frequency of grey scale joint synovitis with treatment over time (CMC: carpometacarpal; MCP: metacarpophalangeal; DIP: distal interphalangeal; PIP: proximal interphalangeal: IP; interphalangeal)

Synovitis was usually mild (grade 1). 13 (15.1%) of 86 joints with synovitis at baseline had changes that were of grade 2 or 3, in nine patients. At subsequent time points, grade 2 or 3 changes were seen in 7 (10.3%) of 68 joints with synovitis in six patients at week 12, 9 (10.1%) of 89 joints with synovitis in nine patients at week 24 and 7 (14.9%) of 47 joints in four patients at week 52. Severe synovitis (grade 3) was seen in only three joints throughout the study – in one joint in one patient at week 0, and in two different joints in one patient at different time points (week 12 and week 52).

5.4.6 Associations between Clinical and Sonographic Outcomes

5.4.6.1 Correlation between ultrasound and clinical entheseal assessments

The accuracy of clinical examination to detect enthesitis is known to be inferior to imaging, although several assessment tools are still advocated for use in patients with

PsA, such as the LEI and MASES. It is not known how these assessments perform in psoriasis patients with subclinical disease, or if they are able to detect emerging pathology. Table 5.17 demonstrates the level agreement prior to treatment between clinical examination and ultrasound (inflammatory lesions only) at several anatomical sites (where a peripheral enthesis was accessible for both assessments).

	CE<US %	US<CE %	PEA %	Sp0 % (n/N)	Sp1 % (n/N)	Kappa (95% CI)	PABAK
Site	n=46	n=46	n=46				
Medial humeral epicondyle	24%	-	76%	85% (60/71)	48% (10/21)	0.37 (0.12, 0.62)	0.52
Lateral humeral epicondyle	41%	4%	54%	70% (48/69)	9% (2/23)	-0.03 (-0.19, 0.13)	0.09
Quadriceps	41%	4%	54%	70% (48/69)	9% (2/23)	-0.03 (-0.19, 0.13)	0.09
Proximal patellar	30%	-	70%	81% (60/74)	22% (4/18)	0.16 (-0.04, 0.36)	0.39
Distal patellar	54%	7%	39%	56% (36/64)	- (0/28)	-0.13 (-0.28, 0.01)	-0.22
Proximal Achilles	13%	7%	80%	89% (72/81)	18% (2/11)	0.08 (-0.25, 0.41)	0.61
Plantar fascia	17%	2%	80%	89% (70/79)	31% (4/13)	0.23 (-0.09, 0.55)	0.61

Table 5.17. Agreement between clinical examination and ultrasound findings at week 0 (CE=clinical examination; PABAK=Prevalence-adjusted, bias-adjusted Kappa; PEA=percentage exact agreement; Sp0=category-specific proportion of agreement (absent); Sp1=category-specific proportion of agreement (present)).

Given the preclinical stage of enthesitis in the patient cohort, it is not surprising that agreement between clinical and sonographic assessments was poor. At worst, ultrasound detected an abnormality in 54% of all distal patellar tendon insertions scanned where clinical examination was found to be normal (percentage exact agreement (PEA) 39%). At best, ultrasound found an abnormality in 13% of proximal Achilles tendon entheses when clinical examination was normal (PEA 80%).

5.4.6.2 Correlation between enthesopathy scores and cutaneous outcomes

Cutaneous Psoriasis (PASI Score)

No consensus exists for the best measure of success for a drug therapy in psoriasis. The degree of improvement in PASI score is the most widely cited in clinical trials, and as therapeutics have advanced, the goal posts have moved – first from PASI 50 (i.e. the number of patients achieving at least 50% improvement in their PASI score from baseline at the primary endpoint), to PASI 75, and now PASI 90 and PASI 100 (complete clearance) are emerging as attainable outcomes. In this cohort, overall clinical response was excellent, with 21 of 23 patients achieving at least a 75% improvement by week the primary endpoint of week 24, and 17 of 23 achieving PASI 90. The latter was selected as the benchmark for skin improvement to permit comparison of change in enthesopathy scores between two groups.

In these analyses, values at each time point were compared according to PASI 90 status, controlling for baseline values of the relevant enthesopathy score and baseline PASI (Table 5.18).

Enthesopathy Score	Unadjusted mean (SD)		Adjusted mean*		Difference* (95% CI)	Effect size**
12 weeks	PASI 90 - Yes n=10	PASI 90 - No n=13	PASI 90 -Yes n=10	PASI 90 - No n=13		
Inflammation score	5.7 (4.3)	7.6 (5.3)	6.9	6.7	0.2 (-2.5, 2.8)	0.00
Chronicity score	5.6 (6.1)	8.2 (5.4)	6.7	7.3	-0.6 (-3.1, 1.8)	0.02
Total score	11.3 (9.4)	15.8 (8.6)	13.7	13.9	-0.2 (-4.00, 3.67)	0.00
24 weeks	PASI 90 - Yes n=17	PASI 90 - No n=6	PASI 90 - Yes n=17	PASI 90 - No n=6		
Inflammation score	5.8 (6.0)	5.2 (2.6)	5.6	5.9	-0.3 (-4.5, 3.8)	0.00
Chronicity score	9.5 (7.3)	8.2 (4.0)	9.7	7.6	2.1 (-1.4, 5.5)	0.08
Total score	15.3 (12.3)	13.5 (2.6)	15.2	13.9	1.3 (-4.8, 7.3)	0.01
52 weeks	PASI 90 - Yes n=14	PASI 90 - No n=6	PASI 90 - Yes n=14	PASI 90 - No n=6		
Inflammation score	5.2 (5.2)	3.7 (2.8)	5.0	4.2	0.8 (-3.8, 5.5)	0.01
Chronicity score	9.4 (7.7)	6.7 (4.8)	9.4	6.7	2.7 (-2.3, 7.8)	0.08
Total score	14.6 (11.1)	10.3 (5.9)	14.3	11.2	3.0 (-5.2, 11.3)	0.04

Table 5.18. Difference in enthesopathy scores from baseline according to PASI 90 status at each time point (*Adjusted for baseline enthesopathy score and baseline PASI **Partial Eta squared)

There were no substantive differences in inflammation score according to PASI 90 status at any of the time-points. Perhaps counterintuitively, patients who achieved PASI 90 status tended to have higher chronicity scores at 24 and 52 weeks, which was also the case in the raw data without adjustment for baseline values. However, effect size was small and only a small number of patients (n=6) had not achieved PASI 90 at these visits, limiting the accuracy of the data.

Nail Psoriasis (mNAPSI Score)

At week 0, the mNAPSI score correlated with inflammation scores for the entheses (rho=0.37) and synovial joints (rho=0.44). The link between nail disease and PsA is established, but it is unknown if improvements in nail disease with therapy are a marker

of underlying improvement in subclinical enthesitis. Table 5.19 compares the change in enthesopathy scores with the change in mNAPSI scores with treatment from week 0 at each time point in patients with nail disease at baseline (n=17).

Outcome:	**Association with change in mNAPSI: Spearman's rho**		
Change in…	12 weeks n=17	24 weeks n=17	52 weeks n=17
Inflammation score	rho=0.26	rho=0.08	rho=-0.01
Chronicity score	rho=-0.13	rho=-0.49	rho=-0.18
Total score	rho=0.11	rho=-0.32	rho=-0.01

Table 5.19. Association between the change in enthesopathy scores and the change in mNAPSI scores from baseline in patients with nail disease at each time point

In patients with nail involvement at week 0, there were no substantive (|rho|>0.3) associations between changes in mNAPSI and changes in inflammatory enthesopathy scores. At week 24 there was an inverse association with chronic enthesopathy score (the greater the reduction in mNAPSI, the greater the increase in chronic enthesopathy score); however, this seemed to be due to one patient with a large reduction (>80) in mNAPSI whose chronic enthesopathy score had increased. When this patient was excluded, the association disappeared (n=16, rho=-0.05).

5.4.6.3 Correlation between enthesopathy scores and other patient factors

Assessments were made between the change in enthesopathy scores and gender, age, body mass index and smoking status to determine if any of these variables appeared to influence the response to ustekinumab therapy.

Table 5.20 displays the change in enthesopathy scores according to gender at each time point.

Enthesopathy Score	Unadjusted mean (SD)		Adjusted mean*		Difference* (95% CI)	Effect size*
Week 0	Male n=12	Female n=11				
Inflammation score	9.3 (8.2)	10.4 (4.8)				
Chronicity score	5.4 (4.2)	10.6 (6.0)				
Total score	14.8 (11.0)	21.1 (8.9)				
Week 12	Male n=12	Female n=11	Male n=12	Female n=11		
Inflammation score	6.4 (6.2)	7.2 (3.1)	6.8	6.8	0.0 (-2.6, 2.5)	0.00
Chronicity score	5.8 (5.1)	8.5 (6.3)	8.2	5.8	2.5 (0.2, 4.8)	0.20
Total score	12.2 (10.5)	15.6 (7.3)	14.6	13.0	1.6 (-2.2, 5.5)	0.04
Week 24	Male n=12	Female n=11	Male n=12	Female n=11		
Inflammation score	6.0 (5.9)	5.4 (4.7)	6.3	5.0	1.3 (-2.2, 4.8)	0.03
Chronicity score	8.0 (5.2)	10.4 (7.9)	10.8	7.3	3.5 (0.5, 6.5)	0.22
Total score	14.0 (10.5)	15.7 (11.1)	16.7	12.8	4.0 (-1.5, 9.5)	0.10
Week 0 (in those with week 52 data)	Male n=10	Female n=10				
Inflammation score	8.2 (5.5)	10.7 (4.9)				
Chronicity score	4.7 (3.9)	11.0 (6.1)				
Total score	12.9 (7.3)	21.7 (9.2)				
Week 52	Male n=10	Female n=10	Male n=10	Female n=10		
Inflammation score	5.3 (5.1)	4.2 (4.2)	5.8	3.7	2.2 (-1.9, 6.3)	0.07
Chronicity score	7.2 (7.4)	10.0 (6.6)	10.3	6.9	3.5 (-2.1, 9.0)	0.09
Total score	12.5 (11.6)	14.2 (8.4)	16.1	10.6	5.5 (-2.9, 13.9)	0.10

Table 5.20. Comparison of change in enthesopathy scores over time according to gender (*Adjusted for baseline enthesopathy score)

At baseline, females had higher scores for inflammatory and chronic entheseal lesions than males. Consequently, when follow-up values were adjusted for baseline scores, males tended to have higher scores at follow-up than females. Adjusted inflammatory scores were substantively higher in males at 52 weeks because females had shown proportionally greater improvements from baseline. In females, the chronicity scores were stable over time, whilst in males the scores at 24 and 52 weeks increased relative to baseline.

Associations between the change in enthesopathy scores with treatment from week 0 at each time point and age (Table 5.21), BMI (Table 5.22) and smoking status (Table 5.23) were also examined:

Outcome:	**Association with age: Spearman's rho**		
Change in…	12 weeks n=23	24 weeks n=23	52 weeks n=20
Inflammation score	-0.11	-0.03	-0.36
Chronicity score	-0.05	0.25	0.21
Total score	-0.11	0.22	-0.16

Table 5.21. Association between age and change in enthesopathy scores from baseline.

Outcome:	**Association with BMI: Spearman's rho**		
Change in…	12 weeks n=23	24 weeks n=23	52 weeks n=20
Inflammation score	-0.11	-0.11	-0.09
Chronicity score	-0.32	-0.15	-0.32
Total score	-0.21	-0.21	-0.22

Table 5.22. Association between BMI and change in enthesopathy scores from baseline over time

There were no consistent associations between age or BMI and any of the entheseal scores across the different visits. There was a negative correlation between age and inflammation score at 52 weeks but this was not present at week 12 or 24. There was a negative correlation between BMI and chronicity score at week 12 and 52 but not at week 24. These associations were very weak, only just above the pre-specified cut-off (0.3).

Enthesopathy Score	Unadjusted mean (SD)		Adjusted mean*		Difference* (95% CI)	Effect size*
Week 0	Smoker n=15	Non-smoker n=8				
Inflammation score	9.7 (5.1)	10.3 (9.3)				
Chronicity score	8.9 (5.6)	5.9 (5.6)				
Total score	18.7 (8.1)	16.1 (14.2)				
Week 12	Smoker n=15	Non-smoker n=8	Smoker n=15	Non-smoker n=8		
Inflammation score	6.6 (5.0)	7.1 (5.0)	6.7	6.9	-0.2 (-2.8, 2.4)	0.00
Chronicity score	7.8 (5.8)	5.6 (5.7)	6.8	7.5	-0.6 (-3.1, 1.8)	0.02
Total score	14.4 (8.6)	12.8 (10.4)	13.7	14.0	-0.3 (-4.3, 3.6)	0.00
Week 24	Smoker n=15	Non-smoker n=8	Smoker n=15	Non-smoker n=8		
Inflammation score	5.8 (5.0)	5.5 (6.2)	5.9	5.3	0.6 (-3.1, 4.3)	0.01
Chronicity score	10.3 (6.1)	5.9 (7.1)	9.3	8.8	0.5 (-2.8, 3.7)	0.00
Total score	16.1 (9.5)	12.4 (12.7)	15.4	13.7	1.7 (-4.1, 7.4)	0.02
Week 0 (in those with week 52 data)	Smoker n=17	Non-smoker n=7				
Inflammation score	10.5 (4.9)	7.6 (5.8)				
Chronicity score	9.5 (5.9)	4.9 (5.2)				
Total score	19.9 (7.7)	12.4 (10.4)				
Week 52	Smoker n=13	Non-smoker n=7	Smoker n=13	Non-smoker n=7		
Inflammation score	4.5 (4.8)	5.1 (4.5)	4.1	6.0	-1.9 (-2.5, 6.2)	0.05
Chronicity score	9.6 (7.3)	6.7 (6.5)	8.2	9.3	-1.1 (-6.6, 4.4)	0.01
Total score	14.2 (10.1)	11.9 (10.1)	12.2	15.4	-3.2 (-11.9, 5.4)	0.04

Table 5.23. Comparison of change in enthesopathy scores over time according to smoking status (*Adjusted for baseline enthesopathy score)

There were no consistent associations between smoking status and enthesopathy score; adjusting for baseline scores, at week 24 there were no large differences according to

smoking status. Smokers tended to have higher scores than non-smokers because their inflammation scores had improved to a lesser degree, and their chronicity scores had increased. However, in patients with data at week 52 the opposite was true. The small sample size may be limiting the accuracy of these assessments.

5.4.6.4 Correlation between enthesopathy scores and laboratory outcomes

Median baseline PASI scores were higher in patients positive for HLA-Cw06 in this cohort. However, median PASI scores and the median percentage reduction from baseline at weeks 12, 24 and 52 did not differ according to HLA-Cw06 status at any of the follow-up visits (Table 5.24).

PASI Score	**Median Score (IQR)**		**Median % reduction (IQR)**	
	Cw06 - Yes n=15	Cw06 – No n=8	Cw06 - Yes n=15	Cw06 - No n=8
Week 0	25.7 (14.3, 29.7)	14.9 (12.3, 17.4)		
Week 12	2.3 (1.4, 3.9)	2.3 (0.9, 4.0)	88 (85, 95)	87 (72, 93)
Week 24	0.6 (0.0, 3.9)	0.4 (0.0, 2.5)	97 (91, 100)	97 (84, 100)
	Cw06 - Yes n=12	Cw06 - No n=8	Cw06 - Yes n=12	Cw06 – No n=8
Week 0 (in those with week 52 data)	26.5 (16.9, 32.6)	14.9 (12.3, 17.4)		
Week 52	0.3 (0.0, 4.6)	0.1 (0.0, 0.4)	99 (81, 100)	99 (97, 100)

Table 5.24. Comparison of median PASI score and median percentage reduction in PASI score according to HLA-Cw06 status (NB: Due to extreme skew in the PASI scores, only unadjusted scores at each visit could be calculated).

It is not known if the reported phenomenon of enhanced efficacy of ustekinumab in patients with the HLA-Cw06 allele extends to the musculoskeletal manifestations of psoriatic disease, and in particular, subclinical enthesopathy. Table 5.25 compares the change in enthesopathy scores from baseline at each time point according to HLA-Cw06 status in this cohort.

Enthesopathy Score	Unadjusted mean (SD)		Adjusted mean*		Difference* (95% CI)	Effect size*
Week 0	Cw06 - Yes n=15	Cw06 - No n=8				
Inflammation score	9.5 (7.7)	10.6 (4.2)				
Chronicity score	7.7 (6.2)	8.3 (5.0)				
Total score	17.2 (12.0)	18.9 (6.8)				
Week 12	Cw06 - Yes n=15	Cw06 - No n=8	Cw06 - Yes n=15	Cw06 - No n=8		
Inflammation score	6.5 (5.9)	7.4 (2.3)	6.7	6.9	-0.2 (-2.9, 2.4)	0.00
Chronicity score	7.5 (6.4)	6.3 (4.5)	7.7	5.9	1.8 (-0.5, 4.0)	0.12
Total score	13.9 (11.0)	13.6 (4.1)	14.4	12.8	1.6 (-2.2, 5.5)	0.04
Week 24	Cw06 - Yes n=15	Cw06 - No n=8	Cw06 - Yes n=15	Cw06 - No n=8		
Inflammation score	6.2 (6.2)	4.8 (3.2)	6.4	4.4	2.1 (-1.5, 5.6)	0.07
Chronicity score	9.9 (7.5)	7.6 (4.1)	10.1	7.2	2.9 (0.0, 5.8)	0.18
Total score	16.1 (12.9)	12.4 (2.6)	16.6	11.4	5.2 (-0.1, 10.5)	0.17
Week 0 (in those with week 52 data)	Cw06 - Yes n=12	Cw06 - No n=8				
Inflammation score	8.7 (5.9)	10.6 (4.2)				
Chronicity score	7.6 (6.7)	8.3 (5.0)				
Total score	16.3 (10.7)	18.9 (6.8)				
Week 52	Cw06 - Yes n=12	Cw06 – No n=8	Cw06 - Yes n=12	Cw06 - No n=8		
Inflammation score	4.4 (4.5)	5.3 (5.0)	4.7	4.8	-0.1 (-4.3, 4.2)	0.00
Chronicity score	8.8 (8.2)	8.3 (5.1)	9.1	7.9	1.1 (-3.8, 6.1)	0.01
Total score	13.3 (12.2)	13.5 (5.6)	14.0	12.4	1.5 (-6.4, 9.4)	0.01

Table 5.25. Comparison of change in enthesopathy scores over time according to HLA-Cw06 status

These data show that in this cohort, there appears to be no advantage to possessing the HLA-Cw06 allele in terms of response in subclinical enthesopathy. At 12 and 24 weeks, there was preliminary descriptive evidence that patients' positive for HLA-Cw06 had higher chronicity scores, although this effect was not seen in the patients with data available at week 52.

Trends relating to HLA-B27 status could not be assessed in this small cohort as there was only one patient in the positive group.

5.4.7 Feasibility of a large scale, head-to-head comparator, randomised controlled trial of anti-IL-12/23p40 in the treatment of subclinical enthesitis

One of the aims of this study was to assess the feasibility of a large, head-to-head comparator randomised controlled trial (RCT) of subclinical enthesitis. The data generated, while unable to conclusively prove the efficacy of ustekinumab in the treatment of subclinical enthesopathy, have highlighted some encouraging trends to support the value of a larger, adequately powered study.

Because there was evidence that inflammatory and chronic entheseal scores change in opposite directions with therapy, it would not be appropriate to use the total enthesopathy score as an outcome in a future clinical trial. Whilst inflammatory changes showed the greatest change with therapy, prevention of chronic structural progression may be the ultimate aim clinically.

Sample sizes have been provided in the following table for future trials using either inflammatory enthesopathy score or chronic enthesopathy score at 24 weeks as the primary outcome (Table 5.26). Standard deviations for changes from baseline have been assumed to be the same as those observed in this study. Two between-group intervals have been considered, equivalent to assuming the value observed at week 24 in patients treated with ustekinumab would be 80% or 85% as high as that seen in controls, that groups would be randomised 1:1 and that they would be compared using an independent samples T-test. Alpha has been set at 0.05, 1-Beta at 0.9.

	Week 24	20% improvement over controls		15% improvement over controls	
Outcome	Mean ± SD UST	Interval to detect	Sample size	Interval to detect	Sample size
Inflammation Score	5.7 ± 5.3	1.43	291 per group	1.01	579 per group
Chronic Damage Score	9.1 ± 6.5	2.28	171 per group	1.61	343 per group

Table 5.26. Sample size calculations for a larger head-to-head comparator RCT, using the different enthesopathy scores as outcome measures.

Based on these estimates, a full trial appears feasible, although a multi-centre approach should be adopted. In this study, 36 of 73 (49%) patients initially screened had at least one inflammatory entheseal lesion in keeping with the OMERACT ultrasound definition of enthesopathy. Therefore, not allowing for exclusions for other reasons (e.g. contraindications to biologic therapy), approximately 600 patients would need to be screened to attain the desired sample size, which is too many for a single centre.

Consideration should be given to including an internal pilot study in the full trial, to test whether or not a control group receiving the chosen active comparator would be likely to show progression rates sufficiently high to detect a clinically meaningful difference compared to the group receiving ustekinumab. Stop-go criteria would determine whether to keep recruiting to the full sample size.

In addition, given that enthesopathy scores correlated with age and BMI at baseline (Chapter 4.4.5.5.), and patients positive for the HLA-Cw06 allele may show greater increases in chronicity score, recruitment should be stratified for these variables in any future trials, or they should be considered as covariates to include in adjusted analyses. However, given that HLA-Cw06 associates with psoriasis, and not necessarily with PsA, further considerations around using this genetic marker at all to stratify for arthritis prevention merit consideration.

5.5 Discussion

The presence of antecedent psoriasis in the majority of patients who are destined to develop PsA offers an opportunity to potentially prevent arthritis development if systemic therapy is indicated in the dermatology clinic. The recognition of enthesopathy as the pivotal early lesion provides a key target for assessment, especially through the use of ultrasound during the preclinical phase. The findings in the previous two chapters confirm that subclinical enthesopathy in patients with psoriasis is not uncommon, with 49.3% of

the 73 patients with moderate to severe psoriasis having at least one potentially modifiable inflammatory abnormality at first presentation to dermatology, which is in broad agreement with other ultrasound studies and recent MRI findings. (Gisondi et al., 2008, Gutierrez et al., 2011, Naredo et al., 2011, Faustini et al., 2016, Moshrif et al., 2017).

Data in this chapter show that targeted treatment of psoriasis with a therapeutic agent that has independently been shown to work in PsA, namely anti-IL-12/IL-23, can be associated with regression of subclinical inflammatory entheseal abnormalities. A statistically significant reduction in overall entheseal inflammation scores were seen after just 24 weeks of therapy, and further improvements continued out to week 52, suggesting long term therapy is necessary to obtain maximum improvement and prevent the progression to symptomatic arthritis. All patients remained free of musculoskeletal symptoms with the exception of those who sustained a sports or traumatic injury.

In contrast to inflammatory lesions, chronic damage abnormalities did not significantly change with ustekinumab therapy in this cohort. While some structural lesions worsened, some appeared to decrease in severity or resolve, principally bone erosions, which is a recognised phenomenon in RA (Ideguchi et al., 2006, Rau et al., 2004). Ultrasound studies in SpA have also showed erosion healing over time which likely indicates new bone formation and the reparative phenotype of these conditions (McGonagle et al., 2008). Rates of progression of structural lesions without therapy are not known; one limitation from this study was the failure to include an untreated group of psoriasis patients, which may have helped determine if ustekinumab slowed the development of damage. However, this limitation is hard to overcome, as it would have been unethical to have not treated a group of patients presenting for treatment of psoriasis. One means of circumventing this would to have been to include a group of patients treated with a comparator drug, ideally the first line systemic agent, methotrexate. However, this was designed to be a feasibility study to evaluate the response to ustekinumab, and would have necessitated involving at least one other centre to recruit adequate patients and so it was decided that a comparator arm would not be included. In addition to including a group of patients either not given any systemic therapy or standard treatment with methotrexate, it may have been helpful to re-scan the healthy volunteers after 24 and 52 weeks to indicate the rates of progression the normal population.

As previously hypothesised by McGonagle and colleagues (McGonagle et al., 2007), investigation outside of the enthesis demonstrated dissipation of inflammation throughout the synovio-entheseal complex as described in Chapter 4.1. Ustekinumab appears to lead to a reduction in inflammatory burden within the entire SEC, and even in instances where new areas developed on treatment, these were often transient and resolved as therapy continued, providing hope that if treated early, the evolution of enthesitis into symptomatic PsA can be attenuated.

An interesting observation in this study was the presence of higher entheseal inflammation scores in psoriasis patients who did not smoke at week 0, 12 and 52, and higher chronic damage scores in smokers at all time points. As discussed in Chapter 3.4, tobacco smoking, and specifically nicotine, is demonstrated to have a protective effect in the development of PsA (Eder et al., 2012, Pattison et al., 2008) due to the inhibition of pro-inflammatory pathways, and may account for the lower mean inflammation scores in those who smoked. Compelling experimental evidence also associates nicotine to chronic damage changes and degeneration of the intervertebral discs within the spine, with downregulation of the proliferation rate and glycosaminoglycan biosynthesis of disc cells (Elmasry et al., 2015, Akmal et al., 2004). Moreover, smoking causes the constriction of the vascular network, reducing the exchange of nutrients and anabolic agents from the blood vessels to bone, and this may explain why more chronic damage abnormalities were seen in those who smoked tobacco.

One limitation of this study was the lack of histological confirmation of the abnormalities seen on ultrasound. This would have been particularly helpful for the evaluation of synovial changes, which overall were mild and only seen in grey scale. Some of these changes may have been physiological, and given the distribution of abnormalities (with the most frequent abnormalities seen at the thumb carpometacarpal joint and wrist), there is a possibility that these were due to degenerative disease such as osteoarthritis. This may account for why some abnormalities were fluctuant and some were not modifiable with therapy.

The relatively small number of patients investigated in this pilot study prevents any definite conclusions from being drawn on the effectiveness of ustekinumab in treating subclinical enthesitis, bursitis, tenosynovitis and synovitis, although the trends identified are encouraging. These data are in keeping with and extended the findings from recently published reports of good sonographic responses in entheseal abnormalities after treatment with TNF inhibitors in patients with psoriasis (Acquacalda et al., 2015) and spondyloarthritis (Naredo et al., 2010, Aydin et al., 2010) which also included only small number of patients.

Unfortunately, no demographic or clinical ‘biomarkers’ were identified in this cohort that could be used to predict which patients had the greatest response within the SEC to IL-12/IL-23 inhibition. In the previous chapters, it was observed that patients with more severe nail disease and patients with a higher BMI had greater inflammation scores, and age correlated with chronic damage scores. However, with treatment, no consistent associations were found between the change in enthesopathy scores and the skin response, nor the change in mNAPSI score, age, BMI and smoking status. It is likely that the small sample size is limiting the accuracy of these assessments and future testing is advocated in a larger, adequately powered clinical trial.

HLA-Cw06 is accepted as the psoriasis susceptibility gene with the greatest effect and observations have suggested that this genetic polymorphism may serve as a pharmacogenetic marker to predict clinical response to immunomodulatory agents including ustekinumab (Warren and Griffiths, 2005). Skin responses to ustekinumab have been shown to be superior in HLA-Cw06 positive patients (PASI 75 response at week 12: 96.4% compared to 65.2% in HLA-Cw06 negative patients) by Talamonti and colleagues, and supported by data from a Chinese psoriasis cohort (Chiu et al., 2014, Talamonti et al., 2013). However, although median baseline PASI scores were higher in patients who were positive for HLA-Cw06, data from this cohort show that there appears to be no advantage to possessing the HLA-Cw06 allele in terms of response in subclinical enthesopathy. Median PASI scores and the median percentage reduction from baseline at weeks 12, 24 and 52 did not differ according to HLA-Cw06 status at any of the follow-up visits. This lack of effect is again most probably due to the small sample size.

One of the aims of this chapter was to assess the feasibly of a larger head-to-head comparator RCT in subclinical enthesitis, and the data generated has provided preliminary support to the value of an adequately powered study. Aiming to demonstrate a meaningful difference (i.e. 20% improvement) in inflammation score over a competitor drug, a sample size of 582 patients (291 per group) would need to be recruited. Using a multi-centre approach with six or more specialist centres, a full trial would be feasible, and the larger sample size would hopefully allow a more accurate evaluation of any relationship with HLA-Cw06 status or other clinical parameters.

Despite the small sample size and other limitations in this chapter, these data suggest that ustekinumab does appear to be capable of regressing subclinical enthesopathy and potentially stem the evolution of PsA in patients who require systemic therapy for moderate to severe psoriasis, and support the proposal for a larger multi-centre RCT in order to confirm these observations.

5.6 Conclusion

Data within this chapter support the recognition of enthesitis as a target for assessment (using ultrasound) and intervention in the preclinical phase of PsA using skin directed biologic therapy. Inhibition of IL-12/IL-23 not only provided an excellent reduction in the severity and extent of skin disease, but was accompanied by a statistically significant reduction in subclinical entheseal inflammation (42% at week 24, 52% at week 52), while chronic damage parameters remained largely static. No correlations were observed between sonographic improvement and any demographic or clinical parameters,

although the small sample size is likely to have limited the accuracy of these assessments.

Futher investigation of the natural evolution of subclinical enthesopathy in both patients with psoriasis and healthy volunteers is required to acertain if a slowing of disease progression and development of PsA occurred as a consequence of ustekinumab therapy. However, these data highlight encouraging trends, and sample size estimates for a larger prospective longitudinal head-to-head study with a comparator drug would be feasibile if a multi-centre approach is adopted.

Chapter 6
Comparison of the MRI Appearances of Axial and Peripheral Enthesitis in Patients with Psoriasis in Secondary Care and Healthy Controls

6.1 Introduction

High-field magnetic resonance imaging (MRI) is widely considered the gold standard imaging modality for visualising the soft tissue and bony pathology in PsA, especially within the sacroiliac joints and axial skeleton (Ostergaard et al., 2007, van der Heijde et al., 2005, McQueen et al., 2007a). Three dimensional image acquisition, high reproducibility, ability to detect bone marrow oedema/osteitis and delineation of soft tissue pathologies have helped MRI find definite applications in the diagnosis, definition of pathogenesis and measurement of therapeutic outcomes in PsA (Poggenborg et al., 2015c). Conventional MRI permits visualisation of only one anatomical area but has been effectively used to demonstrate subclinical enthesopathy in patients with psoriasis without PsA at several sites including the hand (Faustini et al., 2016, Offidani et al., 1998), the foot (Erdem et al., 2008), the knees (Emad et al., 2012, Emad et al., 2010), and the lumbosacral spine and sacroiliac (SI) joints (Hamdy et al., 2015).

The heterogeneity of joint involvement in PsA can be appreciated through the emerging technique of whole body MRI (WBMRI), which has permitted comprehensive evaluation of the early stages of enthesopathy at both axial and peripheral sites in patients with PsA. However, to date, no studies have utilised WBMRI to assess the extent of subclinical musculoskeletal disease in patients with psoriasis.

Only one WBMRI study has evaluated enthesopathy in healthy subjects (without known musculoskeletal disease) alongside patients with psoriatic arthritis and axial spondyloarthritis (Poggenborg et al., 2015b). Healthy subjects were not free from enthesopathy, and although the MRI enthesitis scores were higher in patients with PsA or SpA, the entheseal sites with identifiable WBMRI enthesitis were the same in the healthy subject group. This supports the findings of Benjamin et al who demonstrated microscopic inflammatory changes at sites of high mechanical stress and microtrauma in normal aged cadaveric entheses, which were similar to those seen in patients with early PsA (McGonagle et al., 2009b, Benjamin and McGonagle, 2007) and thought to be part of the normal healing process.

This study aims to assess the utilisation of WBMRI to assess the extent, distribution, severity and type of inflammatory abnormalities and structural changes in both the peripheral and axial skeleton in asymptomatic patients with psoriasis, and compare those findings with a cohort of healthy volunteers.

6.2 Methods

6.2.1 Participant Recruitment

This study was conducted in one centre in the United Kingdom – Chapel Allerton Hospital (part of Leeds Teaching Hospitals NHS Trust), with imaging performed within the Leeds Musculoskeletal Biomedical Research Unit. The study was conducted in accordance with the Declaration of Helsinki and approved by the Leeds East Research Ethics Committee.

6.2.1.1 Participant Identification and Recruitment

Twenty-eight newly referred adult patients with moderate-to-severe chronic plaque psoriasis and 23 healthy controls participated in this study. Patients with psoriasis were included if they did not have musculoskeletal signs or symptoms consistent with a clinical diagnosis of PsA but did have evidence of active subclinical enthesitis in at least one site on ultrasound examination of the peripheral entheses, and were systemic (DMARD) and biologic treatment naïve. These patients and volunteers were the same as included the ultrasound study (Chapter 4) and precise detail on recruitment is described in Chapters 4.2.1.1. (patients with psoriasis) and 4.2.1.2. (healthy volunteers). Healthy volunteers were recruited from staff members and their family and friends in the Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM) and Leeds Institute of Cancer and Pathology (LICAP) at the University of Leeds. During recruitment, it was ensured that there were no contraindications to MRI in any participants. A standard safety patient-completed questionnaire was filled in and reviewed by the radiographer prior to every scan (Appendix 10).

Written consent was obtained from all participants prior to the collection of any clinical or imaging data, which permitted the use of data for research purposes and storage. Participants were made aware that the WBMRI scans would only be reported for abnormalities within the musculoskeletal system, and that pathology in any other bodily systems may not be seen and reported. Conversely, they were made aware that gross pathology in other systems may be identified, in which instance they were assured they would be informed in a timely manner and referred to the appropriate service/specialist.

6.2.2 Inclusion/Exclusion Criteria

6.2.2.1 Patients with psoriasis

- Age 18 or over
- First presentation to dermatology secondary care services
- Diagnosis of chronic plaque psoriasis (confirmed by a dermatologist, the candidate LS) with a PASI score ≥10, with symptoms for more than twelve months
- No prior treatment with PUVA phototherapy, systemic immunosuppressants or DMARDs, biologic or small molecule therapies or alkylating agent for psoriasis or any other condition
- No symptoms or clinical signs of PsA, or diagnosis of any other rheumatological disorder
- No contraindications to biological therapy (Appendix 6)
- No contraindications to MRI scanning, including:
    - Implanted electrical/electronic devices including pacemakers, implantable defibrillators, neuromodulators, insulin pumps or implanted hearing aids
    - Intracranial metal clips
    - Metallic bodies in the eye
    - Severe claustrophobia
- Presence of at least one inflammatory entheseal abnormality (thickening, hypoechogenicity and/or power Doppler signal) in at least one peripheral enthesis (identified through an ultrasound screening programme, described in Chapter 3).

6.2.2.2 Healthy Controls

- Age 18 and over
- No personal history of psoriasis, psoriatic arthritis or other rheumatological condition
- No prior use of any immunosuppressant, biologic or long term non-steroidal anti-inflammatory therapy (for any indication)
- No contraindications to MRI scanning (Appendix 10)

6.2.3 Data Collection

The candidate (LS) carried out all data collection. Magnetic resonance image acquisition and storage was undertaken by an experienced MRI/research radiographer (RE)

proficient in performing WBMRI, within the Leeds Musculoskeletal Biomedical Research Unit (LMBRU) at Chapel Allerton Hospital.

Clinical data obtained in the consultation was recorded on a paper record and then transposed into an encrypted password-protected database on the University of Leeds server for analysis. Care was taken to ensure the check integrity of the dataset at upload. Paper record forms are stored in a locked filing cabinet within a locked room within LIRMM, in accordance with the University's Information Security Policy. Magnetic resonance images were stored in a password-protected database and analysed using OsiriX DICOM viewer.

6.2.4 Clinical Assessment

6.2.4.1 Patients with Psoriasis

Prior to the MRI scan, the candidate (LS) conducted a thorough history and examination of each patient. Recorded participant-reported data included:

- Demographic data (age, gender)
- Fitzpatrick skin type
- Social history (smoking (pack years), alcohol consumption (units/week) and employment)
- Past medical and surgical history, including a detailed history of skin and joint disease
- Family history
- Medications (current prescribed, over-the-counter, alternative and psoriasis-specific medicines, and any previous psoriasis therapies)
- Age of psoriasis symptom onset
- Areas ever affected by psoriasis
- Areas currently affected by psoriasis
- Current or previous musculoskeletal symptoms

Clinical examination data comprised of the following:

- Baseline observations (height, weight, BMI, blood pressure and heart rate)
- An assessment of psoriasis severity and extent – BSA and PASI (Appendix 7) score (Chapter 4.1.2.4.1.)
- An assessment of nail psoriasis severity and extent – mNAPSI (Appendix 8) score (Chapter 4.1.2.4.1.)
- The presence of any signs of PsA (joint swelling and/or tenderness, clinical enthesitis or dactylitis)

- An assessment for clinical enthesitis (defined as tenderness, when the enthesis was palpated with a pressure of the thumb sufficient to blanche the nail bed) at 29 entheseal locations (Chapter 4.2.4.1.2.).

6.2.4.2 Healthy Volunteers

Recorded participant-reported data included:

- Demographic data (age, gender)
- Fitzpatrick skin type
- Social history (smoking (pack years), alcohol consumption (units/week) and employment)
- Past medical and surgical history, including a detailed history of skin and joint disease
- Family history
- Medications (current prescribed, over-the-counter and alternative therapies)

Baseline observations (blood pressure and heart rate) were recorded in addition to height, weight and BMI.

6.2.5 Whole Body Magnetic Resonance Imaging (WBMRI)

6.2.5.1 WBMRI Protocol

WBMRIs were performed on a 3 Tesla (3T) high field MRI unit (Verio, Siemens Healthcare, Erlangen, Germany) using multiple coils (4-channel flex coils for shoulders, spine array coils for spine, body matrix coil for pelvis and knees, quadrature head coil for feet. T1-weighted (turbo spin echo) and short τ inversion recovery (STIR) sequences were performed in a total of seven stations, with coronal slice orientation (shoulders, costochondral joints, hips and knees), coronal oblique orientation (sacroiliac (SI) joints), sagittal orientation (cervicothoracic and thoracolumbar spine), and axial orientation (knees and feet). T2 ‘fat sat’ sequences were also performed with coronal oblique orientation for the SI joints. Gadolinium was not administered due to the potential to cause nephrogenic systemic fibrosis, especially as the patients and volunteers were asymptomatic. The technical parameters are shown in Table 6.1. Total scan time was 55 minutes and was generally well tolerated by participants.

Station	Sequence	Orientation	TR (ms)	TE (ms)	FOV (mm)	Matrix	Slice thick (mm)
Shoulders and Costochondral Joints	STIR	Coronal	4500	101.0	500	384x384	4
Upper Spine	T1	Saggital	500	11.0	450	512x512	4
	STIR	Saggital	4500	94.0	450	512x512	4
Lower Spine	T1	Saggital	500	11.0	450	512x512	4
	STIR	Saggital	4500	94.0	450	512x512	4
SIJs	T1	Coronal oblique	700	10.0	240	384x384	4
	T2 Fat Sat	Coronal oblique	4040	71.0	240	256x256	4
Pelvis/Hips	STIR	Coronal	4500	98.0	450	384x384	4
Knees	STIR	Coronal	4500	73.0	400	448x448	4
		Axial	4500	73.0	400	448x448	4
Feet	T1	Axial	677	12.0	340	512x512	3
	STIR	Axial	6000	85.0	340	512x512	3

Table 6.1. Technical parameters of the WBMRI scan.

6.2.5.2 WBMRI Interpretation

WBMRI were evaluated by a highly experienced rheumatologist (DMcG) experienced with WBMRI, who was blinded to all clinical, biochemical and demographic information. The images were evaluated in a random order. Readability of the scans was assessed for each enthesis as ‘readable’ or ‘not readable’ (e.g. due to artefacts) or ‘not in field of view (FOV)’. All images were analysed for active inflammatory lesions and structural changes at axial (spine and SIJs) and non-axial (peripheral) sites.

6.2.5.2.1 Non-axial (peripheral) sites

Peripheral enthesitis was defined as suggested by Eshed et al (Eshed et al., 2007) as the presence of the following on WBMRI:

- Bone marrow oedema (BMO)/osteitis

- Soft tissue inflammation
- Erosions in adjacent bones
- Enthesophytes in adjacent bones
- Additional findings (e.g. synovitis, bursitis)

At readable peripheral sites, abnormalities were graded from 0-3 depending on severity (0=absent, 1=minor, 2=moderate, 3=severe) for bone marrow oedema, soft tissue inflammation, synovitis and bursitis, and dichotomously (0=absent, 1=present) for erosions and enthesophytes based on the methodology reported by Marzo-Ortega et al (Marzo-Ortega et al., 2001) (Table 6.2). Abnormalities must have been visible in at least two consecutive slices to be scored. Comparison with the opposite site was made for paired entheses.

	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**
Non-axial (peripheral) sites				
Bone marrow oedema (per site)	Absent	Minor	Moderate	Severe
Soft tissue inflammation (per site)	Absent	Minor	Moderate	Severe
Synovitis/effusion (per joint)	Absent	Slight increase in fluid	Moderate increase in fluid	Large increase in fluid
Bursitis (per site)	Absent	Minor	Moderate	Severe
Erosions (per joint)	Absent	Present	-	-
Enthesophytes (per joint)	Absent	Present		

Table 6.2. Scores applied to abnormalities at peripheral sites

The following 45 sites were scored for bone marrow oedema and soft tissue inflammation: tendon insertions at the humeral tuberosity (2), acromioclavicular joint (2) and coracoid process (2), joint capsule insertion at the sternoclavicular joint (2), manubriosternal joint (1), 1st costochondral syndchondrosis (2), 7th costochondral joint (2), tendon insertion at the iliac crest (2), anterior superior iliac spine (2) and ischial tuberosity (2), pubic symphysis fibrocartilage attachments (2), tendon insertions at the greater trochanter of the femur (2), lateral femoral condyle (2), medial femoral condyle

(2), lateral tibial plateau (2), intercondylar notch (2) and inferior pole of the patella (2), quadriceps tendon insertion (2), tendon insertions at the ankle (2), first tarsometatarsal joint of the midfoot (2) and first metatarsophalangeal joint (2) and the insertion sites of the Achilles tendon (2) and the plantar fascia at the calcaneus (2).

The presence of synovitis was assessed at the shoulders (joint capsule, acromioclavicular joint and sternoclavicular joint), hips, knees, ankles, 1st tarsometatarsal joints and 1st metatarsophalangeal joints. Effusions within the subacromial bursae of the shoulders, trochanteric bursae of the hips, pre-patellar bursae and pes anserine bursae at the knees and subcutaneous calcaneal bursae and retrocalcaneal bursae at the ankles were also assessed. Tenosynovitis was assessed at the medial and lateral tendons of the foot.

Erosions were assessed at the 1st tarsometatarsal joint, 1st metatarsal joint and at the insertion sites of the Achilles tendon and plantar fascia into the calcaneus. Enthesophytes were also assessed at the Achilles tendon and plantar fascia insertions.

A high signal on STIR images within the bone marrow or surrounding soft tissue was considered as enthesitis. Synovitis/bursitis were categorised by synovial hypertrophy and the amount of fluid collected within the joint capsule. Bony erosions were scored as cortical defects in T1-weighted sequences.

6.2.5.3 Axial Sites

The spine was divided into 23 individual vertebral units (VU) extending from C2/3 to L5/S1. Each VU within the spine was evaluated separately in the ventral part (vertebral body) and posterior elements (pedicles, facet joints and spinous processes). The SIJs were evaluated at a quadrant level (upper and lower iliac parts, and upper and lower sacral parts) as shown in Figure 6.1.

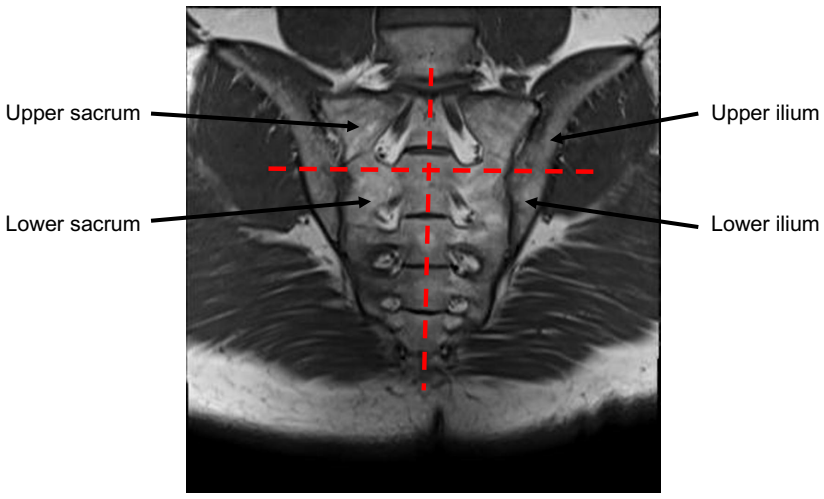


Figure 6.1. Four quadrants of the sacroiliac joints (SIJs)

Images of the axial skeleton were scored for activity using the Berlin modification of the AS spine MRI score (Haibel et al., 2006), which has previously been used to score WBMRI (Althoff et al., 2013). This scoring system encompasses inflammatory abnormalities (BMO) and structural changes (fatty bone marrow infiltration, erosions and bone proliferation) and was proposed by MRI experts from the ASAS/OMERACT study group (Hermann et al., 2012, Rudwaleit et al., 2009) (Table 6.3). Abnormalities must have been visible in at least two consecutive slices to be scored.

	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**
Sacroiliac Joints				
Active inflammation (BMO of quadrant area)	Absent	<33% of quadrant	33-66% of quadrant	>66% of quadrant
Erosions (per quadrant)	Absent	Minor (1-2)	Moderate (3-5)	Multiple (confluent)
Fatty bone marrow infiltration (per quadrant)	Absent	Present	-	-
Sclerosis (per joint)	Absent	Present	-	-
Ankylosis (per joint)	Absent	Present	-	-
Spine				
Active inflammation (BMO of VU area)	Absent	<25% of VU area	25-50% of VU area	>50% of VU area
Erosions (% of bone surface per VU)	Absent	Minor (1-2)	Moderate (3-5)	Multiple (confluent)
Fatty bone marrow infiltration (per VU)	Absent	<25% of VU area	25-50% of VU area	>50% of VU area
Bone proliferation (per VU)	Absent	Syndesmophytes without bridging	Bridging syndesmophytes	Transdiscal ankylosis
Active inflammation of posterior segments (per VU)	Absent	Minor inflammation	Severe inflammation	-

Table 6.3. Berlin modification of the AS spine MRI activity score for axial sites (VU: vertebral unit)

In accordance with published scoring techniques (Althoff et al., 2013), each SIJ was scored from 0-24 (0-3 for each upper and lower ilium, and each upper and lower sacrum) for BMO and erosions, and 0-8 for fatty infiltration, sclerosis and ankylosis. BMO, erosions, fatty infiltration and bone proliferation were scored from 0 to 69 (0-3 in each of 23 VUs), and 0 to 46 (0-2 in each VU) for posterior segment inflammation.

6.2.5.3.1 Spine

Active inflammation (BMO) was defined by the ASAS/OMERACT study group as discreet areas of increased STIR signal with corresponding T1 signal loss, and were scored when located within bone marrow extending out from one or more of the four corners of the vertebral bodies or within the posterior elements (Hermann et al., 2012).

Structural changes were scored within each vertebral body of the spine (not including posterior elements) and defined as follows (Hermann et al., 2012):

- *Fatty bone marrow deposition*: Replacement of the bone marrow by fatty tissue, seen at the vertebral corners and endplates. Decreased STIR signal with corresponding high T1 signal intensity.
- *Erosions*: Disruption of the cortical line, occurring at the vertebral corners and endplates. Hypointense STIR and T1 signal.
- *Syndesmophytes*: Bony outgrowths at anterior, posterior or lateral corners of vertebral bodies (that do not reach adjacent vertebra). STIR and T1 signal isointense to normal bone marrow.
- *Ankylosis*: Bony fusion throughout the disc and/or at the attachment site of the annulus fibrosus (bridging syndesmophytes).

6.2.5.3.2 Sacroiliac Joints

Active inflammation (bone marrow oedema) was defined by the ASAS/OMERACT study group as hyperintense signal on STIR images with corresponding hypointense signal on T1 images, and were scored when located within subchondral bone marrow at periarticular sites (Rudwaleit et al., 2009).

Structural changes were defined as follows (Rudwaleit et al., 2009):

- *Fatty bone marrow infiltration:* Replacement of bone marrow by fatty tissue, resulting from the esterification of fatty acids in inflammatory, often periarticular bone marrow areas. Increased T1 signal.
- *Erosions:* Bony defects at the joint margin (throughout the cartilaginous compartment), initially appearing as single lesions and becoming confluent. Low signal intensity on T1 weighted images. If active, hyperintense signal on STIR and T2-weighted fat saturated images.

- *Ankylosis:* Bony outgrowths appearing along the joint margin, with those directly facing one another fusing to form bridges across the joint. Hypointense STIR and T1 signal.
- *Sclerosis:* Discrete subchondral bands extending at least 5mm from the sacroiliac joint space. Low signal intensity on STIR and T1 images.

6.3 Statistical Analysis

Primary emphasis is placed on descriptive statistics. Results for categorical data are expressed as frequencies and percentages, and continuous variables are given as means (standard deviation, s.d.) or medians (interquartile range, IQR), depending on the distribution. To explore associations between categorical variables, χ^2 test was used. Differences in the frequencies of each MRI abnormality between groups were assessed using independent groups Student's *t*-tests. Differences in the median total scores for each MRI abnormality were analysed using Mann-Whitney *U* tests. *p* values <0.05 were regarded as statistically significant, although results were considered exploratory and would need to be confirmed in a fully powered study.

Missing values, were a joint was within the field of view but unreadable, were considered to have no abnormality (assumed score of zero) when calculating mean overall scores for each MRI abnormality. In a sensitivity analysis, tests were repeated assuming these joints all had the maximum possible score for the relevant abnormalities and there was no change to the overall trends observed. Multiple imputation analysis was not feasible due to the large number of joints relative to the number of participants, which caused imputation models to fail to converge.

Correlations between demographic and clinical parameters and total scores for each MRI abnormality were analysed by Spearman rank correlation; absolute rho values >0.3 are considered to indicate substantive correlation. Statistical analysis was performed using IBM© SPSS© version 24.0.

6.4 Results

6.4.1 Patient Characteristics

6.4.1.1 Patients with Psoriasis

15 male and 13 female patients, aged between 20 and 74 years (mean 46.5 years) were consented to participate in the study. No patients had been diagnosed with any rheumatological disorder, nor did they report symptoms consistent with inflammatory

back pain. Schobers test was negative in all participants. The majority (75%) of patients had type I psoriasis, the remainder developing psoriasis after the age of 40. Psoriasis severity was variable with PASI scores ranging from 10-60 (median [IQR] 17.1 [12.0, 26.6]) and duration of psoriasis varied from 1 to 53 years (median 18.0 [7.7, 26.5] years). One patient was skin type V, the remainder were Caucasian (skin type I-III). Body mass index (BMI) ranged from 19.6kg/m^2 to 46.0kg/m^2, with a median of 29.6 (28.2, 33.9) kg/m^2. Chapter 4.4.1.1. provides further detail about family history, past medical history, smoking status and alcohol consumption within this cohort. Table 4.8. details the anatomical distribution of psoriasis in this group. 15 of 28 patients carried the HLA-Cw06 allele, and only one patient exhibited HLA-B27 positivity.

6.4.1.2 Healthy Control Group Volunteers

12 male and 11 female volunteers, aged between 22 and 59 years (mean 39.3 years) were recruited from staff (and their family and friends) within the University of Leeds. No volunteers had previously been diagnosed with psoriasis or any rheumatological disorder, and none reported any symptoms consistent with inflammatory back pain. Schobers test was negative in all volunteers. One volunteer was skin type IV, the remainder being Caucasian (skin types I-III). BMI ranged from 19.3kg/m^2 to 49.1kg/m^2 (median 26.8 [24.6, 31.5] kg/m^2). Chapter 4.4.1.2. provides further detail about family history, past medical history, smoking status and alcohol consumption. Table 4.7. shows the demographic similarities between the psoriasis patient cohort and healthy volunteer group. 3 volunteers carried the HLA-Cw06 allele, and no volunteers were positive for HLA-B27.

6.4.2 Readability of MRI

6.4.2.1 Non-axial (Peripheral) Sites

The readability of WBMRI for evaluation of individual entheses is shown in Table 6.4. WBMRI allowed evaluation of 1178 of 1260 entheses within the peripheral skeleton of patients with psoriasis and 967 of 1035 entheses in healthy volunteers. Overall, 93.5% of entheses were within the field of view (FOV) and readable and 6.5% were within the FOV but not readable (due to insufficient image quality, movement artefact and off-centre artefact) for both groups. No entheseal sites were outside the FOV, principally due to the non-inclusion of the upper limb entheses.

All pelvic, greater trochanter, medial femoral condyle, plantar fascia and Achilles tendon entheses could be assessed in ≥95% of participants. In contrast, readability was less good (≤90%) for the 7th costochondral joint (18% and 13% not readable, for psoriasis

and healthy volunteer groups respectively), manubriosternal joint (14%, 13%), lateral femoral condyle of the knee (12%, 13%), 1st metatarsophalangeal joint (14%, 11%), patella ligament insertion into patella (11%, 13%) and quadriceps tendon insertion (11%, 13%). Sagittal slices were not available for the knee and ankle/foot which would have improved readability at these sites.

Patients (n=28)				Healthy Volunteers (n=23)			
In FOV and readable n/28(%)	In FOV, but not readable n/28(%)	In FOV and readable n/56(%) [*n/28(%)]	In FOV, but not readable n/56(%) [*n/28(%)]	In FOV and readable n/23(%)	In FOV, but not readable n/23(%)	In FOV and readable n/46(%) [*n/23(%)]	In FOV, but not readable n/46(%) [*n/23(%)]
No. of patients		**No. of entheses**		**No. of patients**		**No. of entheses**	
Supraspinate tendon insertion at humeral tuberosity							
26 (93)	2 (7)	54 (96)	2 (4)	20 (87)	3 (13)	42 (91)	4 (9)
Acromioclavicular joint							
26 (93)	2 (7)	54 (96)	2 (4)	21 (91)	2 (9)	43 (93)	3 (7)
Coracoid process							
26 (93)	2 (7)	54 (96)	2 (4)	21 (91)	2 (9)	43 (93)	3 (7)
Sternoclavicular joint							
25 (89)	3 (11)	50 (89)	6 (11)	21 (91)	2 (9)	42 (91)	4 (9)
1st costochondral synchondrosis							
24 (86)	4 (14)	49 (88)	7 (13)	21 (91)	2 (9)	42 (91)	4 (9)
7th costochondral joint							
23 (82)	5 (18)	46 (82)	10 (18)	20 (87)	3 (13)	40 (87)	6 (13)
Manubriosternal joint*							
24 (86)	4 (14)	24 (86)	4 (14)	20 (87)	3 (13)	20 (87)	3 (13)
Iliac crest							
28 (100)	0 (0)	56 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)
Anterior superior iliac spine							
28 (100)	0 (0)	56 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)
Ischial tuberosity							
28 (100)	0 (0)	56 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)
Pubic symphysis							
27 (96)	1 (4)	55 (98)	1 (2)	23 (100)	0 (0)	46 (100)	0 (0)
Greater trochanter							

Patients (n=28)				Healthy Volunteers (n=23)			
In FOV and readable n/28(%)	In FOV, but not readable n/28(%)	In FOV and readable n/56(%) [*n/28(%)]	In FOV, but not readable n/56(%) [*n/28(%)]	In FOV and readable n/23(%)	In FOV, but not readable n/23(%)	In FOV and readable n/46(%) [*n/23(%)]	In FOV, but not readable n/46(%) [*n/23(%)]
No. of patients		**No. of entheses**		**No. of patients**		**No. of entheses**	
28 (100)	0 (0)	56 (100)	0 (0)	22 (96)	1 (4)	44 (96)	2 (4)
Lateral femoral condyle							
24 (86)	4 (14)	49 (88)	7 (13)	19 (83)	4 (17)	40 (87)	6 (13)
Medial femoral condyle							
26 (92)	2 (7)	53 (95)	3 (5)	21 (91)	2 (9)	44 (96)	2 (4)
Lateral tibial plateau							
26 (92)	2 (7)	52 (93)	4 (7)	20 (87)	3 (13)	41 (89)	5 (11)
Intracondylar notch							
25 (89)	3 (11)	51 (91)	5 (9)	20 (87)	3 (13)	42 (91)	4 (9)
Patella ligament insertion into patella							
24 (86)	4 (14)	50 (89)	6 (11)	19 (83)	4 (4)	40 (87)	6 (13)
Quadriceps insertion into patella							
24 (86)	4 (14)	50 (89)	6 (11)	19 (83)	4 (1)	40 (87)	6 (13)
Ankle joint attachments							
25 (89)	3 (11)	51 (91)	5 (9)	22 (96)	1 (4)	45 (98)	1 (2)
1st Tarsometatarsal Joint							
26 (92)	2 (7)	53 (95)	3 (5)	21 (91)	2 (9)	43 (93)	3 (7)
1st Metatarsophalangeal Joint							
24 (86)	4 (14)	48 (86)	8 (14)	20 (87)	3 (13)	41 (89)	5 (11)
Achilles tendon insertion							
28 (100)	0 (0)	56 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)
Plantar Fascia at calcaneus							
27 (96)	1 (4)	55 (98)	1 (2)	22 (96)	1 (4)	45 (98)	1 (2)

Table 6.4. WBMRI readability at 45 entheseal sites in the peripheral skeleton of patients with psoriasis and healthy volunteers.

The readability of WBMRI for the assessment of individual bursae is shown in Table 6.5. WBMRI allowed the evaluation of 329 of 336 bursae within patients with psoriasis and 268 of 276 bursae in healthy volunteers. Overall, 97.5% of bursae due for inclusion were within the FOV and readable. 2.5% of bursae were within the FOV but not readable for

all participants and none were outside the FOV. The worst anatomical site for visualisation was at the knee, namely the pre-patellar bursa and pes anserine bursa (both seen in 91.3% of scans in the healthy volunteer group). The exclusion of sagittal slices of the knee may have had a negative impact on readability.

Patients (n=28)				**Healthy Volunteers (n=23)**			
In FOV and readable n/28 (%)	In FOV, but not readable n/28 (%)	In FOV and readable n/56 (%)	In FOV, but not readable n/56 (%)	In FOV and readable n/23 (%)	In FOV, but not readable n/23 (%)	In FOV and readable n/46 (%)	In FOV, but not readable n/46 (%)
No. of Patients		**No. of Bursae**		**No. of Patients**		**No. of Bursae**	
Subacromial bursae							
26 (92.9)	2 (7.1)	54 (96.4)	2 (3.6)	21 (91.3)	2 (8.7)	43 (93.5)	3 (6.5)
Greater trochanteric bursae							
28 (100)	0 (0)	56 (100)	0 (0)	22 (95.7)	1 (4.3)	44 (95.7)	2 (4.3)
Pre-patellar bursae							
26 (92.9)	2 (7.1)	54 (96.4)	2 (3.6)	20 (87.0)	3 (13.0)	42 (91.3)	4 (8.7)
Pes anserine bursae							
26 (92.9)	2 (7.1)	54 (96.4)	2 (3.6)	21 (91.3)	2 (8.7)	42 (91.3)	4 (8.7)
Achilles bursae							
28 (100)	0 (0)	56 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)
Retrocalcaneal bursae							
27 (96.4)	1 (7.1)	55 (98.2)	1 (1.8)	23 (100)	0 (0)	46 (100)	0 (0)

Table 6.5. WBMRI readability of 12 bursae in the peripheral skeleton of patients with psoriasis and healthy volunteers.

The readability of WBMRI for evaluation of individual synovial joints is shown in Table 6.6. At some sites, assessment of synovial fluid was possible where it was not possible to see the entheseal insertion. WBMRI allowed evaluation of 438 of 448 synovial joints within the peripheral skeleton of patients with psoriasis and 368 of 385 joints in healthy volunteers. Overall, 96.7% of synovial joints due for inclusion were within the FOV and readable. 3.3% were within the FOV but not readable for all participants. No synovial joints were outside the FOV. All sternoclavicular, acromioclavicular, shoulder, hip, knee and ankle joints could be assessed in ≥95% of participants. Readability was less favourable in the feet, with (≤90%) for the 1st metatarsophalangeal joints (3.6% and 6.5% not readable, for psoriasis and healthy volunteer groups respectively) and 1st metatarsophalangeal joints (5.4%, 10.9%).

Patients (n=28)				Healthy Volunteers (n=23)			
In FOV and readable n/28(%)	In FOV, but not readable n/28(%)	In FOV and readable n/56(%) [*n/28(%)]	In FOV, but not readable n/56(%) [*n/28(%)]	In FOV and readable n/23(%)	In FOV, but not readable n/23(%)	In FOV and readable n/46(%) [*n/23(%)]	In FOV, but not readable n/46(%) [*n/23(%)]
No. of patients		**No. of entheses**		**No. of patients**		**No. of entheses**	
Sternoclavicular joints							
26 (92.9)	2 (7.1)	54 (96.4)	2 (3.6)	21 (91.3)	2 (8.7)	44 (95.7)	2 (4.3)
Acromioclavicular joints							
26 (92.9)	2 (7.1)	54 (96.4)	2 (3.6)	21 (91.3)	2 (8.7)	44 (95.7)	2 (4.3)
Shoulder joints							
25 (89.3)	1 (10.7)	55 (98.2)	1 (1.8)	22 (95.7)	1 (4.3)	45 (97.8)	1 (2.2)
Hip joints							
28 (100)	0 (0)	56 (100)	0 (0)	22 (95.7)	1 (4.3)	45 (97.8)	1 (2.2)
Knee joints							
28 (100)	0 (0)	56 (100)	0 (0)	22 (95.7)	1 (4.3)	44 (95.7)	2 (4.3)
Ankle joints							
28 (100)	0 (0)	56 (100)	0 (0)	22 (95.7)	1 (4.3)	45 (97.8)	1 (2.2)
1st Tarsometatarsal joints							
25 (89.3)	1 (10.7)	54 (96.4)	2 (3.6)	21 (91.3)	2 (8.7)	43 (93.5)	3 (6.5)
1st Metatarsophalangeal joints							
24 (85.7)	2 (7.1)	53 (94.6)	3 (5.4)	20 (87.0)	3 (13.0)	41 (89.1)	5 (10.9)

Table 6.6. WBMRI readability of 16 synovial joints in the peripheral skeleton of patients with psoriasis and healthy volunteers.

The readability of WBMRI for the evaluation of erosions and enthesophytes is shown in Table 6.7. WBMRI allowed the assessment of 217 of 224 sites (erosions) and 111 of 112 sites (enthesophytes) in patients with psoriasis, and 175 of 184 sites (erosions) and 91 of 92 sites (enthesophytes) in healthy volunteers. Visualisation of bone abnormalities was better at site of tendon insertions into the calcaneus compared to the insertions in the forefoot.

Patients (n=28)				Healthy Volunteers (n=23)			
In FOV and readable n/28 (%)	In FOV, but not readable n/28 (%)	In FOV and readable n/56 (%)	In FOV, but not readable n/56 (%)	In FOV and readable n/23 (%)	In FOV, but not readable n/23 (%)	In FOV and readable n/46 (%)	In FOV, but not readable n/46 (%)
No. of Patients		**No. of Joints**		**No. of Patients**		**No. of Joints**	
1st Tarsometatarsal joint (erosions only)							
26 (92.9)	2 (7.1)	53 (94.6)	3 (5.4)	21 (91.3)	2 (8.7)	43 (93.5)	3 (6.6)
1st Metatarsophalangeal joint (erosions only)							
26 (92.9)	2 (7.1)	53 (94.6)	3 (5.4)	20 (87.0)	3 (13.0)	41 (89.1)	5 (10.9)
Achilles tendon insertion into calcaneus (erosions and enthesophytes)							
28 (100)	0 (0)	56 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)
Plantar fascia insertion into calcaneus (erosions and enthesophytes)							
27 (96.4)	1 (3.6)	55 (98.2)	1 (1.8)	22 (95.7)	1 (4.3)	45 (97.8)	1 (2.2)

Table 6.7. WBMRI readability of 8 sites of potential erosions and 4 sites of potential enthesophytes in the peripheral skeleton of patients with psoriasis and healthy volunteers.

6.4.2.2 Spine and Sacroiliac Joints

Full evaluation of all 23 vertebral units and 8 sacroiliac joint quadrants was possible in all 28 patients and all 23 healthy volunteers.

6.4.3 MRI Abnormalities

6.4.3.1 Non-axial (Peripheral) Skeleton

6.4.3.1.1 Active Inflammation (Bone Marrow Oedema and Soft Tissue Inflammation)

Bone marrow oedema (BMO) and soft tissue inflammation (STI) were assessed at 45 entheseal sites in each participant. All patients with psoriasis had at least one enthesis with inflammatory change (BMO or STI), compared to 14 of 23 (60.9%) healthy volunteers. 110 of 1180 (9.3%) visible entheses (i.e. within FOV) exhibited at least one inflammatory change in the psoriasis patient group (47/110 BMO, 59/110 STI, 4/110 BMO and STI), compared to 27 of 968 (2.8%) visible entheses within the healthy volunteer group (12/27 BMO, 15/27 STI) (p<0.00001).

Participants had between 0 and 8 (mean (±s.d.) 1.82 ±1.66) BMO lesions per patient in the psoriasis group, and between 0 and 3 (mean 0.52±0.85) BMO lesions per volunteer

in the healthy cohort. Patients with psoriasis had between 0 and 6 (mean 2.25±1.46) STI lesions per patient and healthy volunteers had between 0 and 3 (mean 0.65±0.94) STI lesions per volunteer. Overall, participants with psoriasis had significantly more inflammatory lesions (BMO and/or STI) than healthy volunteers (p=0.035), with a mean of 4.04±2.37 inflammatory lesions in patients compared to 1.17±1.23 inflammatory lesions in healthy volunteers.

BMO and STI occurred infrequently in the same enthesis. 21 of 28 psoriasis patients had both lesions of BMO and STI, of which only four had BMO and STI at the same site (in one enthesis each – three at the supraspinatus tendon insertion at the humeral tuberosity, and one at the insertion of the plantar aponeurosis). Only 3 of 23 healthy volunteers had at least one lesion of both BMO and STI, but no participants in this group had concurrent BMO and STI at the same enthesis (Figure 6.2).

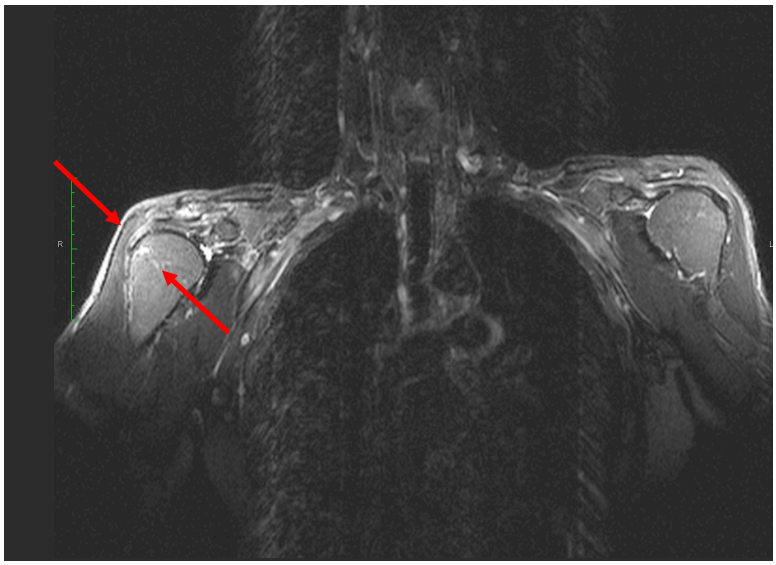


Figure 6.2. Coronal short τ inversion recovery (STIR) WBMRI sequence showing grade 1 bone marrow oedema within the right humeral tuberosity at the insertion of the supraspinatus tendon, and surrounding grade 1 soft tissue inflammation in a patient with moderate to severe psoriasis.

The frequency of BMO and STI at each enthesis, at both the entheseal level and patient level, is shown in Table 6.8.

	Entheseal Level						Participant Level					
	No. of BMO lesions (% of BMO lesions within readable FOV)			No. of STI lesions (% of STI lesions within readable FOV)			No. of participants with BMO (% of participants with BMO within readable FOV)			No. of participants with STI (% of participants with STI within readable FOV)		
	Psoriasis Patients	Healthy Volunteers	Group diff. (p=)	Psoriasis Patients	Healthy Volunteers	Group diff. (p=)	Psoriasis Patients	Healthy Volunteers	Group diff. (p=)	Psoriasis Patients	Healthy Volunteers	Group diff. (p=)
Supraspinate tendon insertion at humeral tuberosity	15 (27.8)	5 (11.9)	0.057	4 (7.4)	1 (2.4)	0.272	**14 (53.8)**	**3 (15.0)**	**0.007**	4 (15.4)	1 (5.0)	0.262
Acromioclavicular joint	**9 (16.7)**	**0 (0.0)**	**0.005**	0 (0.0)	0 (0.0)	NA	**6 (23.1)**	**0 (0.0)**	**0.018**	0 (0.0)	0 (0.0)	NA
Coracoid process	1 (1.9)	0 (0.0)	0.370	0 (0.0)	0 (0.0)	NA	1 (3.8)	0 (0.0)	0.364	0 (0.0)	0 (0.0)	NA
Sternoclavicular joint	1 (2.0)	1 (2.4)	0.901	0 (0.0)	0 (0.0)	NA	1 (4.0)	1 (4.8)	0.900	0 (0.0)	0 (0.0)	NA
1st costochondral process	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
7th costochondral joint	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Manubriosternal joint	2 (8.3)	1 (5.0)	0.662	0 (0.0)	0 (0.0)	NA	2 (8.3)	1 (5.0)	0.662	0 (0.0)	0 (0.0)	NA
Iliac crest	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Anterior superior iliac spine	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Ischial tuberosity	0 (0.0)	0 (0.0)	NA	3 (5.4)	0 (0.0)	0.111	0 (0.0)	0 (0.0)	NA	2 (7.1)	0 (0.0)	0.191
Pubic symphysis	2 (3.6)	1 (2.2)	0.666	0 (0.0)	0 (0.0)	NA	2 (7.4)	1 (4.3)	0.650	0 (0.0)	0 (0.0)	NA
Greater trochanter	0 (0.0)	0 (0.0)	NA	**32 (57.1)**	**9 (20.5)**	**0.000**	0 (0.0)	0 (0.0)	NA	**19 (67.9)**	**5 (22.7)**	**0.002**
Lateral femoral condyle	0 (0.0)	1 (2.5)	0.266	1 (2.0)	0 (0.0)	0.364	0 (0.0)	1 (5.3)	0.255	1 (4.2)	0 (0.0)	0.368
Medial femoral condyle	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Lateral tibial plateau	0 (0.0)	0 (0.0)	NA	1 (1.9)	0 (0.0)	0.372	0 (0.0)	0 (0.0)	NA	1 (3.8)	0 (0.0)	0.375
Intracondylar notch	**7 (13.7)**	**0 (0.0)**	**0.013**	0 (0.0)	0 (0.0)	NA	**5 (20.0)**	**0 (0.0)**	**0.034**	0 (0.0)	0 (0.0)	NA
Patella ligament insertion into patella	4 (8.0)	0 (0.0)	0.067	10 (20.0)	3 (7.5)	0.094	2 (8.3)	0 (0.0)	0.198	8 (33.3)	3 (15.8)	0.190
Quadriceps tendon insertion into patella	1 (2.0)	0 (0.0)	0.368	2 (4.0)	1 (2.5)	0.694	1 (4.2)	0 (0.0)	0.368	2 (8.3)	1 (5.3)	0.695
Ankle joint attachments	2 (3.8)	0 (0.0)	0.184	0 (0.0)	0 (0.0)	NA	1 (4.0)	0 (0.0)	0.343	0 (0.0)	0 (0.0)	NA
1st Tarsometotarsal joint	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
1st Metatarsophalangeal joint	5 (10.4)	1 (2.4)	0.135	0 (0.0)	0 (0.0)	NA	4 (16.7)	1 (5.0)	0.225	0 (0.0)	0 (0.0)	NA
Achilles tendon insertion	0 (0.0)	2 (4.3)	0.115	3 (5.4)	0 (0.0)	0.111	0 (0.0)	2 (8.7)	0.111	2 (7.1)	0 (0.0)	0.182
Plantar fascia insertion at calcaneus	2 (3.6)	0 (0.0)	0.196	7 (12.7)	1 (2.2)	0.054	2 (7.4)	0 (0.0)	0.192	**7 (25.9)**	**1 (4.5)**	**0.044**

Table 6.8. Comparison of percentage frequency of readable inflammatory entheseal lesions (BMO and STI) within FOV, in patients with psoriasis (n=28) and healthy volunteers (n=23). BMO: bone marrow oedema; STI: soft tissue inflammation; FOV: field of view. Bold text denotes $p<0.05$

Large joint enthesitis was not infrequent in patients with psoriasis, particularly at the shoulders (supraspinatus insertion 53.8% vs. 5.0% healthy volunteers, p=0.007, acromioclavicular joint tendon insertion 23.1% vs. 0% healthy volunteers, p=0.018) (Figure 6.3) and knees (intracondylar notch 20.0%, vs. 0% healthy volunteers, p=0.034) (Figure 6.4). BMO was observed in patients, but not healthy volunteers, at the patellar ligament insertion into distal patella (8.3%) and quadriceps insertion (4.2%) (p>0.05) (Figure 6.5).

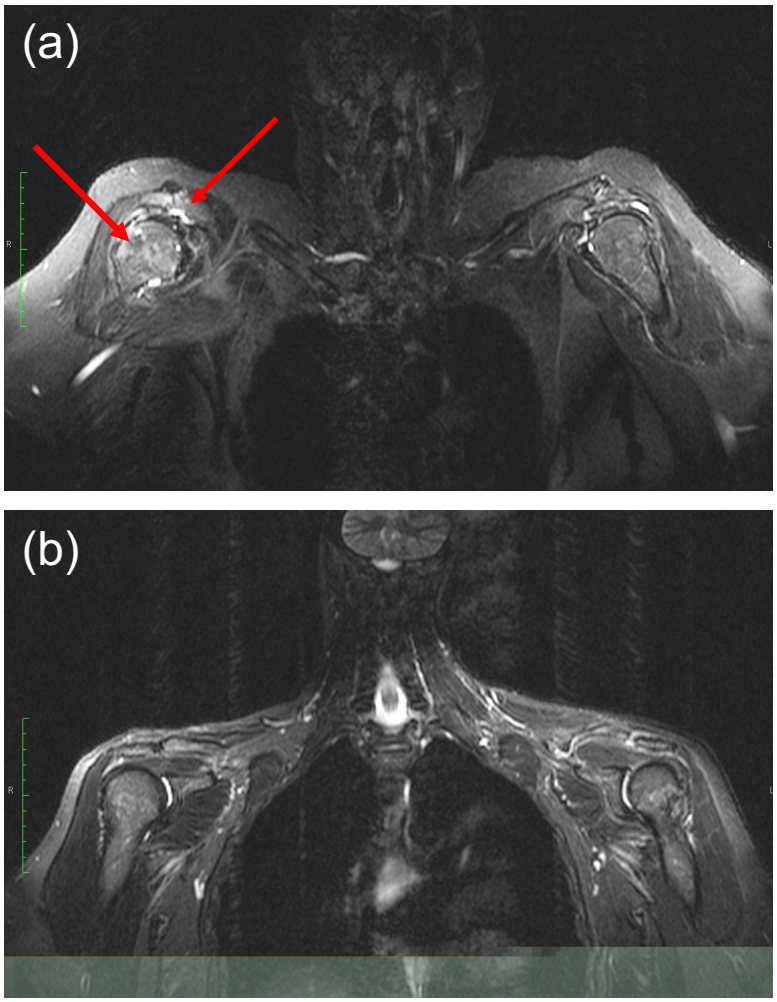


Figure 6.3. Coronal short τ inversion recovery (STIR) WBMRI sequences comparing (a) grade 3 bone marrow oedema the right acromioclavicular joint and right humeral head in a patient with psoriasis (arrows) with (b) a normal shoulder in a healthy volunteer.

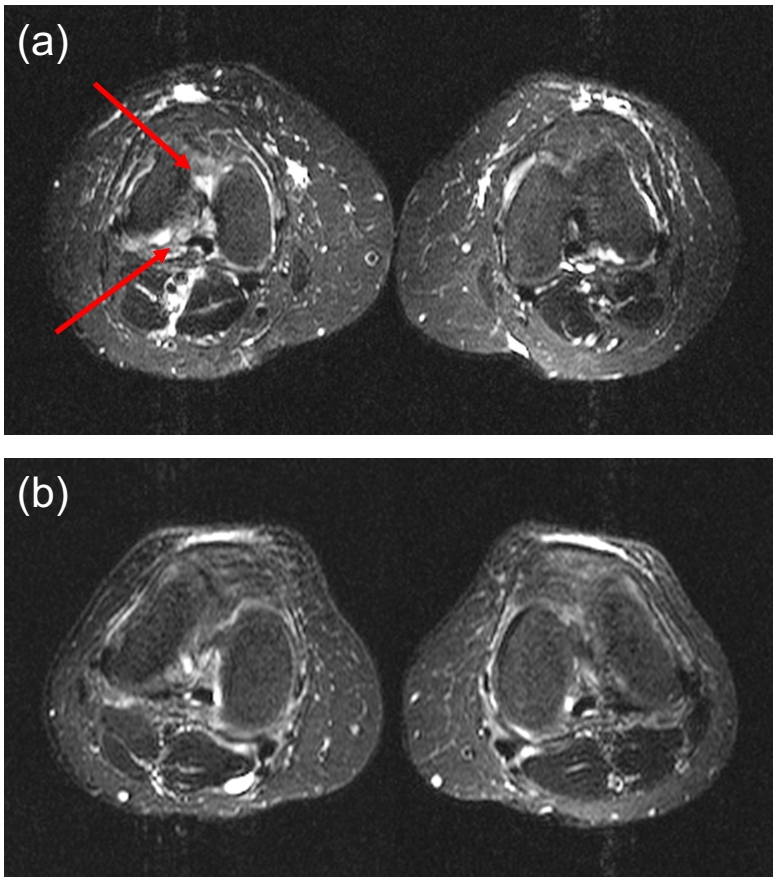


Figure 6.4. Axial short τ inversion recovery (STIR) WBMRI sequences comparing (b) normal knees in a healthy volunteer with (a) grade 2 bone marrow oedema within the intercondylar notch of the right knee in a patient with psoriasis.

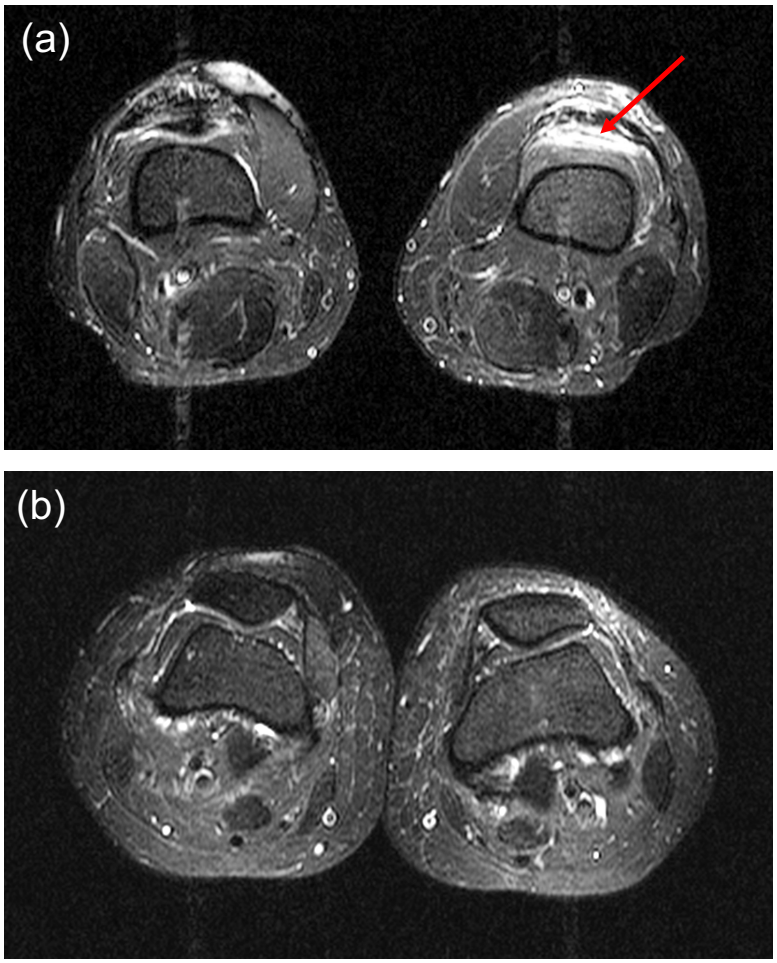


Figure 6.5. Axial short τ inversion recovery (STIR) WBMRI sequences comparing (b) normal knees in a healthy volunteer with (a) grade 3 bone marrow oedema in the left superior patella at the insertion of the quadriceps tendon in a patient with psoriasis.

Both groups showed high rates of STI in the tissues surrounding the greater trochanter, although this was observed with significantly greater frequency in the patients with psoriasis than in healthy volunteers (67.9% and 22.7% of participants, respectively, p=0.002). A significantly greater number of patients also had STI at the plantar fascia insertion than healthy volunteers (25.9% and 4.5% respectively, p=0.044) (Figure 6.6).

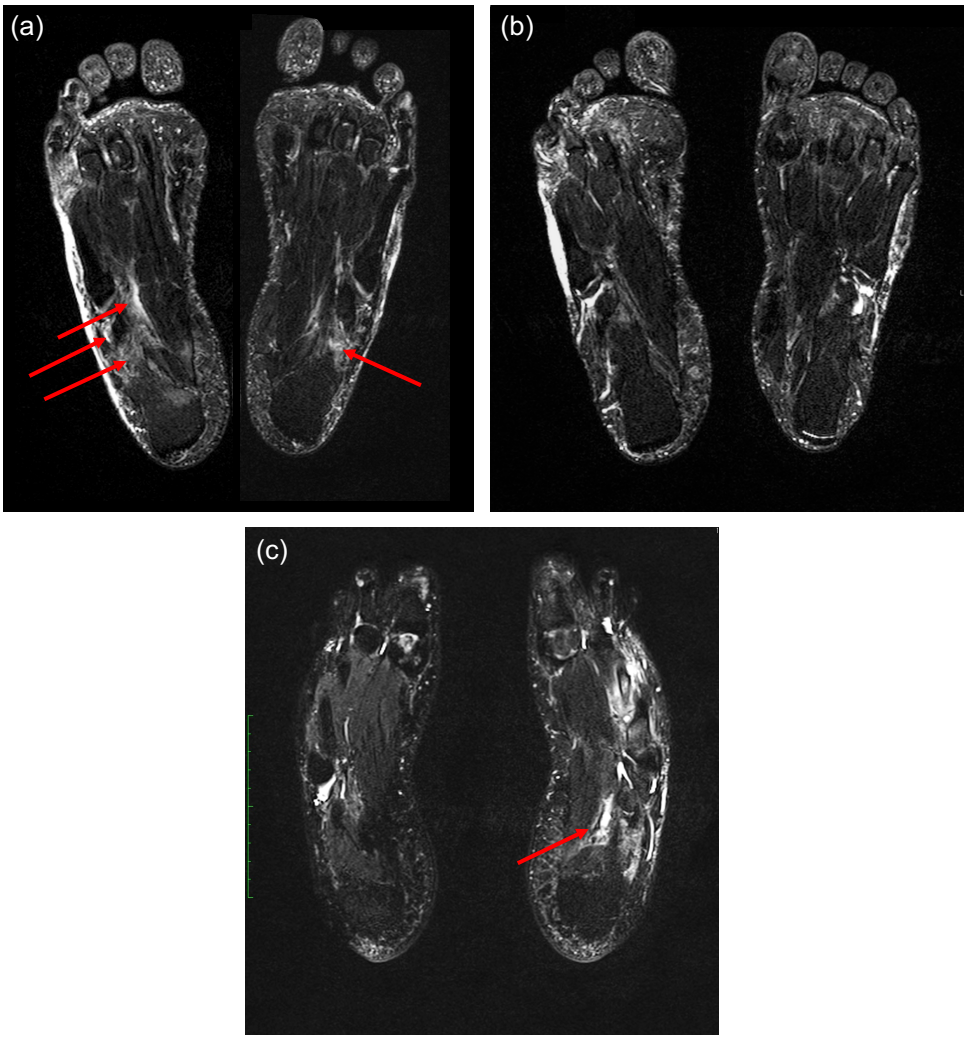


Figure 6.6. Long axis short τ inversion recovery (STIR) WBMRI sequences showing comparing (a) bone marrow oedema and soft tissue inflammation at the plantar fascia insertion of the right foot (grade 3) and left foot (grade 1) in a patient with psoriasis with (b) normal plantar fascia insertions in a healthy volunteer and (c) grade 1 soft tissue inflammation surrounding the left plantar fascia insertion in a healthy volunteer.

Comparison between the two participant groups of the percentage frequency of inflammatory entheseal lesions at each enthesis is shown in Figure 6.7 (BMO) and Figure 6.8 (STI).

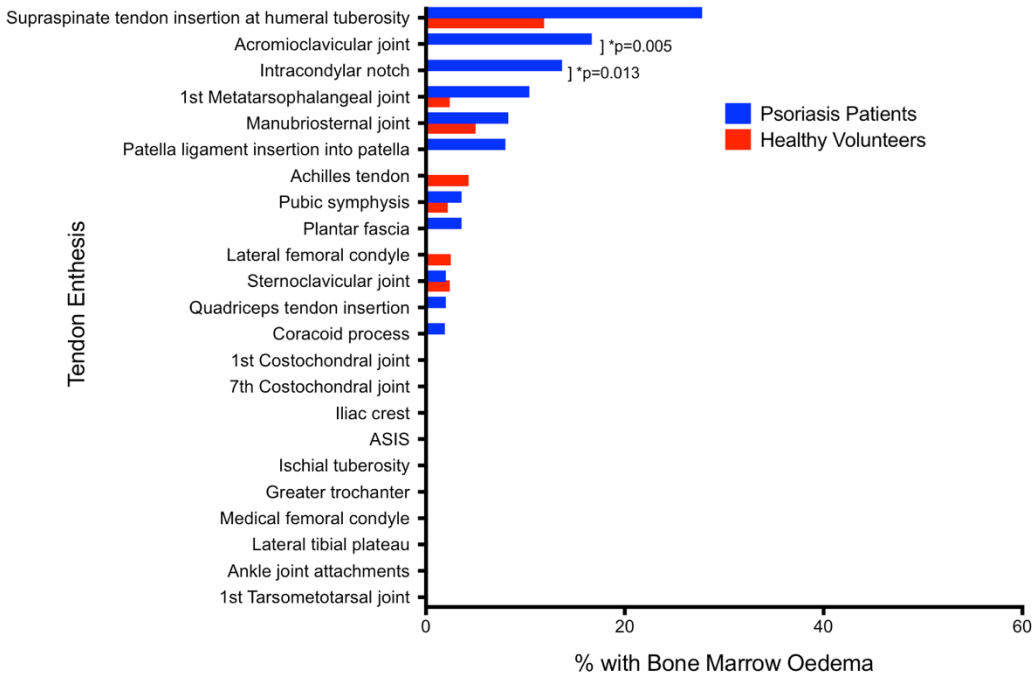


Figure 6.7. Comparison of percentage frequency of entheses with bone marrow oedema (BMO) between patients with psoriasis and healthy volunteers at each site (*p* values are only shown for entheses where the difference between groups <0.05).

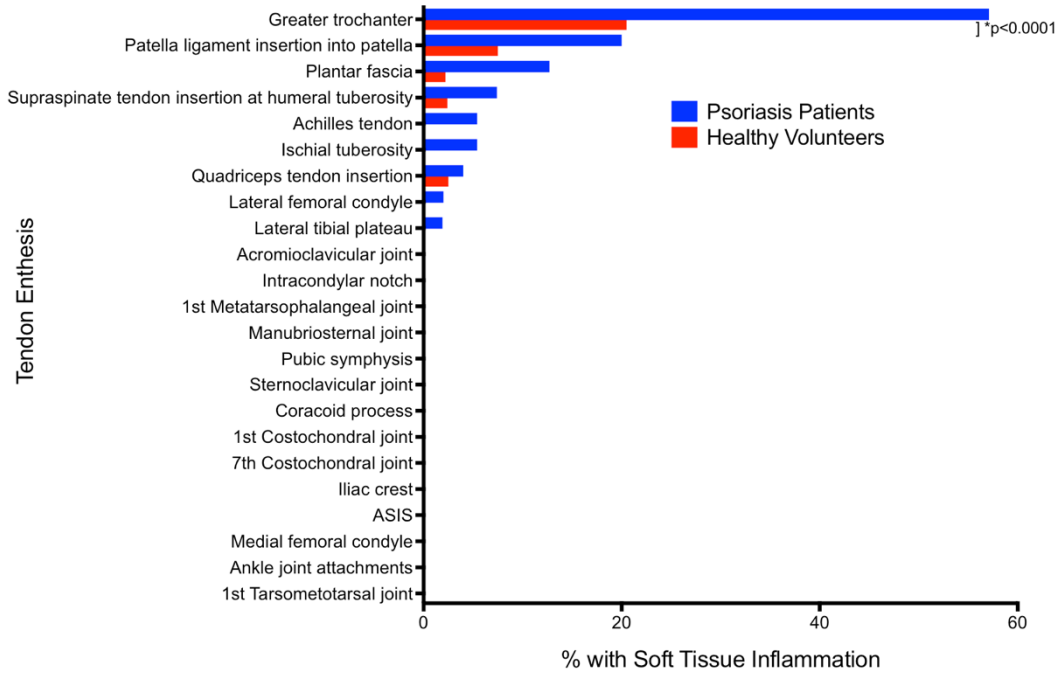


Figure 6.8. Comparison of percentage frequency of entheses with soft tissue inflammation (STI) between patients with psoriasis and healthy volunteers at each site (*p* values are only shown for entheses where the difference between groups <0.05).

Neither group demonstrated any inflammatory abnormalities at the 1st costochondral process, 7th costochondral joint, iliac crest, anterior superior iliac spine, medial femoral condyle nor the 1st tarsometatarsal joint. Enthesitis was identified in patients with psoriasis only at the coracoid process, lateral tibial plateau and ankle joint attachments, although rates were very low (<4%).

The majority of inflammatory abnormalities were minor in both groups. In healthy volunteers, all 27 lesions (BMO and STI) were grade 1, with the exception of one lesion at one site in one patient (grade 2 STI at the inferior patella). In patients with psoriasis, 11 of 114 (9.6%) of abnormalities were of moderate severity (grade 2), and 4/114 (3.5%) were severe (grade 3).

Total scores (calculated from entheses within FOV and readable) ranged from 0-9 for BMO and 0-6 for STI in the patient group, compared with 0-3 for BMO and 0-2 for STI in the healthy volunteer group. The distribution of total BMO scores and total STI scores within each group are compared in Figure 6.9.

Median [interquartile range, IQR] scores were significantly greater for both BMO and STI in the psoriasis patient group (BMO: 2 [1,2.75] psoriasis patients, 0 [0,0] healthy volunteers, p=0.000; STI 2.5 [1,4] psoriasis patients, 0 [0,0] healthy volunteers, p=0.000).

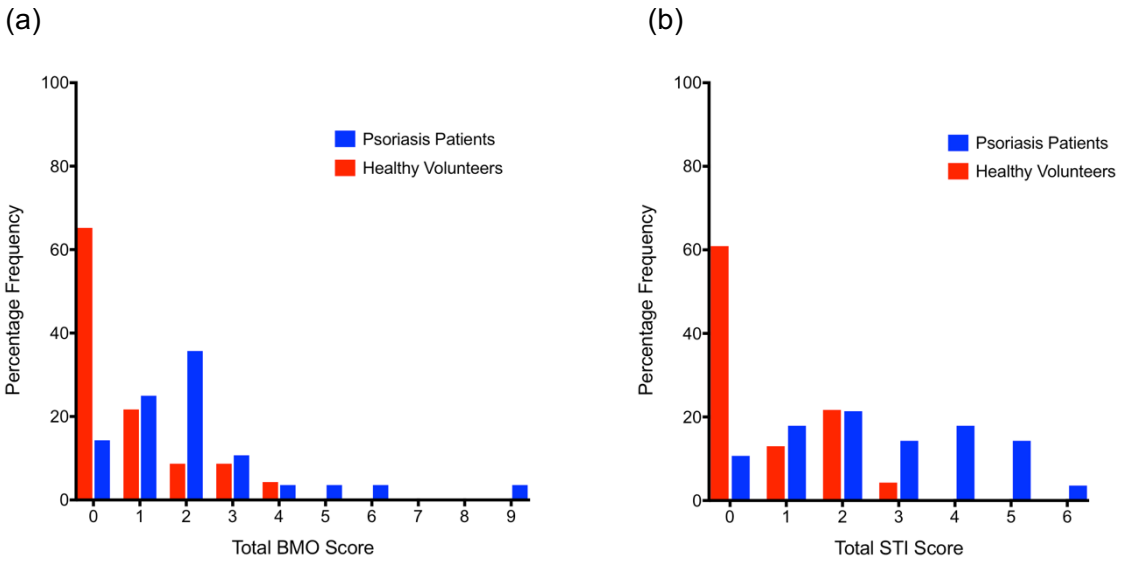


Figure 6.9. Comparison of distribution of total (a) BMO and (b) STI scores in patients with psoriasis and healthy volunteers.

6.4.3.1.2 Bursitis

Bursitis, as defined by a subjective increase in fluid, was assessed at 12 sites in each participant. Bursitis was prevalent in both groups, but occurred with greatest frequency

in the psoriasis group, affecting 75.0% (21/28) of patients compared to 60.9% (14/23) of healthy volunteers. The burden of bursitis was significantly greater in the 28 patients with psoriasis, with 57 of 329 (17.3%) visible bursae (i.e. within FOV) exhibiting at least one inflammatory change, compared to 25 of 263 (9.5%) visible bursae in the 23 healthy volunteers (p=0.006).

Participants had between 0 and 5 (mean (±s.d.) 2.04±1.60) areas of bursitis per patient in the psoriasis group, and between 0 and 4 (mean 1.09±1.24) areas per volunteer in the healthy cohort (p=0.257).

Bursitis was seen in the psoriasis patient group in all six anatomical sites assessed, whereas no abnormalities were seen in the subacromial and pes anserine bursae in healthy volunteers (Table 6.9).

	Burseal Level			Participant Level		
	No. of lesions (% of lesions within readable FOV)			No. of participants (% of participants with bursitis within readable FOV)		
	Psoriasis Patients	Healthy Volunteers	Group diff. (p=)	Psoriasis Patients	Healthy Volunteers	Group diff. (p=)
Subacromial bursae	**7 (13.0)**	**0 (0.0)**	**0.014**	**5 (19.2)**	**0 (0.0)**	**0.034**
Greater trochanteric bursae	31 (55.4)	19 (43.2)	0.227	18 (64.3)	12 (54.5)	0.485
Pre-patellar bursae	7 (13.2)	2 (4.8)	0.163	5 (19.2)	1 (5.0)	0.243
Pes anserine bursae	1 (1.8)	0 (0.0)	0.380	1 (3.7)	0 (0.0)	0.373
Achilles bursae	2 (3.6)	1 (2.2)	0.678	1 (3.6)	1 (4.3)	0.887
Retrocalcaneal bursae	9 (16.4)	3 (6.5)	0.128	6 (22.2)	2 (8.7)	0.193

Table 6.9. Comparison of percentage frequency of readable bursitis lesions within FOV, in patients with psoriasis (n=28) and healthy volunteers (n=23). FOV: field of view. Bold text denotes p<0.05.

Bursitis was commonly observed in both patients and volunteers, with only a significant difference between the groups seen at the subacromial bursa (19.2% patients vs. 0% volunteers, p=0.034). Bursitis frequently occurred at sites of observed STI in all participants (Figure 6.10).

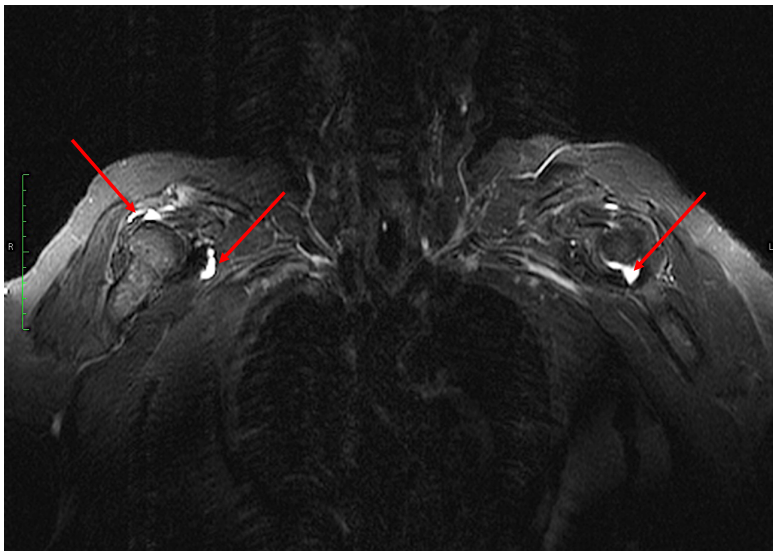


Figure 6.10. Coronal short τ inversion recovery (STIR) WBMRI sequence showing bilateral grade 1 subcoracoid bursitis in a patient with psoriasis.

In both groups, the greater trochanteric bursa was most commonly inflamed, although most abnormalities were mild/grade 1 (64.3% and 54.5% in psoriasis patients and healthy volunteers, respectively). Differences between groups at the bursal level can be seen in Figure 6.11.

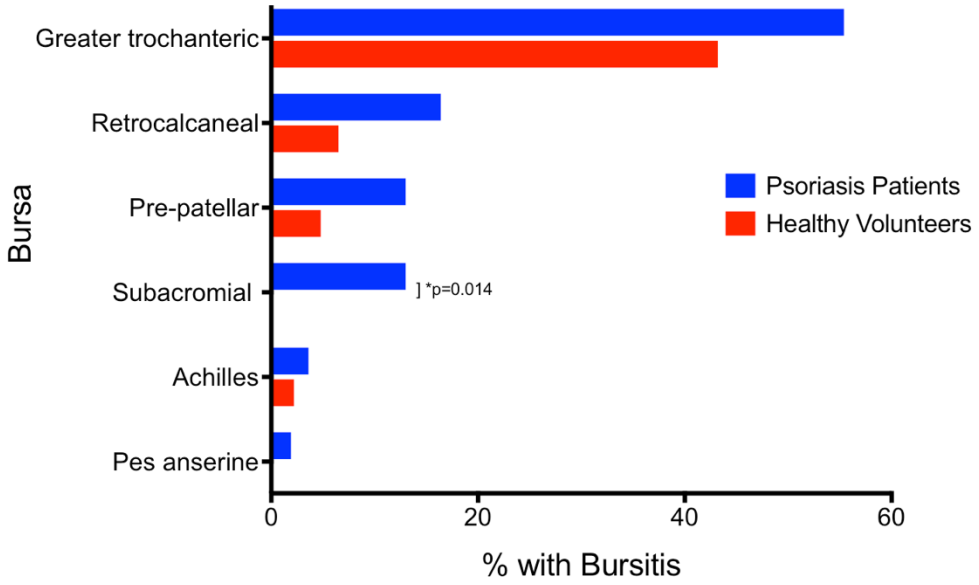


Figure 6.11. Comparison of percentage frequency of bursitis lesions between patients with psoriasis and healthy volunteers at each site. (*p* values are only shown for entheses where the difference between groups <0.05).

The majority of abnormalities (>95%) were of minor (grade 1) severity in both groups, with one participant in each group exhibiting moderate bursitis in two bursae each.

Amongst the healthy volunteers, one participant had ipsilateral grade 2 bursitis in the Achilles and retrocalcaneal bursae and on further questioning reported problems with Achilles tendonitis secondary to recreational running (Figure 6.12). One psoriasis patient had greater trochanteric bursitis bilaterally with no history of trauma.

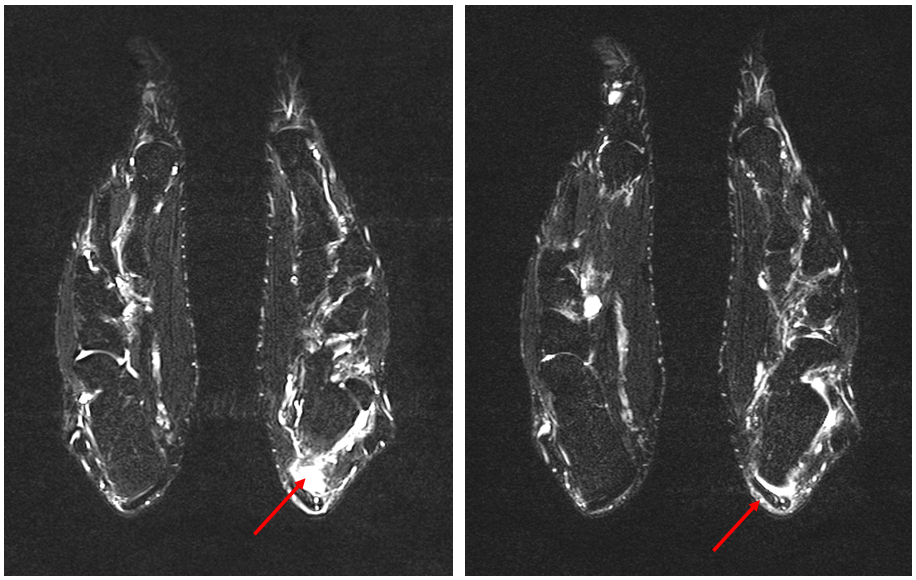


Figure 6.12. Long axis short τ inversion recovery (STIR) WBMRI sequences showing grade 2 left retrocalcaneal bursitis in a healthy volunteer who was undertaking marathon training.

Total scores (calculated from bursae within FOV and readable) ranged from 0-5 in patients with psoriasis, and 0-4 in volunteers. The distribution of total bursitis scores within each group are compared in Figure 6.13. Median [IQR] scores were significantly greater in the psoriasis patient group (2 [0.25,4] in psoriasis patients, 1 [0,2] healthy volunteers, p=0.033).

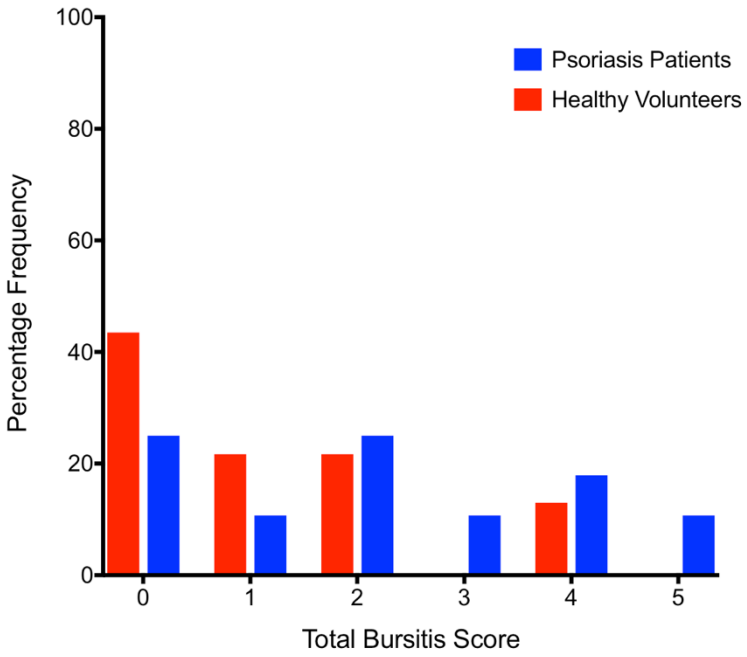


Figure 6.13. Comparison of distribution of total bursitis scores in patients with psoriasis and healthy volunteers.

6.4.3.1.3 Synovitis

A subjective assessment of synovial joint fluid volume as a surrogate for potential joint synovitis was made at 16 joints in each participant to evaluate for the presence of synovitis. The presence of synovitis was common amongst all participants, with 92.9% (26/28) of patients with psoriasis and 82.6% (19/23) healthy volunteers having at least one area of increased synovial fluid suggestive of inflammation. True synovial thickening was difficult to determine in the absence of contrast enhancement (Figure 6.14).

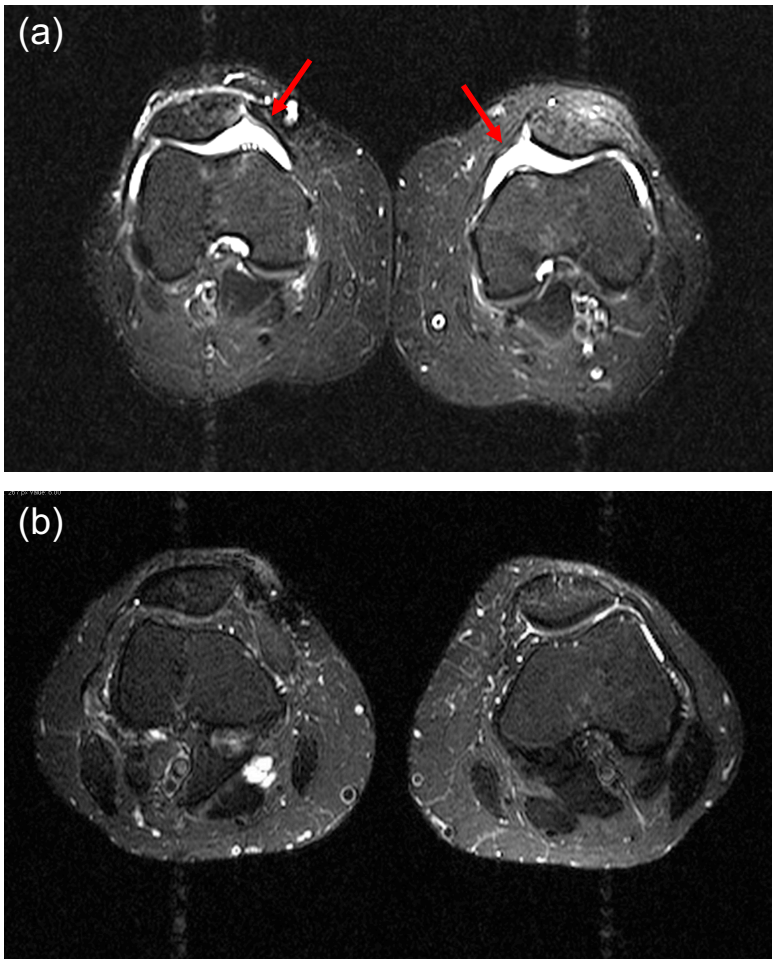


Figure 6.14. Axial short τ inversion recovery (STIR) WBMRI sequences comparing (b) normal knees in a healthy volunteer with (a) bilateral grade 1 synovitis (increased fluid volume within the joint capsule) in the knees of a patient with psoriasis.

The overall burden of synovitis was marginally higher in the psoriasis group, affecting 88 of 438 (20.1%) visible joints (i.e. within FOV) in patients, compared with 58 of 351 (16.5%) joints in volunteers but did not reach significance (p=0.199). Participants had between 0 and 7 (mean (±s.d.) 3.14±1.80) areas of synovitis per patient in the psoriasis group, and between 0 and 6 (mean 2.52±1.88) areas per participant amongst healthy volunteers (p=0.985).

Synovitis was seen in patients with psoriasis in all areas except for the tarsometatarsal joints. Synovitis was not seen in volunteers in the sternoclavicular, acromioclavicular and metatarsophalangeal joints (Table 6.10).

	Joint Level			Participant Level		
	No. of lesions (% of lesions within readable FOV)			No. of participants (% of participants with synovitis within readable FOV)		
	Psoriasis Patients	Healthy Volunteers	Group diff. (p=)	Psoriasis Patients	Healthy Volunteers	Group diff. (p=)
Sternoclavicular joints	1 (1.9)	0 (0.0)	0.364	1 (3.8)	0 (0.0)	0.364
Acromioclavicular joints	4 (7.4)	0 (0.0)	0.065	3 (11.5)	0 (0.0)	0.108
Shoulder joints	10 (18.2)	6 (13.3)	0.511	6 (22.2)	4 (18.2)	0.727
Hip joints	10 (17.9)	5 (11.1)	0.343	6 (21.4)	3 (13.6)	0.477
Knee joints	33 (58.9)	22 (50.0)	0.373	17 (60.7)	11 (50.0)	0.449
Ankle joints	27 (48.2)	23 (51.1)	0.772	15 (53.6)	13 (59.1)	0.696
Tarsometatarsal joints	0 (0.0)	2 (4.7)	0.109	0 (0.0)	1 (4.8)	0.252
Metatarsophalangeal joints	3 (5.7)	0 (0.0)	0.122	2 (7.7)	0 (0.0)	0.205

Table 6.10. Comparison of percentage frequency of readable bursitis lesions within FOV, in patients with psoriasis (n=28) and healthy volunteers (n=23). FOV: field of view.

In both groups, the greatest burden of synovitis was in the knee (60.8% and 50.0% in patients and volunteers respectively) and ankle joints (53.6%, 59.1%), followed by the hip (21.4%, 13.6%) and shoulder joints (24.0%, 18.2%) (Figure 6.15).

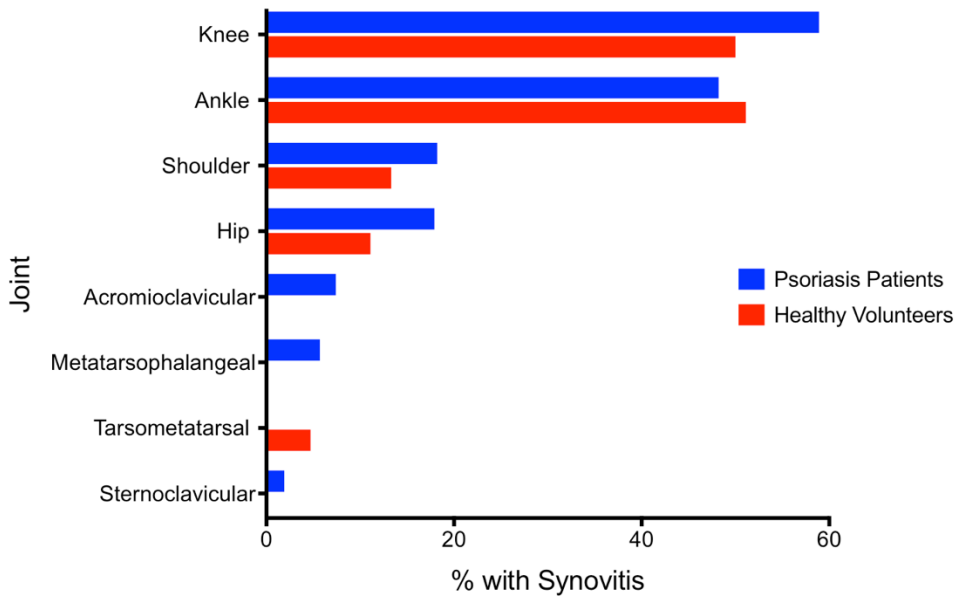


Figure 6.15. Comparison of percentage frequency of synovitis lesions between patients with psoriasis and healthy volunteers at each site.

Total scores (calculated from synovial joints within FOV and readable) ranged from 0-7 in patients with psoriasis, and 0-6 in healthy volunteers. The distribution of total synovitis scores within each group are compared in

Figure 6.16. No statistical difference in median [IQR] score between participant groups was observed (3 [2,4] psoriasis patients, 2 [1,4] healthy volunteers, *p*=0.220).

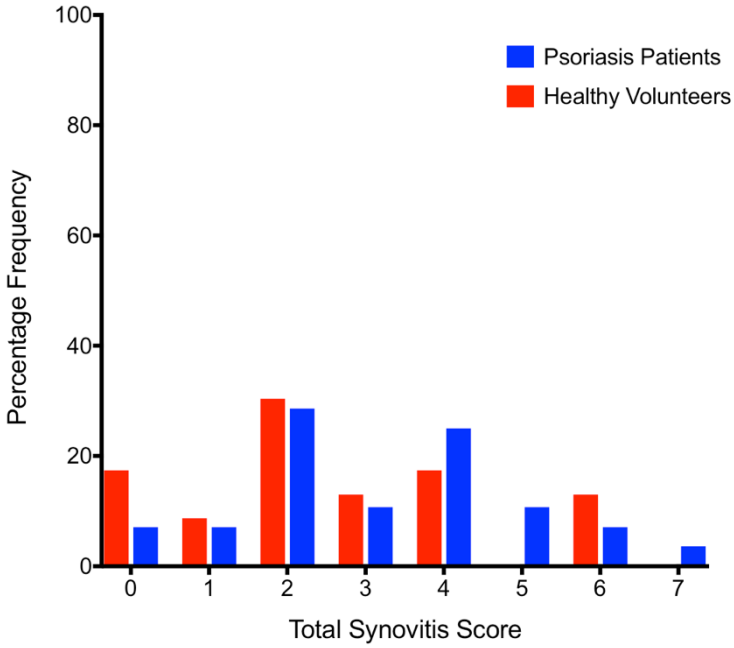


Figure 6.16. Comparison of distribution of total synovitis scores in patients with psoriasis and healthy volunteers.

6.4.3.1.4 Tenosynovitis

Tenosynovitis was assessed at four sites in each participant (medial and lateral tendons of the foot bilaterally). Inflammation of the tendon sheaths was uncommon, and only observed in patients with psoriasis, in the lateral tendons (7.1% patients, *p*=0.191) (Table 6.11). All abnormalities were mild.

	Tendon Level			Participant Level		
	No. of lesions (% of lesions within readable FOV)			No. of participants (% of participants with tenosynovitis within readable FOV)		
	Psoriasis Patients	Healthy Volunteers	Group diff. (p=)	Psoriasis Patients	Healthy Volunteers	Group diff. (p=)
Lateral tendons	4 (7.1)	0 (0.0)	0.064	2 (7.1)	0 (0.0)	0.191
Medial tendons	0 (0.0)	0 (0.0)	N/A	0 (0.0)	0 (0.0)	N/A

Table 6.11. Comparison of percentage frequency of readable tenosynovitis within FOV, in patients with psoriasis (n=28) and healthy volunteers (n=23). FOV: field of view.

Total scores for tenosynovitis, calculated from foot tendons within FOV and readable, ranged from 0-2 in the psoriasis group (26/28 patients had no tenosynovitis, and 2/28 each scored 2). Median [IQR] scores in both groups were 0 [0,0], with no observed statistical difference (p=0.195).

6.4.3.1.5 Structural Changes

Osseous destructions/erosions (examined at four sites per participant) and bony proliferations (examined at two sites per participant) were not identified at any locality in either group.

6.4.3.2 Axial Skeleton - Spine

6.4.3.2.1 Active Inflammation

In total, 18 of 28 (64.3%) psoriasis patients had at least one VU exhibiting active inflammation (BMO) within the spine compared with 7 of 23 (30.4%) of healthy volunteers on STIR images. Of the 18 psoriasis patients with BMO, 15 showed subchondral BMO alone, and 3 showed BMO and structural changes. No individuals had isolated structural changes in either group. The majority of abnormalities were found within the bone marrow of the vertebral corners, although in some extended across the vertebral endplate or superior and inferior corners joined together to cause a ‘white out’ where inflammation was most active (Figure 6.17).

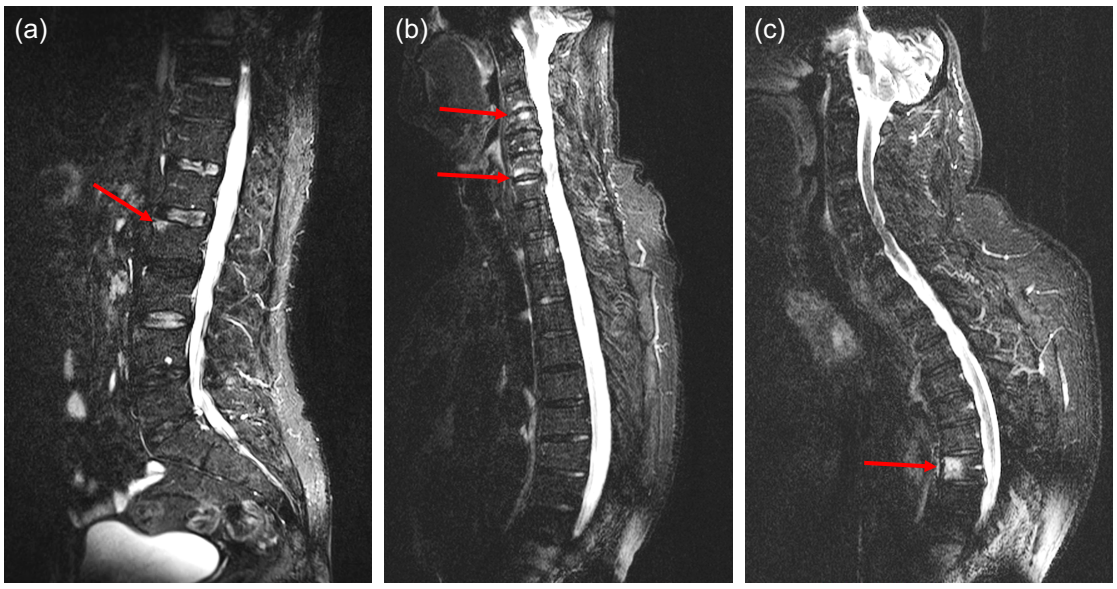


Figure 6.17. Saggital short τ inversion recovery (STIR) WBMRI sequences showing hyperintense signal (osteitis) localised to (a) the anterior superior corner of L1, (b) the

vertebral endplates of C3/4 and C6/7 and (c) the inferior and superior anterior corners of T7 causing a white out of 50% of the vertebral unit in a patient with psoriasis.
In the psoriasis group, participants had between 0 and 6 BMO lesions each, with five patients having lesions at three or more sites, which is highly suggestive of axial SpA (Hermann et al., 2012). All healthy volunteers had between 0 and 2 BMO lesions each.

Only one psoriasis patient had active inflammation within the posterior elements (facet joints) at two sites (nil in volunteer group) (Figure 6.18).

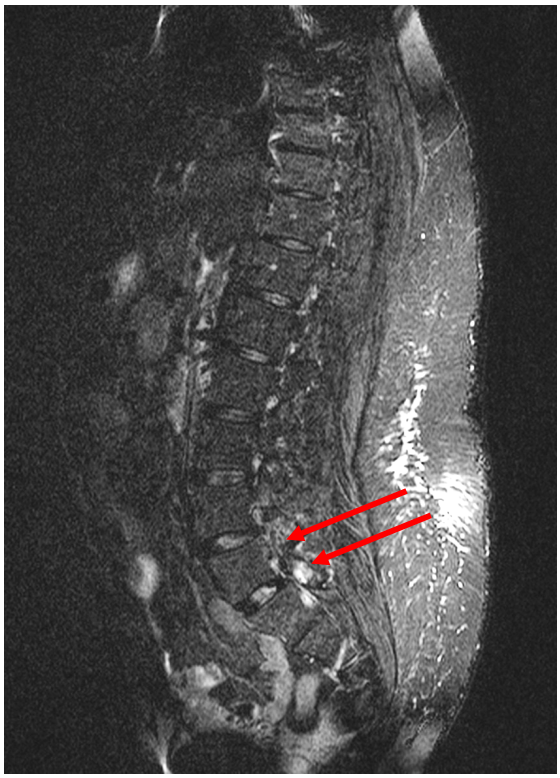


Figure 6.18. Saggital short τ inversion recovery (STIR) sequence WBMRI of lower spine showing hyperintense signal (posterior element inflammation) within the facet joints of L4/5 (grade 1) and L5/S1 (grade 2).

In total, 41 active inflammatory lesions were identified within all vertebral units assessed in the psoriasis group, the majority of which were generally low grade (grade 1: 28/41; grade 2: 12/41; grade 3: 1/41). In the healthy volunteer group, 10 VUs exhibited BMO, which were also mostly low grade (grade 1: 9/10, grade 3: 1/10).

Overall mean BMO scores per subject were therefore low, although significantly higher in the psoriasis patient group (median [IQR] 1 [0,3] out of 69 possible scoring points) compared with the healthy volunteer group (0 [0,1], p=0.007) (Table 6.12). The distribution of total scores for BMO within each group are compared in Figure 6.19.

	Psoriasis Patients		Healthy Volunteers	
	Range	**Median [IQR]**	**Range**	**Median [IQR]**
Bone marrow oedema score (0-69)	0-9	1 [0-3]*	0-4	0 [0,1]*
Erosion score (0-69)	0	0 [0,0]	0	0 [0,0]
Fatty bone marrow infiltration score (0-69)	0-5	0 [0,0]	0	0 [0,0]
Inflammation of posterior segments (0-69)	0-3	0 [0,0]	0	0 [0,0]

Table 6.12. Comparison between psoriasis patients and healthy volunteers of scores for all abnormalities in the spine. (*) denotes significance at 0.05 level.

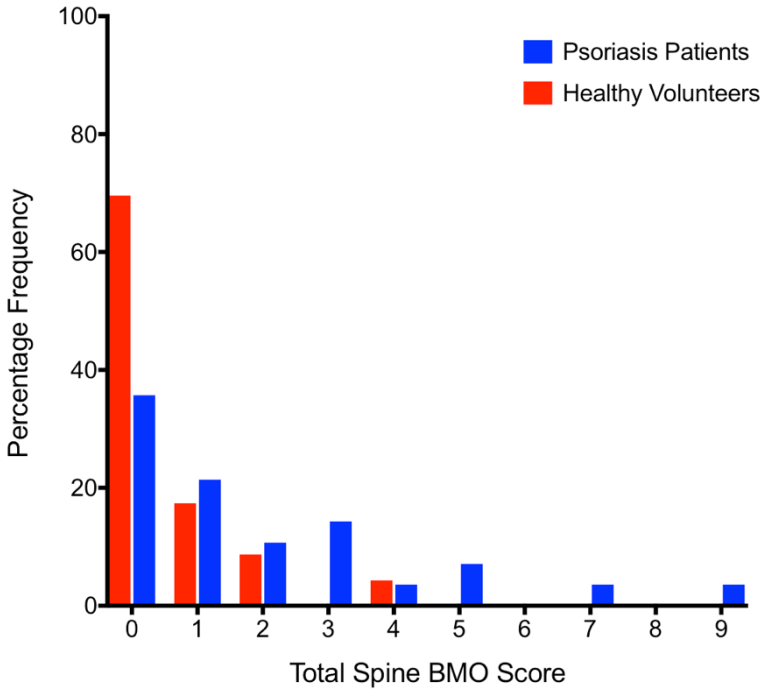


Figure 6.19. Comparison of the distribution of total spine BMO scores between patients with psoriasis and healthy volunteers.

The distribution of total scores for posterior segment inflammation were limited (Figure 6.20).

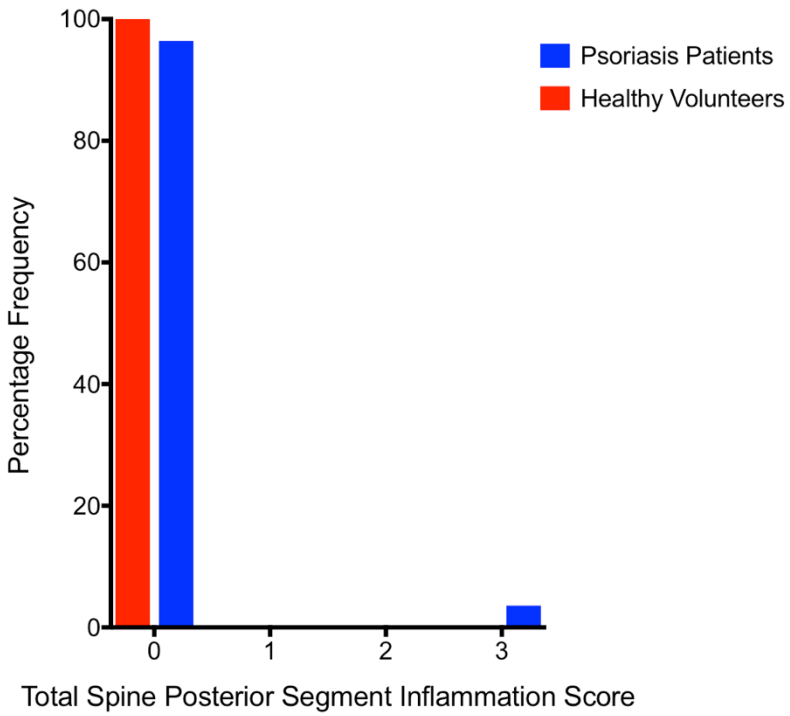


Figure 6.20. Comparison of distribution of total spine posterior segment inflammation scores in patients with psoriasis and healthy volunteers.

In patients with psoriasis, the most common sites of vertebral body inflammation (BMO) were the lumbar and lower thoracic spine - L5/S1 (10/43 lesions), followed by L3/4 (5/43 lesions), T8/9 (4/43 lesions) and C5/6 (3/43 lesions). Overall however, in both groups, all lesions were generally distributed throughout the spine (Table 6.13).

Vertebral Unit	BMO						Fatty Infiltration						Posterior Segment Inflammation					
	Grade 1		Grade 2		Grade 3		Grade 1		Grade 2		Grade 3		Grade 1		Grade 2		Grade 3	
	PsO	HV	PsO	HV	PsO	HV	PsO	HV	PsO	HV	PsO	HV	PsO	HV	PsO	HV	PsO	HV
C2/3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C3/4	**1**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C4/5	**1**	0	**1**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C5/6	**1**	**1**	**1**	0	**1**	0	0	0	0	0	0	0	0	0	0	0	0	0
C6/7	0	**1**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C7/T1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
T1/2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
T2/3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
T3/4	0	**1**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
T4/5	**1**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
T5/6	**1**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
T6/7	**1**	0	**1**	0	0	0	**1**	0	0	0	0	0	0	0	0	0	0	0
T7/8	**1**	**1**	**1**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
T8/9	**4**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
T9/10	**2**	**1**	0	0	0	0	**1**	0	0	0	0	0	0	0	0	0	0	0
T10/11	**2**	0	0	0	0	0	**1**	0	0	0	0	0	0	0	0	0	0	0
T11/12	0	0	0	0	0	0	**1**	0	0	0	0	0	0	0	0	0	0	0
T12/L1	**1**	0	**1**	0	0	0	**1**	0	0	0	0	0	0	0	0	0	0	0
L1/2	**2**	0	0	0	0	0	**1**	0	0	0	0	0	0	0	0	0	0	0
L2/3	**2**	**1**	0	0	0	**1**	0	0	0	0	0	0	0	0	0	0	0	0
L3/4	**3**	**1**	**2**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
L4/5	0	**1**	**1**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
L5/S1	**5**	**1**	**4**	0	0	0	**1**	0	**1**	0	0	0	**1**	0	**1**	0	0	0
TOTAL	**28**	**9**	**12**	**0**	**1**	**1**	**7**	0	**1**	0	0	0	**1**	0	**1**	0	0	0

Table 6.13. Comparison of the distribution and grade of BMO, fatty infiltration and posterior segment inflammation lesions throughout the spine between psoriasis patients (PsO) and healthy volunteers (HV) (C=cervical, T=thoracic, L=lumbar, S=sacral).

6.4.3.2.2 Structural Changes

No structural abnormalities were seen in any healthy volunteers. Within the psoriasis patient group, fatty infiltration of the bone marrow was an uncommon finding, with only four patients exhibiting low grade changes (grade 1 or 2) which affected less than 50% of the vertebral body (Figure 6.21). Three of these patients had fatty infiltration at only one site, and the fourth had changes at five sites, only one of which was associated with inflammatory change (Figure 6.22).

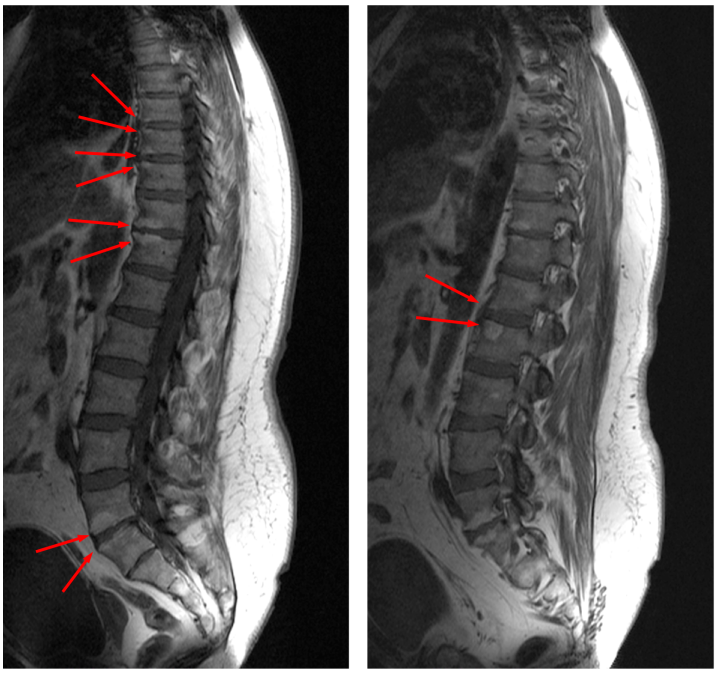


Figure 6.21. Saggital T1w sequence WBMRI images showing five areas of fatty infiltration of the bone marrow in two adjacent slices in one patient at T6/7, T7/8, T9/10, T11/12 and L3/4.

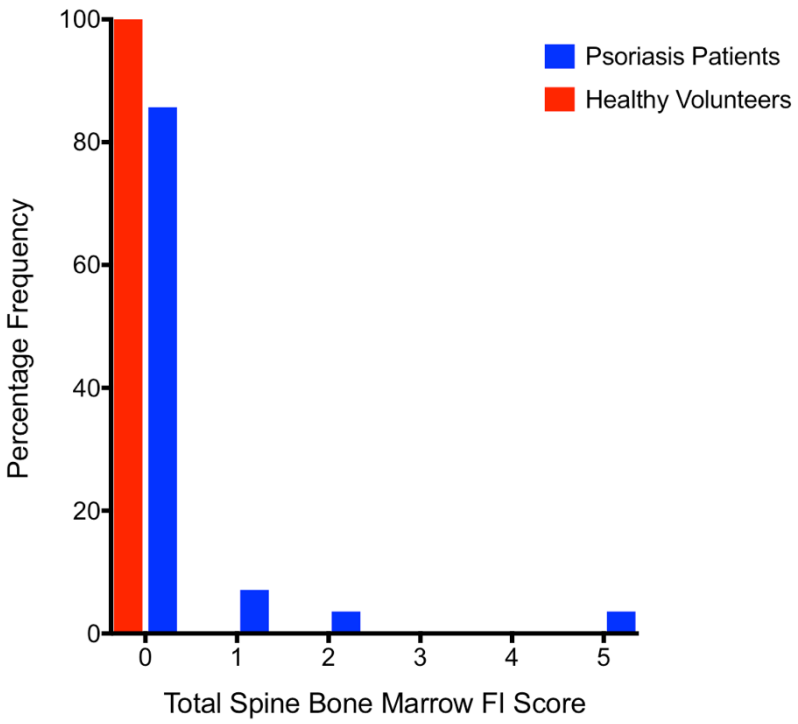


Figure 6.22. Comparison of distribution of total spine bone marrow fatty infiltration (FI) scores in patients with psoriasis and healthy volunteers.

Bone proliferation was identified in four patients (grade 1: 3/4; grade 2: 1/4) at different sites (C4/5, T3/4, T8/9 and L4/5), and in only two did this correspond to a site of active inflammation. No erosions were identified within the spine. Table 6.13 compares the total scores for each abnormality by group.

6.4.3.3 Axial Skeleton - Sacroiliac Joints

6.4.3.3.1 Active Inflammation

In total, 4 of 28 patients (14.3%) had at least one area of BMO within the SIJs. 7 areas of BMO were identified, all grade 1, located in the upper sacrum (3/7), upper ilium (3/7) and lower ilium (1/7). One patient had three involved quadrants, one patient had two, and two patients each had one quadrant involved. One healthy volunteer had one area of BMO (upper ilium, grade 1) (Table 6.14).

Sacroiliac Joint Quadrant	BMO						Erosions					
	Grade 1		Grade 2		Grade 3		Grade 1		Grade 2		Grade 3	
	PsO	HV	PsO	HV	PsO	HV	PsO	HV	PsO	HV	PsO	HV
Upper Ilium	**3**	**1**	0	0	0	0	0	0	0	0	0	0
Lower Ilium	**1**	0	0	0	0	0	**2**	0	0	0	0	0
Upper Sacrum	**3**	0	0	0	0	0	0	**1**	0	0	0	0
Lower Sacrum	0	0	0	0	0	0	0	**1**	0	0	0	0
TOTAL	**7**	0	0	0	0	0	**2**	**2**	0	0	0	0

Table 6.14. Comparison of the distribution and grade of BMO lesions and erosions throughout the sacroiliac joints between psoriasis patients (PsO) and healthy volunteers (HV).

The distribution of total SIJ BMO scores is shown in Figure 6.23.

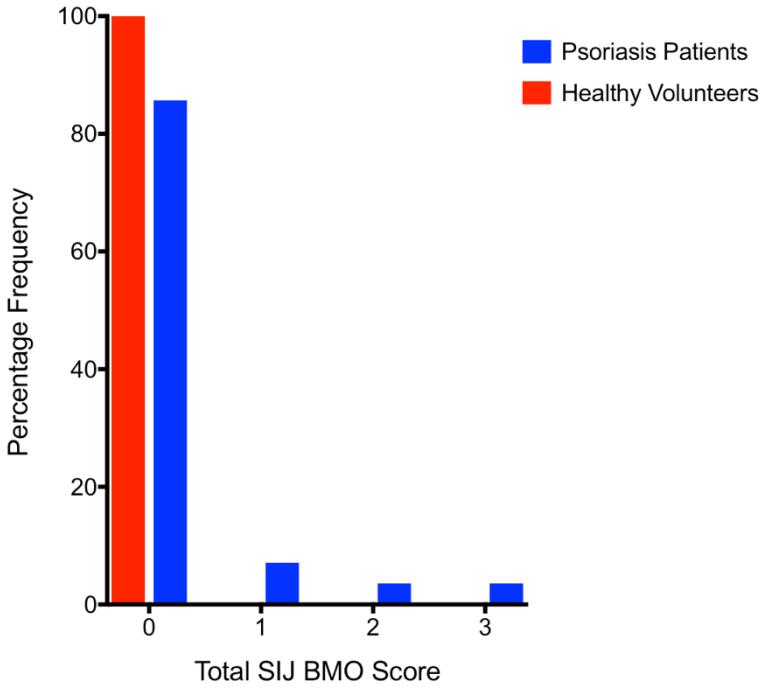


Figure 6.23. Comparison of distribution of total SIJ BMO scores in patients with psoriasis and healthy volunteers (SIJ: sacroiliac joint).

Overall SIJ median [IQR] active inflammation scores were therefore low with no difference observed between the groups (0 [0,0] out of a possible 24 scoring points for both groups, p=0.226) (Table 6.15).

	Psoriasis patients		Healthy Volunteers	
	Range	**Median [IQR]**	**Range**	**Median [IQR]**
Bone marrow oedema score (0-24)	0-3	0 [0,0]	0-1	0 [0,0]
Erosion score (0-24)	0-2	0 [0,0]	0-2	0 [0,0]
Fatty bone marrow infiltration score (0-8)	0	0 [0,0]	0	0 [0,0]
Ankylosis score (0-4)	0	0 [0,0]	0	0 [0,0]
Sclerosis score (0-2)	0	0 [0,0]	0	0 [0,0]

Table 6.15. Comparison between psoriasis patients and healthy volunteers of scores for all abnormalities in the SIJs. (*) denotes significance at 0.05 level.

6.4.3.3.2 Structural Changes

Structural changes within the SIJs were rare, with no identifiable areas of bone marrow infiltration, ankylosis or sclerosis seen in either patients with psoriasis or healthy volunteers. Erosions were seen in two psoriasis patients (lower ilium bilaterally in both, grade 1), and one volunteer (unilateral upper and lower sacrum, grade 1) (Table 6.14). The distribution of total erosion scores is shown in Figure 6.24. Median scores in both groups were 0 [0,0], p=0.428 (Table 6.15).

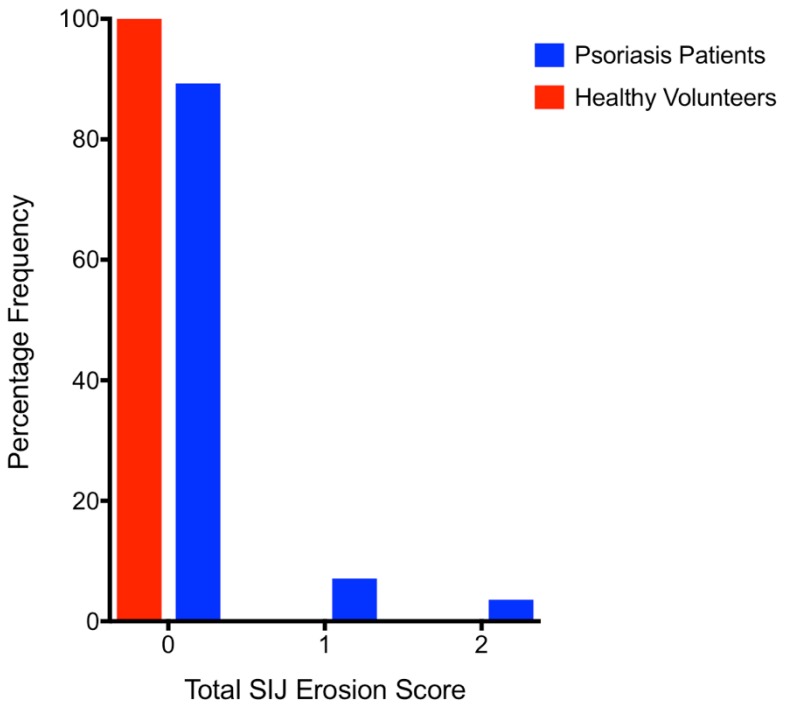


Figure 6.24. Comparison of distribution of total SIJ erosion scores in patients with psoriasis and healthy volunteers (SIJ: sacroiliac joint).

6.4.4 Correlation between MRI Abnormalities and Clinical Characteristics

6.4.4.1 Peripheral Skeleton

In psoriasis patients with nail involvement (n=21), there was a weak positive association between modified nail psoriasis index (mNAPSI) score and total BMO score (Spearman's rho=0.404) and between mNAPSI score and total STI score (rho=0.369). A weak positive association was also seen between total STI score and the presence of gluteal cleft psoriasis (rho=0.326). The presence of psoriasis at other sites did not correlate with the total score of any MRI abnormality, nor was any association found between total scores and PASI score or the body surface area affected with psoriasis. The duration of psoriasis did not correlate with any MRI abnormality, although a weak correlation was found between the age of onset of psoriasis and total STI score (rho=0.327).

A positive PEST questionnaire (score ≥3/5) showed weak association with inflammation scores (total BMO score (rho=0.415) and total STI score (rho=0.382)), but not total synovitis, bursitis or erosion scores.

No associations were found between age, gender, smoking status, alcohol consumption, BMI, HLA-Cw06 status or HLA-B27 status and total score for any MRI abnormality in either group.

6.4.4.2 Axial Skeleton

In patients with psoriasis, a positive correlation was identified between the age of the patient and total BMO score in the spine (rho=0.536) and the age of onset of psoriasis and the total spine BMO score (rho=0.466). A weak association was also found between total spine BMO score and smoking (current or previous) (rho=0.418). In those patients with nail psoriasis (n=21), a weakly positive correlation was identified between mNAPSI total and total spine BMO score (rho=0.349) and also total spine fatty infiltration score (rho=0.350). The presence of psoriasis at other sites did not correlate with any MRI abnormality, nor was any association found between any total MRI scores and the duration or severity of psoriasis (PASI score/BSA). No association was found with HLA status.

In the sacroiliac joints, total BMO score showed weak positive correlation with HLA-B27 status (rho=0.309), in addition to the duration of psoriasis (rho=0.327). In contradiction to the spine, there was a negative association between total SIJ BMO score and the age of onset of psoriasis (rho=-0.462). No correlations were identified with total fatty infiltration scores, total ankylosis scores nor erosion scores.

No associations were found between any MRI abnormalities in the spine or SIJs and age, gender, alcohol consumption, BMI or PEST score in either patients with psoriasis or healthy volunteers.

6.5 Discussion

Despite the potential of WBMRI as an emerging tool in identifying widespread inflammation in all forms of SpA, only a few studies have used WBMRI in prospective studies of patients with psoriatic arthritis, axial spondyloarthritis and healthy volunteers to assess enthesitis, synovitis and destructive bony changes (Weckbach et al., 2011, Althoff et al., 2013, Poggenborg et al., 2015a, Poggenborg et al., 2015b, Song et al., 2011a, Karpitschka et al., 2013). This prospective pilot data is the first to demonstrate the ability of WBMRI to evaluate early and subclinical peripheral and axial inflammatory and structural damage abnormalities in asymptomatic patients with psoriasis. In this chapter, it was demonstrated that psoriasis patients had both higher axial and peripheral entheseal related abnormalities compared to healthy controls.

A small number of authors to date have used conventional MRI in patients with psoriasis and without clinical peripheral or axial joint involvement to assess for the presence of

enthesitis at a specific anatomical location. There are no published data for comparison using WBMRI to identify multiple disease manifestations in both the axial and peripheral skeleton in psoriasis patients. However, in SpA, investigation of inflammatory lesions in the spine and SIJs by WBMRI have previously been compared with conventional MRI, finding a strong correlation and comparable readability between the two methods (Weber et al., 2009, Weber et al., 2010). No evaluations of the performance of WBMRI compared with conventional MRI in assessing active inflammatory lesions within the peripheral skeleton have been published.

Several WBMRI studies have included healthy volunteers for comparison with disease groups, including PsA, SpA and AS, but not subclinical enthesopathy. Comparable with this study, Poggenborg et al observed WBMRI enthesitis at several non-axial sites in healthy volunteers in two studies (Poggenborg et al., 2015a, Poggenborg et al., 2015b), and reported that BMO was markedly more frequent in patients with established PsA and SpA. Poggenborg et al identified enthesitis in healthy subjects in similar entheses, although often with higher frequency, including the supraspinatus tendon insertion at the humerus (13% compared with 15% in this study), quadriceps tendon insertion (13% vs. 5.3%), greater trochanter (58% vs. 22.7%) and Achilles tendon insertion (28% vs. 8.7%) (Poggenborg et al., 2015a).

The presence of inflammatory abnormalities in healthy volunteers is not a novel concept. Imaging abnormalities are widely reported in healthy volunteers, especially in people undergoing elite training (Kiuru et al., 2005). At the histological level, Benjamin et al identified microscopic inflammatory changes due to the normal healing process at sites of microtrauma following mechanical stress, which are similar to, although less pronounced than, those seen in patients with early PsA (McGonagle et al., 2011, McGonagle et al., 2009b, Benjamin and McGonagle, 2007). However, the detection of inflammatory changes in some healthy volunteers indicates a need to define appropriate definitions and cut-offs of pathology on WBMRI in future studies, before the method is used in clinical practice. Nevertheless, BMO and STI were seen with greater frequency in psoriasis patients and it may be difficult to define such definitions when the changes amongst asymptomatic patients are subtle.

Readability of WBMRI in this study was excellent in axial sites and good at peripherally located joints. Problems including the fingers, elbows and wrist joints in the imaging volume have been previously reported (Althoff et al., 2007, Poggenborg et al., 2015b, Poggenborg et al., 2015a) due to restrictions in the maximum width of field of view (FOV) and were therefore excluded in this study. Unlike previous studies, all entheses and joints were within the FOV, although some were not readable (Poggenborg et al., 2015a). Poorer readability had several causes, including movement artefacts, off-centre artefact (longer distance from the centre of the MRI unit decreasing field homogeneity) and in

smaller joints, insufficient spatial resolution. Areas such as the spine and SI joints were favoured by being positioned close to the coil and the centre of the magnetic field, providing excellent readability. Image quality was lower if the area scanned was at the periphery of the scanner.

Although image acquisition was not consistently of sufficient quality for robust and reliable assessment in absolutely all joints of interest, improvements in hardware, more refined techniques of image acquisition and optimal patient positioning have meant that more peripheral entheses and joints were within FOV in this study than in previous studies. For example, the first costochondral synchondrosis was visualised in this study in 86% of psoriasis patients and 91% of healthy volunteers, compared with just 29% in one previously published study (Poggenborg et al., 2015a). Similarly, at the knee, 5% of patellar ligament insertions (into the patella) were in FOV and readable in the previous study, compared to 86% in psoriasis patients in this study, due to refinements in technique, the use of external coils and coil placement.

Acceptable readability in this study therefore allowed one of the most comprehensive assessments of the peripheral and axial skeleton to date. In patients with psoriasis, there are no studies using WBMRI for comparison, but studies using conventional MRI have investigated the knee (Emad et al., 2012, Emad et al., 2010), the small entheses of the hands (Faustini et al., 2016, Offidani et al., 1998), the feet (Erdem et al., 2008), and the lumbosacral spine and sacroiliac joints (SIJs) (Hamdy et al., 2015). In the peripheral skeleton, each of these studies demonstrated a high proportion of inflammatory abnormalities in patients with psoriasis, with the proportion of participants having at least one inflammatory MRI abnormality ranging from 47% and 94.8%. The lowest rates were seen in studies of the hands (47% and 68%), which were not included in this WBMRI protocol. Given that these data are from individual anatomical sites, it is not therefore surprising that all psoriasis patients in this study (which included 23 different anatomical sites bilaterally) had at least one inflammatory MRI abnormality in the peripheral skeleton.

In the axial skeleton, the findings in this study are supported by those of Hamdy et al, who found comparable but slightly lower rates of active inflammation in the spine (64.3% vs. 44%) and SIJs (14.3% vs. 10%) of asymptomatic patients with psoriasis (Hamdy et al., 2015). The lower rates may be attributable to the fact that some patients in the study by Hamdy and colleagues had received treatment, which although not specified, could have been disease modifying therapy, and the authors comment that bone marrow oedema can disappear with treatment. In addition, Hamdy and colleagues restricted their investigation to the lumbosacral spine, whereas this study included the entire spine. This investigation identified lesions in the cervical and thoracic portions in addition to the lumbosacral spine, which may account for the greater proportion of patients with

inflammatory lesions. Indeed, the most common sites of inflammation in non-radiographic ax-SpA, as assessed by WBMRI, are reported to be not localised to just the lumbosacral spine, but also the lower thoracic spine, which reflects the distribution of lesions seen in this cohort of psoriasis patients (Althoff et al., 2013) and reflects earlier WBMRI reports in patients with established SpA (Weber et al., 2007). As previously described in ax-SpA (Bennett et al., 2009), most BMO lesions affected the corners of the vertebral units, but where inflammation was substantial, there were examples of vertebral endplate osteitis and of inferior and superior corners within the same vertebral unit joining up to create a 'white out' appearance. There was, on occasion, difficulty in determining if an area of signal change could be due to degenerative disease or subclinical ax-SpA, and where any doubt existed, sites were scored as zero. This may have led to minimal under-reporting of spine osteitis.

Although there are no other MRI studies of the SIJs in patients with psoriasis and no joint disease, higher rates of have been reported in patients with PsA, psoriasis and asymptomatic sacroiliac involvement, with 33.3% of patients having MRI evidence of sacroilitis (Ibrahim and El-Shazly, 2011). It has been reported that in patients with non-radiographic axial spondyloarthritis and without active sacroilitis on MRI, lesions in the spine may appear earlier than in the SIJs, thus representing the subclinical or pre-disease status (Direz et al., 2010), which may account for the higher proportion of spinal involvement compared with sacroiliac inflammation seen in this study and that by Hamdy et al (Hamdy et al., 2015).

Regarding the peripheral skeleton, Emad et al identified bone marrow oedema in 20.8% of knees scanned in 48 asymptomatic patients with psoriasis (Emad et al., 2012), which is comparable to 22.9% of knees in this cohort. Soft tissue inflammation was greater in those scanned by Emad and colleagues (60.4% vs. 25.0%) in a comparable population (mean age in years 42.2 vs. 46.5, BMI in kg/m^2 34.2 vs. 29.6, proportion of males 45.8 vs. 53.6) (Emad et al., 2012). In a second study including just six psoriasis patients, Emad identified less bone marrow oedema (16.7%) and more soft tissue inflammation (33.3%), demonstrating the variation that can occur amongst populations, even when selected from the same clinic (Emad et al., 2010).

In this MRI protocol, it was not possible to measure true synovial thickening due to the lack of gadolinium contrast enhancement. As a marker of inflammation within the synovium, the volume of fluid was analysed. Fluid in the knee and ankle joints, at a low level, is common amongst the general population, and so high rates of 'synovitis' (or effusion) were expected in both groups, although higher rates were anticipated in patients with psoriasis. McGonagle and colleagues identified that when compared with patients with RA, patients with SpA had much greater rates of perientheseal high signal (comparable with fluid or oedema) outside the joint ($p=0.01$) and suggested that new

onset synovitis was a common pathological association of entheseal abnormalities in PsA and related spondyloarthropathies (McGonagle et al., 1998b). Subclinical synovitis has also been reported to occur frequently in SpA-related diseases alongside subclinical enthesitis (identified both by ultrasound and MRI), in the absence of clinical joint symptoms (Naredo et al., 2011, Emad et al., 2012).

In this study, 60.7% of patients had evidence of some degree of subclinical synovial inflammation at the knee, all of which was mild (grade 1). While high, this was significantly lower than that found by Emad and colleagues, where all patients scanned had some degree of knee effusion (97.1% mild, 2.1% moderate). The difference between these studies is likely to be attributable to the lack of saggital T1-weighted gadolinium-enhanced fat-saturated views in this MRI protocol (only coronal and axial views were captured), which Emad and colleagues used in their 2012 study and others to quantify maximal synovial thickness and fluid volume (Emad et al., 2010, Emad et al., 2012, Emad et al., 2009). This may have therefore lead to an under-assessment of synovitis in this study.

Previous microarthroscopy studies compared with histopathological findings have shown that joint effusion and synovitis can be differentiated through the use of contrast enhanced MR study (Ostendorf et al., 2001) and elimination of contrast enhancement is shown to result in low specificity for detecting true synovitis (Stomp et al., 2015). Short τ inversion recovery (STIR) sequences do not differentiate between synovitis and physiological joint fluid, which could also have led to an over-reporting of physiological fluid as abnormal in the healthy volunteer group and may explain why no significant differences were seen between the groups (Rudwaleit et al., 2009). In this study, 59.1% of healthy volunteers were assessed to have mild ankle effusion/synovitis, compared with no volunteers in the cohort examined by Erdem and colleagues, who included saggital T1-weighted spin echo sequences in their protocol (Erdem et al., 2008).

Aside from the knee, foot and ankle involvement has been reported to occur in 50-70% of patients with PsA (Weishaupt et al., 1999, Gladman, 1998) and often develops early in the disease (Gladman, 1998). As described in established PsA, this study found that inflammation was not only localised within the joint capsule, but also showed extracapsular involvement with oedema of the neighbouring soft tissues and occasional tenosynovitis. Assessments of tenosynovitis were only made in the foot as it was thought that these weight-bearing sites would be the most susceptible to microtrauma and therefore be most likely to exhibit subclinical inflammation.

The MRI assessment of tenosynovitis in patients with psoriasis has been previously reported in both the foot and the hand (Erdem et al., 2008, Faustini et al., 2016). In the flexor tendons of the hand, Faustini and colleagues observed similar rates of tenosynovitis to this study in both psoriasis patients (4% vs. 7.1%) and healthy volunteers

(both 0%) (Faustini et al., 2016). In the foot, higher rates were observed by Erdem (19% in psoriasis patients, 0% In healthy volunteers), although as discussed, saggital views were obtained of the foot and ankle which may have facilitated more accurate assessment of early disease (Erdem et al., 2008). In addition, a greater reduction in image quality and more off-centre artefact was observed at the extremities, which may have reduced the readability of WBMRI compared to images obtained by Erdem et al using conventional MRI of the foot and ankle specifically. Similarly, a reduction in image quality and a lack of saggital views may have limited assessment of bursitis. Erdem et al identified retrocalcaneal bursitis in 50% and retroachilles bursitis in 4% of patients with psoriasis, compared with 16.4% and 3.6% in this cohort, respectively. These data confirm the work of McGonagle and colleagues in PsA, which show how entheseal inflammation, even at the earliest stage, appears to dissipate to surrounding structures within the synovio-entheseal complex in patients with psoriatic disease, principally to the joint capsule with resultant synovitis but also to perientheseal tendons and bursa (McGonagle et al., 2007).

In terms of chronic damage lesions, erosive changes and enthesophytes appear not to be a significant feature associated with subclinical enthesopathy. Structural abnormalities were only assessed in the peripheral skeleton at the feet and ankles and as expected (given the primacy of joint disease in psoriasis patients), none were found in either group. Erdem and colleagues used conventional MRI to assess the feet and ankles of patients with psoriasis and found only one of 26 had one bone erosion, and enthesophytes were not seen (Erdem et al., 2008). Similarly, in a study of 75 patients with early ax-SpA (symptom duration <5 years) assessed by WBMRI, no erosions were detected in any patients in the peripheral joints, including the shoulder, pelvis, hip, knee, ankle (Achilles and plantar fascia insertions) and mid-foot (Althoff et al., 2007).

In the spine, the fatty romanus lesion is defined as a diagnostic imaging feature of axial-SpA (Bennett et al., 2010) and in keeping with this, no lesions were identified in any healthy volunteers. Single areas of fatty infiltration have a low diagnostic utility for SpA, but three or more lesions are highly diagnostic (Bennett et al., 2009). Fatty replacement of the bone marrow was seen at five sites in one patient, which was a surprise in the absence of back pain symptoms. Longitudinal follow up of this patient with repeated MRI scanning is desirable. No syndesmophytes were seen in any participant, although this is not unexpected as MRI is not ideal for showing such lesions.

For assessment of the SIJs, T1-weighted sequences with fat saturation and T2-weighted gradient echo sequences were included in the WBMRI protocol. The ASAS/OMERACT MRI group report that while T1-weighted sequences are usually sufficient to detect structural lesions (sclerosis, fat deposition and ankylosis), these other sequences may better visualise the cartilage in the SIJs, and may therefore be more useful to detect

erosions (Rudwaleit et al., 2009). Despite this comprehensive assessment, erosions were seen in just two patients and one healthy volunteer, with no sclerosis or ankylosis. This was not unexpected as a very low burden of inflammatory disease was seen in patients with psoriasis. In the only published study of patients with psoriasis, only two of 50 patients (both with inflammatory back pain symptoms) showed erosions and periarticular sclerosis, which supports the observations in this study.

It is clear from the results of this study that the presence of subclinical inflammation and structural damage in the peripheral and axial skeleton, as detected by WBMRI, is highly variable amongst patients with psoriasis and has no relation to the age of onset of psoriasis, PASI score or duration of skin disease. Weak associations were found in relation to peripheral inflammation score (BMO and STI) and nail psoriasis, in addition to a weak association between gluteal cleft disease and the presence of perientheseal STI. This is relevant, as it has been suggested that the pattern of psoriasis could serve as a cutaneous biomarker for the subsequent development of PsA. In a recent prospective cohort study, 464 psoriasis patients were followed up for eight years, and an annual incidence rate of 2.7 PsA cases (95% CI 2.1-3.6) per 100 psoriasis patients was observed. In multivariate models, psoriatic nail pitting (relative risk [RR] 2.5, p=0.002) and the presence of uveitis (RR 31.5, p=0.0002) were associated with the development of PsA (Eder et al., 2016). This study followed that of Wilson et al, who performed a larger, retrospective analysis of 1633 subjects with psoriasis and found a cumulative incidence of 1.7%, 3.1% and 5.1% at 5, 10 and 20 years following psoriasis incidence. Psoriasis features associated with higher risk of PsA included nail dystrophy (hazard ratio [HR] 2.93, 95% CI 1.68-5.12) and intergluteal lesions (HR 2.35, 95% CI 1.32-4.19) (Wilson et al., 2009). While interesting that the same skin sites were found in this study, the associations identified were weak and the numbers too low to formally draw conclusions relating to targeted WBMRI screening in patients with nail and gluteal cleft psoriasis in the dermatology clinic.

In summary, in agreement with previous prospective studies of patients with PsA (Weckbach et al., 2011) and SpA using WBMRI (Song et al., 2011a, Karpitschka et al., 2013, Althoff et al., 2013), this technique was able to adequately visualise an extensive number of entheses, joints, bursae and tendons and allow the assessment of widespread inflammation and structural damage in patients with psoriasis and subclinical enthesopathy. Readability overall was very good, and through refinements in technique, patient placement and coil position, was better than in previously published studies. The WBMRI protocol was not designed to visualise the small joints of the hands, and additional conventional MRI images would have been required to provide a more complete assessment and allow comparison with ultrasound findings, but this would have increased the duration of scanning time significantly.

A small number of inflammatory abnormalities were observed in healthy volunteers (2.8% of peripheral entheses) which is likely to represent an acute response to recent microtrauma, although follow-up examinations would have been helpful to confirm resolution. Defining clear cut-offs for pathology in future WBMRI studies could be helpful, although it would be difficult to define such definitions when changes amongst asymptomatic patients are subtle and are of identical morphology to the temporary response seen in healthy individuals to localised injury.

WBMRI assessments did however detect a greater than threefold increase in the number of peripheral entheses with BMO or STI in patients with psoriasis, which compliments the overall findings of ultrasound examinations in these patients. Comparison between WBMRI ultrasound findings at specific entheses is discussed in Chapter 7.4. WBMRI permitted extension of the assessment of subclinical enthesopathy beyond the peripheral skeleton and demonstrated low levels of inflammation within the spine and to a lesser extent, the SIJs. Compared with healthy volunteers, the number of inflammatory lesions observed was four times greater in psoriasis patients in in the spine, and three times greater in the SIJs. Low levels of subclinical inflammation were observed within the surrounding synovio-entheseal complex in both groups, although omission of gadolinium contrast enhancement and absence of saggital views of the knee and ankle made the differentiation between physiological and pathological synovial fluid, and assessment of joint thickness, difficult. Given the primacy of entheseal abnormalities in this cohort, it was not unexpected to find very few structural damage abnormalities in either group. Longer-term follow up of a larger cohort of asymptomatic psoriasis patients without treatment, and healthy volunteers, would be desirable to understand the natural evolution of these abnormalities and assess the rate of progression to symptomatic PsA. However, this would have been difficult in this cohort as these patients were presenting for treatment of moderate to severe psoriasis. Future studies could include patients treated with non-immunomodulatory therapies such as acitretin or fumaric acid esters, although they are slower to act and less efficacious than systemic immunosuppressants and biologic therapies.

6.6 Conclusion

This is the first study to demonstrate the ability of WBMRI to evaluate subclinical peripheral and axial inflammatory and structural damage abnormalities in asymptomatic patients with psoriasis. Readability overall was excellent within the spine and sacroiliac joints, and good overall in the peripheral skeleton, suggesting WBMRI is a useful tool for the rapid assessment of early and evolving psoriatic arthritis.

Abnormalities in healthy volunteers have been demonstrated previously, and relate to microscopic inflammatory changes occurring as part of the normal healing process at sites of microtrauma following mechanical stress. Psoriasis patients had a significantly greater frequency of entheseal-related abnormalities in both the peripheral and axial skeleton compared with healthy volunteers, although the distinction between what is physiological and what is pathological with regard to subtle abnormalities remains a challenge, and the omission of gadolinium contrast further compounded this difficulty.

Chapter 7
Response in MRI Appearances of Axial and Peripheral Subclinical Enthesopathy to Anti-IL-12/23p40 Therapy for Moderate to Severe Psoriasis

7.1 Introduction

Due to its sensitivity and reproducibility, conventional MRI has been widely employed in research trials to investigate treatment responses in patients with spondyloarthritis (SpA) and psoriatic arthritis (PsA) with several studies having shown improvement in enthesopathy using MRI following treatment with TNF-inhibitors (Yanaba et al., 2015, Anandarajah et al., 2010, Mancarella et al., 2010, Marzo-Ortega et al., 2007, Marzo-Ortega et al., 2001). MRI is now used routinely in clinical practice to determine treatment outcomes alongside clinical examination, and due to the lack of ionising radiation, is suitable for repetitive follow-up examinations.

The international OMERACT MRI in inflammatory arthritis group has developed the OMERACT Psoriatic Arthritis Magnetic Resonance Image Scoring System (PsAMRIS) to standardise the evaluation of inflammatory and destructive changes in PsA, but this score only applies to the hands (Ostergaard et al., 2009, McQueen et al., 2007a). Other authors have described scoring systems for bone marrow oedema (BMO), erosions and/or synovitis (Tehranzadeh et al., 2008, Anandarajah et al., 2010) at peripheral sites, and for fatty infiltration lesions (Pedersen et al., 2013) in the axial skeleton, but these have only been used in a few patients and not outside the introducing centre.

The diagnostic utility of whole body MRI (WBMRI) has been studied by several research groups (Appel et al., 2007, Weber et al., 2009, Weckbach et al., 2011) and has been shown to be especially useful for detecting early inflammation and structural damage in different locations of both the axial skeleton (Weckbach et al., 2011, Althoff et al., 2013, Weber et al., 2012) and peripheral joints and entheses (Weckbach et al., 2011, Poggenborg et al., 2015a, Althoff et al., 2007, Eshed et al., 2007). Furthermore, its value as a tool for assessing disease activity and monitoring treatment effects has been studied in patients with axial spondyloarthropathy (ax-SpA) (Song et al., 2011a, Song et al., 2011b, Karpitschka et al., 2013, Song et al., 2015, Althoff et al., 2016) using etanercept, infliximab and sulfasalazine. WBMRI was found to be effective at detecting changes in both active inflammatory lesions (osteitis/BMO, soft tissue inflammation (STI), synovitis and bursitis) (Appel et al., 2007, Song et al., 2011a, Karpitschka et al., 2013, Song et al.,

2015, Althoff et al., 2016) and structural changes (fatty lesions in subchondral bone marrow) (Song et al., 2011b) at both axial and peripheral sites.

To date, virtually all studies investigating the efficacy of ustekinumab in psoriatic arthritis have used clinical assessment and ultrasound. Only one small (n=20), open-label, proof-of-concept study has used conventional MRI to assess the axial skeleton in patients with symptomatic ankylosing spondylitis, and identified a significant reduction in osteitis after 24 weeks of therapy in both the sacroiliac joints (SIJs) and spine (Poddubnyy et al., 2013, Poddubnyy et al., 2014a). There are no data for conventional MRI or WBMRI in the assessment of the peripheral skeleton of patients with PsA following treatment with ustekinumab. As described in Chapter 5.1., given the emergence of IL-23 as a key mediator in the development of spondyloarthropathy-based, entheseal driven pathology (Quinn et al., 2008, Adamopoulos et al., 2011, Sherlock et al., 2012), and the general acceptance of enthesitis as the primary pathology in PsA (Benjamin and McGonagle, 2001), targeting the IL-23/Th17 pathway would therefore seem a logical therapeutic approach to circumvent the progression of inflammation and resultant structural damage.

Although only a few psoriasis patients without arthritis have been studied using MRI, a higher frequency of entheseal abnormalities are reported compared to healthy subjects (Chapter 6). These findings suggest that both conventional and whole-body MRI may detect PsA before it becomes clinically apparent, and in patients with psoriasis who are destined to develop arthritis, this may offer a window of opportunity to potentially prevent arthritis evolution with the early introduction of a skin-directed disease-modifying therapy. Currently, there are no data published on the potentially positive effects of early biologic therapy in patients with psoriasis and subclinical enthesopathy on outcomes in PsA, although increasingly it is assumed that results from rheumatoid arthritis trials (which support very early intervention to induce remission and radiographic non-progression) may be applicable to patients with PsA (Gremese et al., 2013, Bosello et al., 2011, Vermeer et al., 2011).

The aim of this chapter is to investigate the change in active inflammatory lesions and structural abnormalities in the axial and peripheral skeleton seen on WBMRI, following skin directed treatment with anti-IL-12/IL-12p40 monoclonal antibody therapy in asymptomatic patients with psoriasis and subclinical enthesitis.

7.2 Methods

7.2.1 Participant Recruitment

This single-centre proof-of-concept study was conducted entirely at Chapel Allerton Hospital (Leeds Teaching Hospitals NHS Trust), with WBMRI performed within the Leeds Musculoskeletal Biomedical Research Unit. The study was conducted in

accordance with the Declaration of Helsinki and approved by the National Research Ethics Committee – Yorkshire and the Humber (Reference 12/YH/0483). Relevant approvals were also granted by the Medicines and Healthcare Products Regulatory Authority (MHRA) and the Research and Development Unit within Leeds Teaching Hospitals NHS Trust (Reference RR12/10234). The University of Leeds accepted the duties of Sponsor under The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amendment (No.2) Regulations 2006.

7.2.1.1 Sample Size

No formal power calculations were performed as this was an exploratory proof-of-concept study. See Chapter 5.2.1. for further details.

7.2.1.2 Participant Identification and Recruitment

Twenty-three patients who were recruited to participate in an ultrasound study investigating the response of subclinical enthesitis to anti-IL-12/23 p40 therapy in patients with moderate to severe psoriasis were also consented to undergo a whole-body MRI scan during the same appointment attended for each ultrasound scan. Details on recruitment to the ultrasound study are described in Chapter 5.2.2. A standard safety patient-completed MRI questionnaire was filled in and reviewed by the radiographer prior to every scan (Appendix 10).

Written consent was obtained from all participants prior to the collection of any clinical or imaging data, which permitted the use of data for research purposes and storage. Participants were made aware that the WBMRI scans would only be reported for abnormalities within the musculoskeletal system, and that pathology in any other bodily systems may not be seen and reported. Conversely, they were made aware that gross pathology in other systems may be identified, in which instance they were assured they would be informed in a timely manner and referred to the appropriate service/specialist as appropriate.

7.2.2 Inclusion/Exclusion Criteria

7.2.2.1 Inclusion Criteria

See Chapter 5.2.3.1.

7.2.2.2 Exclusion Criteria

See Chapter 5.2.3.2.

7.2.3 Drug Therapy

Chapter 5.2.4. provides information regarding the qualitative and quantitative composition, posology, dosing schedule and known adverse reactions for ustekinumab (experimental name CNTO1275) in addition to concomitant therapies permitted and prohibited during the study.

7.2.4 Participant Visit Schedule

After their initial new patient consultation, patients consenting to participate in the trial attended for a total of six further study visits at weeks 0, 4, 12, 16, 24 and 52. Ustekinumab was administered at weeks 0, 4 and 16 by the candidate (LS), after which time patients continued to received 12-weekly injections given by a dedicated nurse through the BUPA™ Healthcare at Home scheme (Chapter 5.2.5). MRI scans were carried in the Leeds Musculoskeletal Biomedical Research Unit at Chapel Allerton Hospital at weeks 0, 24 and 52 either immediately before or after their ultrasound scan. The full study schedule can be found in Table 5.2. All visits took place within seven days of the scheduled date.

7.2.5 Data Collection

All data collection was carried out by the candidate (LS). Magnetic resonance image acquisition and storage was undertaken by an experienced MRI/research radiographer (RE) proficient in performing WBMRI, within the Leeds Musculoskeletal Biomedical Research Unit (LMBRU) at Chapel Allerton Hospital.

Clinical data obtained in the consultation was recorded on a case report form (CRF) and then transcribed into an encrypted password-protected database on the University of Leeds computer server for analysis. Further information on the type of clinical data captured is described in Chapter 5.2.6. Care was taken to ensure the check integrity of the dataset at upload. Paper record forms are stored in a locked filing cabinet within a locked room within Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM) at Chapel Allerton Hospital, in accordance with the University's Information Security Policy. Magnetic resonance images were stored in a password-protected database and analysed using OsiriX DICOM viewer.

7.2.6 Clinical Assessment

7.2.6.1 Psoriasis Severity and Impact

The severity and impact of psoriasis was assessed at weeks 0, 4, 12, 24 and 52. Details of the assessments are as described in Chapter 5.2.7.1.

7.2.6.2 Psoriatic Arthritis

All accessible peripheral joints were visually examined for swelling and tenderness at weeks 0, 4, 12, 24 and 52. Attempts were also made to elicit tenderness at several entheseal points, in addition to assessment for features of dactylitis. Further detail is provided in Chapter 5.2.7.2. In addition, Schober's test was carried out at each clinical visit to determine patient spinal flexibility.

7.2.7 Laboratory Assessment

Safety monitoring was undertaken in line with standard NHS care procedures and the NICE guidelines for any patient taking a biologic therapy. Monitoring blood samples were analysed at weeks 0, 4, 12, 24 and 52 in the NHS laboratories within Leeds Teaching Hospitals Trust. In addition, anti-CCP antibody and rheumatoid factor were tested alongside two genetic risk alleles for psoriatic arthritis (HLA-Cw06 and HLA-B27). Further detail is provided in Chapter 5.2.8.

7.2.8 Whole Body Magnetic Resonance Imaging (WBMRI)

7.2.8.1 WBMRI Protocol

The WBMRI protocol and technical parameters are described in detail in Chapter 6.2.5.1. Gadolinium contrast was not given. A combination of T1-weighted (turbo spin echo) and short τ inversion recovery (STIR) sequences were performed in a total of 7 stations:

- Coronal slice orientation (shoulders, costochondral joints, hips and knees)
- Coronal oblique orientation (SIJs)
- Sagittal orientation (cervicothoracic and thoracolumbar spine)
- Axial orientation (knees and feet)

T2 'fat sat' sequences were also performed with coronal oblique orientation for the SIJs. Total scan time was 55 minutes and was generally well tolerated by participants.

7.2.8.2 WBMRI Interpretation

WBMRI were evaluated by a highly experienced rheumatologist (DMcG) experienced with the analysis of WBMRI, who was blinded to all clinical, biochemical and demographic information. The images were evaluated together on a patient basis at the end of the trial, but in a random time order. As a safety measure, the images were also reviewed by a NHS musculoskeletal radiologist (PO) within 48 hours of each scan to ensure no gross abnormalities or concerning features were present that required

immediate attention. These analyses did not form part of the WBMRI assessments for the trial and were not available to the rheumatologist (DMcG).

Readability of the scans was assessed for each enthesis as ‘readable’ or ‘not readable’ (e.g. due to artefacts) or ‘not in field of view (FOV)’. All images were analysed for active inflammatory lesions and structural changes at axial (spine and SIJs) and non-axial (peripheral) sites.

7.2.8.2.1 Non-axial (peripheral) sites

Images of the peripheral skeleton were assessed for the presence of enthesitis, comprising of both active inflammation (BMO and adjacent STI) and structural abnormalities (erosions and enthesophytes in adjacent bones). Additional findings within the surrounding synovio-entheseal complex were also assessed (synovitis, bursitis, tenosynovitis).

The severity of all abnormalities was scored from 0-3 with the exception of erosions and enthesophytes (scored 0 or 1, absent or present). Abnormalities must have been visible in at least two consecutive slices to be scored. Comparison with the opposite site was made for paired entheses. In total, 45 sites were scored for BMO and STI, 16 sites for synovitis/effusion, 12 sites for bursitis, 8 sites for erosions and 4 sites for enthesophytes on each WBMRI at each time point. Further detail on the assessment of peripheral sites and scoring is described in Chapter 6.2.5.2.1. and Table 6.2.

7.2.8.3 Axial Sites

The spine was divided into 23 individual vertebral units (VU) extending from C2/3 to L5/S1. Each VU within the spine was evaluated separately in the ventral part (vertebral body) and posterior elements (pedicles, facet joints and spinous processes). The SIJs were evaluated at a quadrant level (upper and lower iliac parts, and upper and lower sacral parts) as shown in Figure 6.1.

Images of the axial skeleton were scored for activity using the Berlin modification of the AS spine MRI score, which encompasses inflammatory abnormalities (BMO) and structural changes (fatty bone marrow infiltration, erosions and bone proliferation) (table 6.3). Abnormalities must have been visible in at least two consecutive slices to be scored.

In accordance with published scoring techniques (Althoff et al., 2013), each SIJ was scored from 0-24 (0-3 for each upper and lower ilium, and each upper and lower sacrum) for BMO and erosions, and 0-8 for fatty infiltration, sclerosis and ankylosis. In the spine, BMO, erosions, bone marrow fatty infiltration and bone proliferation were scored from 0 to 69 (0-3 in each of 23 VUs), and 0 to 46 (0-2 in each VU) for posterior segment

inflammation. The definitions of each MRI abnormality within the spine and SIJs are given in Chapter 6.2.5.3.1. (spine) and Chapter 6.2.5.3.2. (SIJs).

7.3 Statistical Analysis

Descriptive statistics were used primarily throughout, although some exploratory analyses were performed. Results for categorical data are expressed as frequencies and percentages, and continuous variables are given as means (standard deviation, s.d.) or medians (interquartile range, IQR), depending on the distribution. χ^2 test was used to explore associations between categorical variables. Differences in the frequencies of each MRI abnormality in each patient at each time point were assessed using Student's paired *t*-tests. Differences in the median total scores for each MRI abnormality were analysed using Wilcoxon signed-rank tests. *p* values <0.05 were regarded as statistically significant, although results were considered exploratory and would require confirmation in a fully powered study. Statistical analysis was performed using IBM© SPSS© version 24.0.

Missing values, were a joint was within the field of view but unreadable, were considered to have no abnormality (assumed score of zero) when calculating mean overall scores for each MRI abnormality. In a sensitivity analysis, tests were repeated assuming these joints all had the maximum possible score for the relevant abnormalities and there was no change to the overall trends observed. Multiple imputation analysis was not feasible due to the large number of joints relative to the number of patients, which caused imputation models to fail to converge.

7.4 Results

23 patients were recruited to participate in the study. 23 patients reached the primary endpoint of week 24, and 20 reached the secondary endpoint of week 52.

7.4.1 Patient Characteristics

A full description of the distribution of demographic attributes within the cohort of 23 patients (age, gender, skin type, BMI, smoking status and alcohol consumption) is provided in Chapter 5.4.1. Details are also provided about the median age of onset of psoriasis symptoms and the duration of disease, in addition to any family history of psoriatic, musculoskeletal and autoimmune disease, co-morbidities and concomitant medications.

7.4.2 Laboratory Assessment

Serological assessment was satisfactory in all participants at baseline to allow commencement of the IMP. Fluctuations over time were rarely outside normal parameters, those that where are discussed in Chapter 5.4.2. No patients were required to withdraw from the study due to serological abnormalities. All patients were negative for rheumatoid factor, anti-CCP antibody and ANA, and remained so throughout the study. One patient was positive for the HLA-B27 allele, and 15 patients (65.2%) were positive for HLA-Cw06.

7.4.3 Adverse Events

Two serious adverse events (SAEs) were reported to the Sponsor (University of Leeds) and the manufacturer (Janssen Pharmaceutica) during the trial. One was not related to the IMP (road traffic accident resulting in hospitalisation) and for the second, causation was uncertain but may have been related to the IMP (abdominal abscess requiring hospitalisation). The latter was reported to the MHRA through the yellow card scheme. Ten mild and self-limiting adverse events were also recorded and included upper respiratory tract infections (common expected AE, related to IMP), tiredness (common expected AE, related to IMP), follicular abnormalities (unexpected AE, uncertain relationship to IMP, reported to MHRA by yellow card scheme) and shoulder trauma (unexpected AE, not related to the IMP). Chapter 5.4.3. provided further detail.

7.4.4 Clinical Outcomes

7.4.4.1 Skin Disease

Baseline PASI scores ranged from 10.4 to 38.4 (median 18.0 [13.4, 28.4]), with a median BSA of 30% (15%, 40%). By week 24, median PASI had reduced to 0.6 (0, 2.5) and BSA to 1% (0%, 3%), and by week 52, median PASI was 0.1 (0, 2.93) and BSA 0.5% (0%, 2.75%). A further description can be found in Chapter 5.4.4.1., and Table 5.3. shows the distribution and frequency of psoriasis lesions for each anatomical site at each time point.

7.4.4.2 Nail Disease

17 patients had nail involvement (pitting, onycholysis and/or crumbling) at baseline. Changes in modified Nail Psoriasis Severity Index (mNAPSI) scores can be found in Chapter 5.4.4.2.

7.4.5 Readability of MRI

7.4.5.1 Non-Axial (Peripheral) Sites

7.4.5.1.1 Entheses

The readability for individual entheses at each time point is shown in Table 7.1. WBMRI allowed evaluation of 964 of 1035 (93.1%) entheses within the peripheral skeleton of 23 patients at week 0, 971 of 1035 (93.8%) entheses in 23 patients at week 24 and 844 of 900 (93.8%) entheses in 20 patients at week 52. The remaining entheses were within the field of view (FOV) but not readable (due to insufficient image quality, movement artefact and off-centre artefact). Overall, 6.4% of entheses could not be read on all WBMRI analysed. No entheseal sites were outside the FOV as the elbows, wrists and hands were not included in the protocol, and a specific coil was used to capture images of the feet and ankles.

For the purposes of comparison between time points, 914 of 1035 (88.3%) entheses were within FOV and readable at both week 0 and 24, and 790 of 900 (87.8%) at both week 0 and 52. All pelvic, greater trochanter, Achilles tendon and plantar fascia tendon entheses could be assessed in ≥95% of participants. Readability was poorest in the chest (7^{th} costochondral joint, 78-88% and 1^{st} costochondral syndchondrosis, 83-90% readability), first metatarsophalangeal joint (75%-91% readability) and at the knee (lateral femoral condyle, 80-90%; medial femoral condyle, 80-90%; quadriceps insertion, 80%-91%; intracondylar notch, 80-93%; patella ligament insertion, 85-95% readability). Lack of saggital slices are likely to account for the reduction in readability of the knee entheses.

Week 0 (n=23)				Week 24 (n=23)				Week 52 (n=20)			
In FOV and readable n/23(%)	In FOV, but not readable n/23(%)	In FOV and readable n/46(%) [*n/23(%)]	In FOV, but not readable n/46(%) [*n/23(%)]	In FOV and readable n/23(%)	In FOV, but not readable n/23(%)	In FOV and readable n/46(%) [*n/23(%)]	In FOV, but not readable n/46(%) [*n/23(%)]	In FOV and readable n/20(%)	In FOV, but not readable n/20(%)	In FOV and readable n/40(%) [*n/20(%)]	In FOV, but not readable n/40(%) [*n/20(%)]
No. of patients		**No. of entheses**		**No. of patients**		**No. of entheses**		**No. of patients**		**No. of entheses**	
Supraspinate tendon insertion at humeral tuberosity											
21 (91)	2 (9)	44 (96)	2 (4)	20 (87)	3 (13)	43 (93)	3 (7)	19 (95)	1 (5)	39 (98)	1 (2)
Acromioclavicular joint											
21 (91)	2 (9)	44 (96)	2 (4)	22 (96)	1 (4)	45 (98)	1 (2)	18 (90)	2 (10)	38 (95)	2 (5)
Coracoid process											
21 (91)	2 (9)	44 (96)	2 (4)	22 (96)	1 (4)	45 (98)	1 (2)	19 (95)	1 (5)	39 (98)	1 (2)
Sternoclavicular joint											
20 (87)	3 (13)	40 (87)	6 (13)	19 (83)	4 (17)	41 (89)	5 (11)	18 (90)	2 (10)	37 (93)	3 (7)
1st costochondral synchondrosis											
19 (83)	4 (17)	39 (85)	7 (15)	19 (83)	4 (17)	41 (89)	5 (11)	17 (85)	3 (15)	36 (90)	2 (5)
7th costochondral joint											
18 (78)	5 (22)	36 (78)	10 (22)	19 (83)	4 (17)	38 (83)	8 (17)	17 (85)	3 (15)	35 (88)	5 (12)
Manubriosternal joint*											
20 (87)	3 (13)	20 (87)	3 (13)	22 (96)	1 (4)	22 (96)	1 (4)	19 (95)	1 (5)	19 (95)	1 (5)
Iliac crest											
23 (100)	0 (100)	46 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)	20 (100)	0 (0)	40 (100)	0 (0)
Anterior superior iliac spine											
23 (100)	0 (0)	46 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)	20 (100)	0 (0)	40 (100)	0 (0)
Ischial tuberosity											
23 (100)	0 (0)	46 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)	20 (100)	0 (0)	40 (100)	0 (0)

Week 0 (n=23)				Week 24 (n=23)				Week 52 (n=20)			
In FOV and readable n/23(%)	In FOV, but not readable n/23(%)	In FOV and readable n/46(%) [*n/23(%)]	In FOV, but not readable n/46(%) [*n/23(%)]	In FOV and readable n/23(%)	In FOV, but not readable n/23(%)	In FOV and readable n/46(%) [*n/23(%)]	In FOV, but not readable n/46(%) [*n/23(%)]	In FOV and readable n/20(%)	In FOV, but not readable n/20(%)	In FOV and readable n/40(%) [*n/20(%)]	In FOV, but not readable n/40(%) [*n/20(%)]
No. of patients		**No. of entheses**		**No. of patients**		**No. of entheses**		**No. of patients**		**No. of entheses**	
Pubic symphysis											
22 (96)	1 (4)	45 (98)	1 (2)	23 (100)	0 (0)	46 (100)	0 (0)	20 (100)	0 (0)	40 (100)	0 (0)
Greater trochanter											
23 (100)	0 (0)	46 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)	20 (100)	0 (0)	40 (100)	0 (0)
Lateral femoral condyle											
20 (87)	3 (13)	40 (87)	6 (13)	19 (83)	4 (17)	39 (85)	7 (15)	16 (80)	4 (20)	36 (90)	4 (10)
Medial femoral condyle											
21 (91)	2 (9)	43 (93)	3 (7)	20 (87)	3 (13)	42 (91)	4 (9)	16 (80)	4 (20)	36 (90)	4 (10)
Lateral tibial plateau											
22 (96)	1 (4)	44 (96)	2 (4)	20 (87)	3 (13)	41 (89)	5 (11)	16 (80)	4 (20)	36 (90)	4 (10)
Intracondylar notch											
21 (91)	2 (9)	43 (93)	3 (7)	20 (87)	3 (13)	41 (89)	5 (11)	16 (80)	4 (20)	36 (90)	4 (10)
Patella ligament insertion into patella											
20 (87)	3 (13)	41 (89)	5 (11)	20 (87)	3 (13)	40 (87)	6 (13)	18 (85)	2 (15)	38 (95)	2 (5)
Quadriceps insertion into patella											
20 (87)	3 (13)	42 (91)	4 (9)	20 (87)	3 (13)	42 (91)	4 (9)	16 (80)	4 (20)	36 (90)	4 (10)
Ankle joint attachments											
20 (87)	3 (13)	42 (91)	4 (9)	21 (91)	2 (9)	43 (93)	3 (7)	18 (85)	2 (15)	36 (90)	4 (10)
1st Tarsometatarsal Joint											
21 (91)	2 (9)	43 (93)	3 (7)	21 (91)	2 (9)	44 (96)	2 (4)	18 (85)	2 (15)	36 (90)	4 (10)

Week 0 (n=23)				Week 24 (n=23)				Week 52 (n=20)			
In FOV and readable n/23(%)	In FOV, but not readable n/23(%)	In FOV and readable n/46(%) [*n/23(%)]	In FOV, but not readable n/46(%) [*n/23(%)]	In FOV and readable n/23(%)	In FOV, but not readable n/23(%)	In FOV and readable n/46(%) [*n/23(%)]	In FOV, but not readable n/46(%) [*n/23(%)]	In FOV and readable n/20(%)	In FOV, but not readable n/20(%)	In FOV and readable n/40(%) [*n/20(%)]	In FOV, but not readable n/40(%) [*n/20(%)]
No. of patients		**No. of entheses**		**No. of patients**		**No. of entheses**		**No. of patients**		**No. of entheses**	
1st Metatarsophalangeal Joint											
19 (83)	4 (17)	38 (83)	8 (17)	21 (91)	2 (9)	42 (91)	4 (9)	15 (75)	5 (25)	34 (85)	6 (15)
Achilles tendon insertion											
23 (100)	0 (0)	46 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)	19 (95)	1 (5)	38 (95)	2 (5)
Plantar Fascia at calcaneus											
23 (100)	0 (0)	46 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)	19 (95)	1 (5)	39 (98)	1 (2)

Table 7.1. WBMRI readability at 45 entheseal sites in the peripheral skeleton at each time point

7.4.5.1.2 Bursae

The readability of WBMRI for the assessment of individual bursae is shown in Table 7.2. WBMRI allowed the evaluation of 273 of 276 (98.9%) bursae in 23 patients at week 0, 266 of 276 (96.4%) bursae in 23 patients at week 24 and 232 of 240 (96.7%) bursae in 20 patients at week 52. The remaining bursae were within FOV but nor readable. Overall, 2.7% of bursae could not be read on all WBMRI analysed.

For the purposes of comparison between time points, 263 of 276 (95.3%) of bursae were within the FOV and readable at both week 0 and 24, and 230 of 240 (95.8%) at both week 0 and 52. The most difficult anatomical site to assess for bursitis was the knee, but readability was still good, with 94-98% of pre-patellar bursae and 95-98% of pes anserine bursae readable.

7.4.5.1.3 Synovial Joints and Tendons

The readability of WBMRI for the evaluation of synovial joints is shown in Table 7.3. At some sites, assessment of synovial fluid was possible where it was not possible to see the entheseal insertion. WBMRI allowed evaluation of 358 of 368 (97.3%) synovial joints in 23 patients at week 0, 355 of 368 (96.5%) joints in 23 patients at week 24 and 309 of 320 (96.6%) joints in 20 patients at week 52. Overall, 3.2% of synovial joints could not be read on all WBMRI analysed.

For the purposes of comparison between time points, 345 of 368 (93.8%) joints could be visualised and read at both week 0 and 24 and 301 of 320 (94.1%) joints at both week 0 and 52. The most difficult site to analyse was the first metatarsophalangeal joint in the foot, although readability was still good with analysis possible in 91% to 94% of joints. Readability was best at the hip and ankle, followed by the knee.

The lateral and medial tendons of the midfoot were within the FOV and readable in all patients at each time point. In total, 92 tendons in 23 patients were assessed for tenosynovitis at week 0 and 24, and 80 tendons were assessed in 20 patients at week 52.

7.4.5.1.4 Enthesophytes and Erosions

The readability of WBMRI for assessment of structural abnormalities overall was excellent, as shown in Table 7.4. For erosions, WBMRI allowed evaluation of 178 of 184 (96.7%) sites in 23 patients at week 0, 176 of 184 (95.7%) sites in 23 patients at week 24 and 151 of 160 (94.4%) sites in 20 patients at week 52. For enthesophytes, WBMRI allowed assessment of all 92 sites in 23 patients at week 0 and 24, and in 77 of 80 (96.3%) of sites at week 52. The remaining sites were within FOV but not readable.

Week 0				Week 24				Week 52			
In FOV and readable n/23 (%)	In FOV, but not readable n/23 (%)	In FOV and readable n/46 (%)	In FOV, but not readable n/46 (%)	In FOV and readable n/23 (%)	In FOV, but not readable n/23 (%)	In FOV and readable n/46 (%)	In FOV, but not readable n/46 (%)	In FOV and readable n/20 (%)	In FOV, but not readable n/20 (%)	In FOV and readable n/40 (%)	In FOV, but not readable n/40 (%)
No. of Patients		**No. of Bursae**		**No. of Patients**		**No. of Bursae**		**No. of Patients**		**No. of Bursae**	
Subacromial bursae											
22 (96)	1 (4)	44 (96)	2 (4)	23 (100)	0 (0)	45 (98)	1 (2)	19 (95)	1 (5)	39 (98)	1 (2)
Greater trochanteric bursae											
23 (100)	0 (0)	46 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)	20 (100)	0 (0)	40 (100)	0 (0)
Pre-patellar bursae											
22 (96)	1 (4)	45 (98)	1 (2)	22 (96)	1 (4)	43 (94)	3 (7)	18 (90)	2 (10)	38 (95)	2 (5)
Pes anserine bursae											
23 (100)	0 (0)	45 (98)	1 (2)	22 (96)	1 (4)	44 (96)	2 (4)	19 (95)	1 (5)	38 (95)	2 (5)
Achilles bursae											
23 (100)	0 (0)	46 (100)	0 (0)	22 (96)	1 (4)	44 (96)	2 (4)	19 (95)	1 (5)	38 (95)	2 (5)
Retrocalcaneal bursae											
23 (100)	0 (0)	46 (100)	0 (0)	22 (96)	1 (4)	44 (96)	2 (4)	19 (95)	1 (5)	39 (98)	1 (2)

Table 7.2. WBMRI readability at 12 bursae in the peripheral skeleton at each time point

Week 0				Week 24				Week 52			
In FOV and readable n/23(%)	In FOV, but not readable n/23 (%)	In FOV and readable n/46(%)	In FOV, but not readable n/46 (%)	In FOV and readable n/23(%)	In FOV, but not readable n/23 (%)	In FOV and readable n/46(%)	In FOV, but not readable n/46 (%)	In FOV and readable n/20(%)	In FOV, but not readable n/20 (%)	In FOV and readable n/40(%)	In FOV, but not readable n/40 (%)
No. of Patients		**No. of Joints**		**No. of Patients**		**No. of Joints**		**No. of Patients**		**No. of Joints**	
Sternoclavicular joints											
21 (91)	2 (9)	44 (96)	2 (4)	21 (91)	2 (9)	43 (94)	3 (6)	18 (90)	2 (10)	37 (93)	3 (7)
Acromioclavicular joints											
21 (91)	2 (9)	44 (96)	2 (4)	22 (96)	1 (4)	45 (98)	1 (2)	18 (90)	2 (10)	38 (95)	2 (5)
Shoulder joints											
22 (96)	1 (4)	45 (98)	1 (2)	22 (96)	1 (4)	45 (98)	1 (2)	19 (95)	1 (5)	39 (98)	1 (2)
Hip joints											
23 (100)	0 (0)	46 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)	20 (100)	0 (0)	40 (100)	0 (0)
Knee joints											
23 (100)	0 (0)	46 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)	19 (95)	1 (5)	39 (98)	1 (2)
Ankle joints											
23 (100)	0 (0)	46 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)	20 (100)	0 (0)	40 (100)	0 (0)
Tarsometatarsal joints											
21 (91)	2 (9)	44 (96)	2 (4)	21 (91)	2 (9)	44 (96)	2 (4)	19 (95)	1 (5)	39 (98)	1 (2)
Metatarsophalangeal joints											
21 (91)	2 (9)	43 (94)	3 (6)	20 (87)	3 (13)	42 (91)	4 (9)	18 (90)	2 (10)	37 (93)	3 (7)

Table 7.3. WBMRI readability at 16 synovial joints in the peripheral skeleton at each time point

Week 0				Week 24				Week 52			
In FOV and readable n/23 (%)	In FOV, but not readable n/23 (%)	In FOV and readable n/46 (%)	In FOV, but not readable n/46 (%)	In FOV and readable n/23 (%)	In FOV, but not readable n/23 (%)	In FOV and readable n/46 (%)	In FOV, but not readable n/46 (%)	In FOV and readable n/20 (%)	In FOV, but not readable n/20 (%)	In FOV and readable n/40 (%)	In FOV, but not readable n/40 (%)
No. of Patients		**No. of Joints**		**No. of Patients**		**No. of Joints**		**No. of Patients**		**No. of Joints**	
1st Tarsometatarsal joint (erosions only)											
21 (91)	2 (9)	43 (94)	3 (6)	21 (91)	2 (9)	44 (96)	2 (4)	18 (90)	2 (10)	37 (93)	3 (7)
1st Metatarsophalangeal joint (erosions only)											
21 (91)	2 (9)	43 (94)	3 (6)	20 (87)	3 (13)	40 (87)	6 (13)	18 (90)	2 (10)	37 (93)	3 (7)
Achilles tendon insertion into calcaneus (erosions and enthesophytes)											
23 (100)	0 (0)	46 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)	19 (95)	1 (5)	38 (95)	2 (5)
Plantar fascia insertion into calcaneus (erosions and enthesophytes)											
23 (100)	0 (0)	46 (100)	0 (0)	23 (100)	0 (0)	46 (100)	0 (0)	19 (95)	1 (5)	39 (98)	1 (2)

Table 7.4. WBMRI readability of 8 sites of potential erosions and 4 sites of potential enthesophytes in the peripheral skeleton at each time point.

7.4.5.2 Spine and Sacroiliac Joints

Full evaluation of all 23 vertebral units and 8 sacroiliac joint quadrants was possible in all participants at each time point.

7.4.6 MRI Abnormalities

7.4.6.1 Non-axial (Peripheral) Skeleton

7.4.6.1.1 *Active Inflammation (Bone Marrow Oedema and Soft Tissue Inflammation)*

Bone marrow oedema (BMO) and soft tissue inflammation (STI) were assessed at 45 entheseal sites in each participant at each time point. At week 0, 43/964 (4.5%) readable entheses demonstrated BMO, and this remained relatively unchanged after 24 weeks (44/971, 4.5%), and 52 weeks (40/804, 4.7%) of treatment. STI also did not change significantly with ustekinumab therapy, affecting 55/964 (5.7%) of entheses at week 0, 56/971 (5.8%) at week 24 and 49/804 (6.1%) at week 52.

Throughout the study, all patients had at least one inflammatory lesion (BMO, STI or both) at every time point. 19/23 had at least one BMO lesion at week 0, 18/23 at week 24 and 14/20 at week 52. 21/23 had at least one STI lesion at weeks 0 and 24, and 18/20 at week 52.

As found in the previous chapter, BMO and STI occurred infrequently in the same enthesis. 17 of 23 patients at week 0 had both lesions of BMO and STI, of which only five had BMO and STI at the same site (supraspinate tendon insertion at the humeral tuberosity and plantar fascia). 16 of 23 patients at week 24 and 12 of 20 patients at week 52 also had lesions of both BMO and STI, of which only 5 and 4 patients respectively had simultaneous BMO and STI in the same enthesis.

The mean number of lesions per patient was static over time for both BMO and STI. Patients had between 0 and 8 BMO lesions and 0 and 6 STI lesions at every time point. The mean (±s.d.) number of BMO lesions per patient was 1.83 ±1.75 at week 0, 1.91 ±1.86 at week 24 and 1.74 ±2.05 at week 52. The average number of STI lesions per patient was 2.30 ±1.40 at week 0, 2.43 ±1.47 at week 24 and 2.13 ±2.05 at week 52. The overall burden of inflammation (BMO and STI) remained unchanged with treatment, as shown in Figure 7.1.

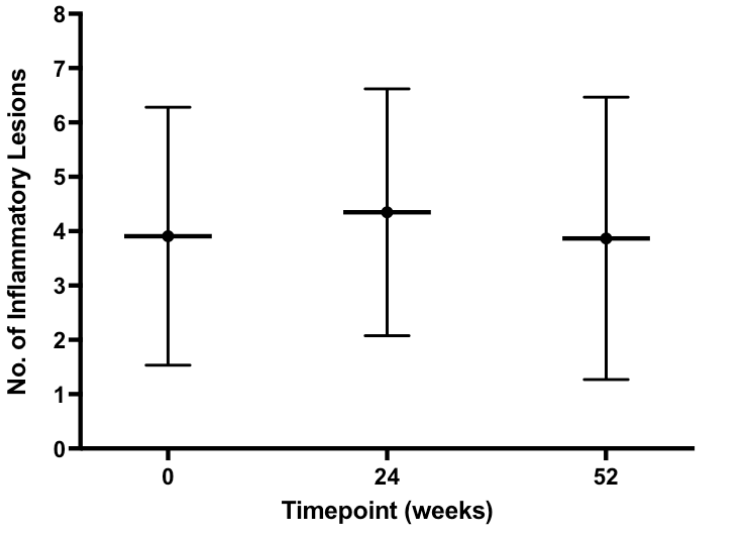


Figure 7.1. Mean (and s.d.) number of inflammatory lesions (BMO and STI) per patient at each time point in the peripheral skeleton.

Comparison of the frequency of BMO and STI at each specific enthesis between weeks 0 and the primary endpoint (week 24) is shown in Table 7.5. An identical comparison between weeks 0 and 52 is shown in Table 7.6. Treatment with ustekinumab for up to one year did not significantly reduce the number of inflammatory lesions identified at any site. However, subclinical inflammation is expected to advance without treatment, and progression does therefore appear to have been limited.

	Entheseal Level						Patient Level					
	No. of BMO lesions (% of BMO lesions within readable FOV)			No. of STI lesions (% of STI lesions within readable FOV)			No. of patients with BMO (% of patients with BMO within readable FOV)			No. of patients with STI (% of patients with STI within readable FOV)		
	Week 0	Week 24	Group diff (p=)	Week 0	Week 24	Group diff (p=)	Week 0	Week 24	Group diff (p=)	Week 0	Week 24	Group diff (p=)
Supraspinate tendon insertion at humeral tuberosity	12 (27.3)	13 (30.2)	0.760	4 (9.1)	4 (9.3)	0.973	11 (52.4)	12 (60.0)	0.623	4 (19.0)	4 (20.0)	0.939
Acromioclavicular joint	6 (13.6)	6 (13.3)	0.967	0 (0.0)	0 (0.0)	NA	4 (19.0)	4 (18.2)	0.942	0 (0.0)	0 (0.0)	NA
Coracoid process	1 (2.3)	0 (0.0)	0.309	0 (0.0)	0 (0.0)	NA	1 (4.8)	0 (0.0)	0.300	0 (0.0)	0 (0.0)	NA
Sternoclavicular joint	1 (2.5)	1 (2.4)	0.986	0 (0.0)	0 (0.0)	NA	1 (5.0)	1 (5.3)	0.970	0 (0.0)	0 (0.0)	NA
1st costochondral process	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
7th costochondral joint	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Manubriosternal joint	2 (10.0)	1 (4.5)	0.493	0 (0.0)	0 (0.0)	NA	2 (10.0)	1 (4.5)	0.493	0 (0.0)	0 (0.0)	NA
Iliac crest	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Anterior superior iliac spine	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Ischial tuberosity	0 (0.0)	0 (0.0)	NA	3 (6.5)	3 (6.5)	1.000	0 (0.0)	0 (0.0)	NA	2 (8.7)	2 (8.7)	1.000
Pubic symphysis	2 (4.4)	1 (2.2)	0.544	0 (0.0)	0 (0.0)	NA	2 (9.1)	1 (4.3)	0.524	0 (0.0)	0 (0.0)	NA
Greater trochanter	0 (0.0)	1 (2.2)	0.315	26 (56.5)	27 (58.7)	0.833	0 (0.0)	1 (4.3)	0.312	15 (65.2)	15 (65.2)	1.000
Lateral femoral condyle	0 (0.0)	1 (2.6)	0.308	1 (2.5)	0 (0.0)	0.320	0 (0.0)	1 (5.3)	0.295	1 (5.0)	0 (0.0)	0.323
Medial femoral condyle	0 (0.0)	2 (4.8)	0.148	0 (0.0)	0 (0.0)	NA	0 (0.0)	1 (5.0)	0.300	0 (0.0)	0 (0.0)	NA
Lateral tibial plateau	0 (0.0)	0 (0.0)	NA	1 (2.3)	1 (2.4)	0.960	0 (0.0)	0 (0.0)	NA	1 (4.5)	1 (5.0)	0.945
Intracondylar notch	7 (16.3)	7 (17.1)	0.922	0 (0.0)	0 (0.0)	NA	5 (23.8)	5 (25.0)	0.929	0 (0.0)	0 (0.0)	NA
Patella ligament insertion into patella	4 (9.8)	4 (10.0)	0.971	8 (19.5)	9 (22.5)	0.741	2 (10.0)	2 (10.0)	1.000	6 (30.0)	6 (30.0)	1.000
Quadriceps tendon insertion into patella	0 (0.0)	0 (0.0)	NA	2 (4.8)	2 (4.8)	1.000	0 (0.0)	0 (0.0)	NA	2 (10.0)	2 (10.0)	1.000
Ankle joint attachments	2 (4.7)	2 (4.8)	0.981	0 (0.0)	0 (0.0)	NA	1 (5.0)	1 (4.8)	0.972	0 (0.0)	0 (0.0)	NA
1st Tarsometotarsal joint	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
1st Metatarsophalangeal joint	4 (10.5)	3 (7.5)	0.593	0 (0.0)	0 (0.0)	NA	3 (15.8)	2 (9.5)	0.550	0 (0.0)	0 (0.0)	NA
Achilles tendon insertion	0 (0.0)	0 (0.0)	NA	3 (6.5)	3 (6.5)	1.000	0 (0.0)	0 (0.0)	NA	2 (8.7)	2 (8.7)	1.000
Plantar fascia insertion at calcaneus	2 (4.3)	2 (4.3)	1.000	7 (15.2)	7 (15.2)	1.000	2 (8.7)	2 (8.7)	1.000	7 (30.4)	7 (30.4)	1.000

Table 7.5. Comparison of the frequency of readable BMO and STI lesions within field of view (FOV) at each enthesis between weeks 0 and 24.

	Entheseal Level						Patient Level					
	No. of BMO lesions (% of BMO lesions within readable FOV)			No. of STI lesions (% of STI lesions within readable FOV)			No. of patients with BMO (% of patients with BMO within readable FOV)			No. of patients with BMO (% of patients with BMO within readable FOV)		
	Week 0	Week 52	Group diff (p=)	Week 0	Week 52	Group diff (p=)	Week 0	Week 52	Group diff (p=)	Week 0	Week 52	Group diff (p=)
Supraspinate tendon insertion at humeral tuberosity	12 (27.3)	11 (28.2)	0.925	4 (9.1)	5 (12.8)	0.585	11 (52.4)	9 (47.4)	0.752	4 (19.0)	4 (21.1)	0.874
Acromioclavicular joint	6 (13.6)	6 (15.8)	0.783	0 (0.0)	0 (0.0)	NA	4 (19.0)	4 (22.2)	0.807	0 (0.0)	0 (0.0)	NA
Coracoid process	1 (2.3)	1 (2.6)	0.931	0 (0.0)	0 (0.0)	NA	1 (4.8)	1 (5.3)	0.942	0 (0.0)	0 (0.0)	NA
Sternoclavicular joint	1 (2.5)	0 (0.0)	0.333	0 (0.0)	0 (0.0)	NA	1 (5.0)	0 (0.0)	0.336	0 (0.0)	0 (0.0)	NA
1st costochondral process	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
7th costochondral joint	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Manubriosternal joint	2 (10.0)	1 (5.3)	0.579	0 (0.0)	0 (0.0)	NA	2 (10.0)	1 (5.3)	0.579	0 (0.0)	0 (0.0)	NA
Iliac crest	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Anterior superior iliac spine	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Ischial tuberosity	0 (0.0)	0 (0.0)	NA	3 (6.5)	3 (7.5)	0.859	0 (0.0)	0 (0.0)	NA	2 (8.7)	2 (10.0)	0.883
Pubic symphysis	2 (4.4)	0 (0.0)	0.177	0 (0.0)	0 (0.0)	NA	2 (9.1)	0 (0.0)	0.167	0 (0.0)	0 (0.0)	NA
Greater trochanter	0 (0.0)	2 (5.0)	0.125	26 (56.5)	23 (57.5)	0.927	0 (0.0)	2 (10.0)	0.120	15 (65.2)	13 (65.0)	0.988
Lateral femoral condyle	0 (0.0)	1 (2.8)	0.289	1 (2.5)	1 (2.9)	0.924	0 (0.0)	1 (6.3)	0.257	1 (5.0)	1 (6.7)	0.833
Medial femoral condyle	0 (0.0)	1 (2.8)	0.271	0 (0.0)	0 (0.0)	NA	0 (0.0)	1 (6.3)	0.245	0 (0.0)	0 (0.0)	NA
Lateral tibial plateau	0 (0.0)	0 (0.0)	NA	1 (2.3)	0 (0.0)	0.363	0 (0.0)	0 (0.0)	NA	1 (4.5)	0 (0.0)	0.387
Intercondylar notch	7 (16.3)	7 (19.4)	0.714	0 (0.0)	0 (0.0)	NA	5 (23.8)	5 (31.3)	0.614	0 (0.0)	0 (0.0)	NA
Patella ligament insertion into patella	4 (9.8)	4 (10.5)	0.910	8 (19.5)	7 (18.4)	0.902	2 (10.0)	2 (11.1)	0.911	6 (30.0)	4 (22.2)	0.587
Quadriceps tendon insertion into patella	0 (0.0)	0 (0.0)	NA	2 (4.8)	2 (5.6)	0.874	0 (0.0)	0 (0.0)	NA	2 (10.0)	2 (12.5)	0.813
Ankle joint attachments	2 (4.7)	2 (5.6)	0.874	0 (0.0)	0 (0.0)	NA	1 (5.0)	1 (5.6)	0.939	0 (0.0)	0 (0.0)	NA
1st Tarsometotarsal joint	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
1st Metatarsophalangeal joint	4 (10.5)	2 (5.9)	0.477	0 (0.0)	0 (0.0)	NA	3 (15.8)	1 (6.7)	0.412	0 (0.0)	0 (0.0)	NA
Achilles tendon insertion	0 (0.0)	0 (0.0)	NA	3 (6.5)	2 (5.3)	0.808	0 (0.0)	0 (0.0)	NA	2 (8.7)	1 (5.3)	0.667
Plantar fascia insertion at calcaneus	2 (4.3)	2 (5.1)	0.866	7 (15.2)	6 (15.4)	0.983	2 (8.7)	1 (5.3)	0.667	7 (30.4)	5 (26.3)	0.769

Table 7.6. Comparison of the frequency of readable BMO and STI lesions within field of view (FOV) at each enthesis between weeks 0 and 52.

At every time point, BMO was most associated with the larger entheses of the shoulders (supraspinate tendon insertion at humeral tuberosity and acromioclavicular joint), and non-existent in the chest (1st and 7th costochondral joints) and pelvis (ischial tuberosity, anterior superior iliac spine and iliac crest) (Figure 7.2). In contrast, STI was associated with the largest (and often weight-bearing) joints, especially the greater trochanter of the hip, knee (patella ligament insertion, quadriceps insertion), ankle (plantar aponeurosis insertion, Achilles tendon insertion) and shoulder (supraspinate tendon insertion) (Figure 7.3 and Figure 7.4).

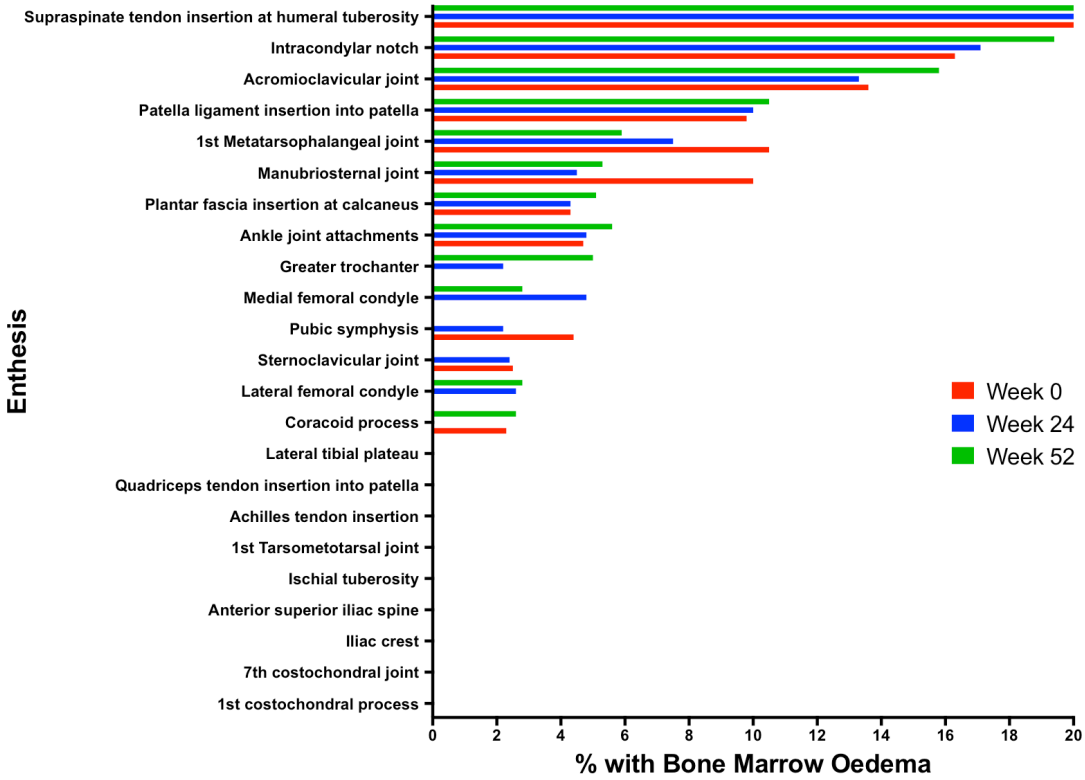


Figure 7.2. Comparison of the percentage frequency of entheses with bone marrow oedema (BMO) at each site with treatment over time.

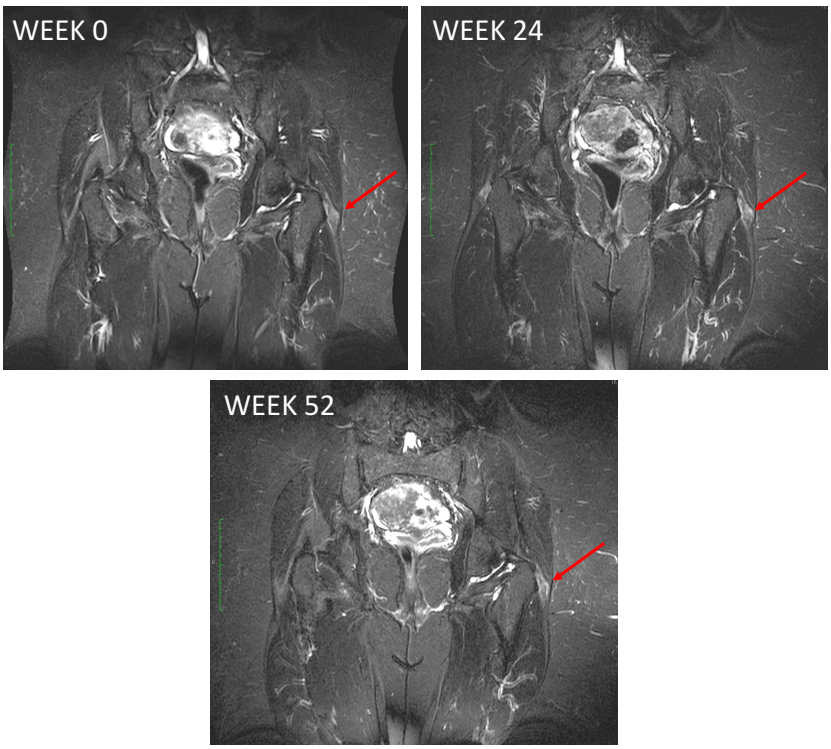


Figure 7.3. Coronal short τ inversion recovery (STIR) sequences showing persistence of grade 2 periarticular soft tissue inflammation surrounding the left greater trochanter during 52 weeks of ustekinumab therapy.

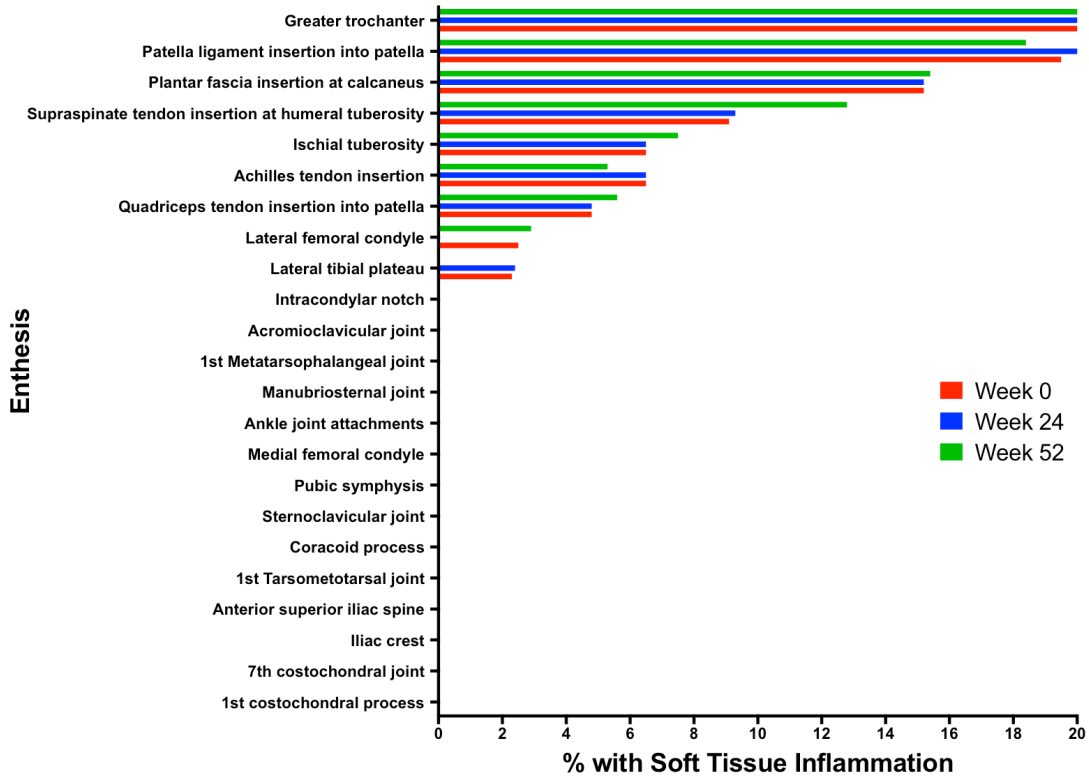
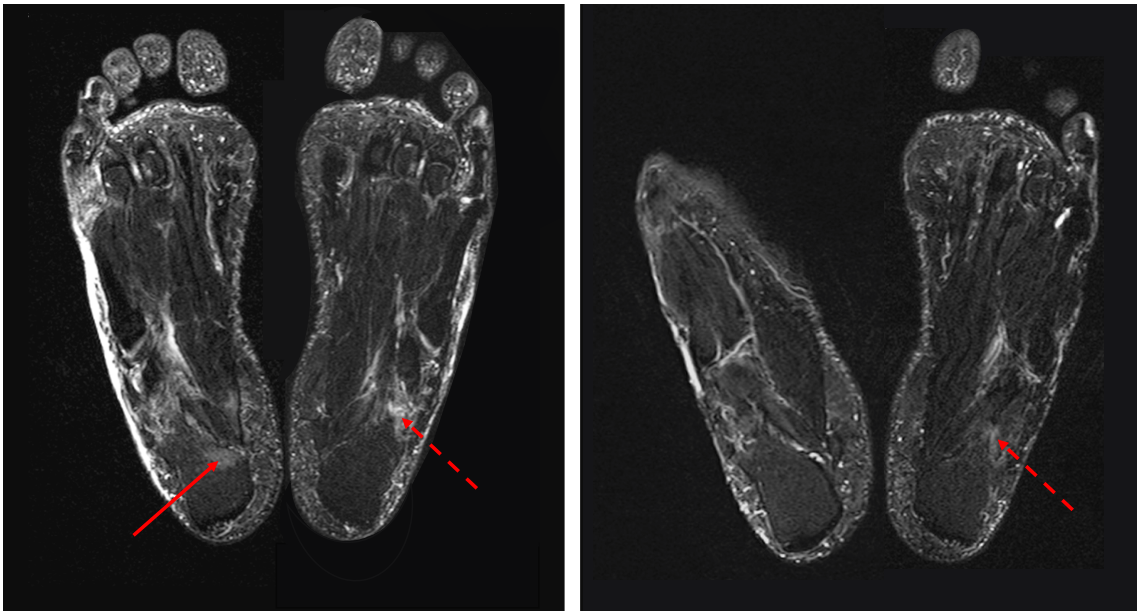


Figure 7.4. Comparison of the percentage frequency of entheses with bone marrow oedema (BMO) at each site with treatment over time.

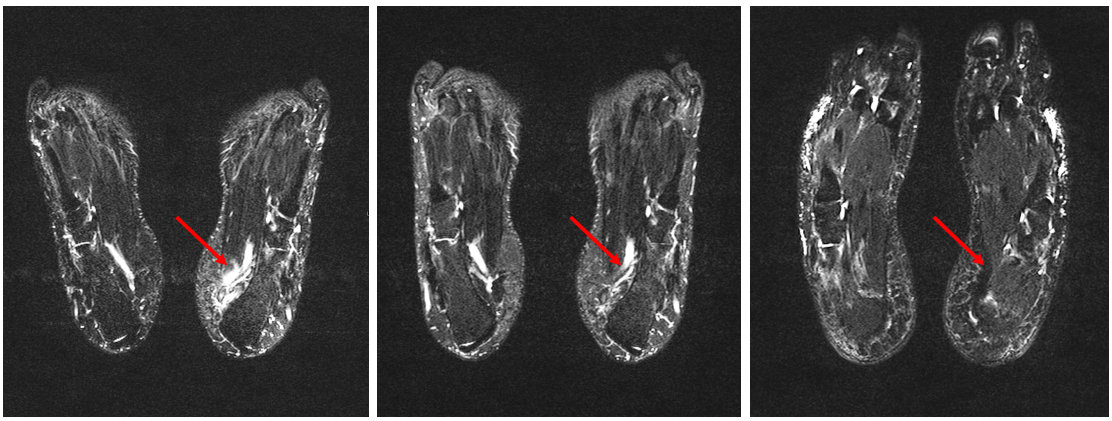
The majority of inflammatory abnormalities were minor (grade 1) throughout the study. At baseline, 4 BMO lesions were of moderate severity (grade 2) and one was severe (grade 3) (Figure 7.5). While the severe lesion improved, three new grade 2 lesions appeared by week 24, although these were all associated with trauma (football injury, sports training and post-femur fracture following an RTA). These persisted out to week 52.



Week 0 Week 52

Figure 7.5. Long axis short τ inversion recovery (STIR) sequences showing grade 3 bone marrow oedema (solid arrow) and grade 2 soft tissue inflammation (dashed arrow) surrounding the insertions of the right and left plantar fascia respectively at baseline, and resolution of bone marrow oedema and improvement in soft tissue inflammation (grade 1) at the same sites after 52 weeks of ustekinumab therapy.

There were five grade 2 STI lesions at week 0 and three grade 3 lesions. These lessened in severity over time, with only five grade 2 STI lesions (and no grade 3 lesions) seen at week 24, and only four grade 2 lesions seen at week 52 (Figure 7.6).



Week 0 Week 24 Week 52

Figure 7.6. Long axis short τ inversion recovery (STIR) sequences showing grade 3 inflammation in the soft tissues surrounding the insertion of the left plantar fascia into calcaneus at week 0, reducing in severity with ustekinumab therapy (grade 2 at week 24 and grade 1 at week 52).

Over time with ustekinumab therapy, new inflammatory lesions did develop, but with low frequency. Table 7.7 demonstrates the relatively static nature of BMO and STI lesions (in terms of severity) between weeks 0 and 24, and Table 7.8 shows that this trend continued out to week 52.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
BMO	All	5	1	900	2	6
	0			865		6
	1	4		32	2	
	2	1	0	3	0	
	3	0	1	0		
STI	All	0	3	909	0	2
	0			858		2
	1	0		46	0	
	2	0	0	5	0	
	3	0	3	0		

Table 7.7. Changes in the score assigned to individual enthesitis lesions between baseline and week 24, where enthesis was in FOV and readable at both time points. ‘New’ lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had ‘resolved’. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
BMO	All	6	1	772	4	7
	0			744		7
	1	5		25	4	
	2	1	0	3	0	
	3	0	1	0		
STI	All	2	3	781	0	4
	0			739		4
	1	2		38	0	
	2	0	0	4	0	
	3	0	3	0		

Table 7.8. Changes in the score assigned to individual enthesitis lesions between baseline and week 52, where enthesis was in FOV and readable at both time points. 'New' lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had 'resolved'. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Overall mean total scores for BMO and STI (both out of maximum of 135) were understandably low given the subclinical nature of musculoskeletal disease within this cohort, and remained low throughout the study. As shown in Figure 7.7, there was no significant change with treatment in BMO score between week 0 (mean score 2.13 ±2.12) and week 24 (2.30 ±2.40) (p=0.935), and between week 0 and week 52 (2.55 ±2.80) (p=0.623). Similarly, as shown in Figure 7.8, there was no significant alteration in STI score between week 0 (mean score 2.87 ±1.74) and week 24 (2.74 ±1.60) (p=0.257) and between week 0 and week 52 (2.70 ±1.56) (p=0.366).

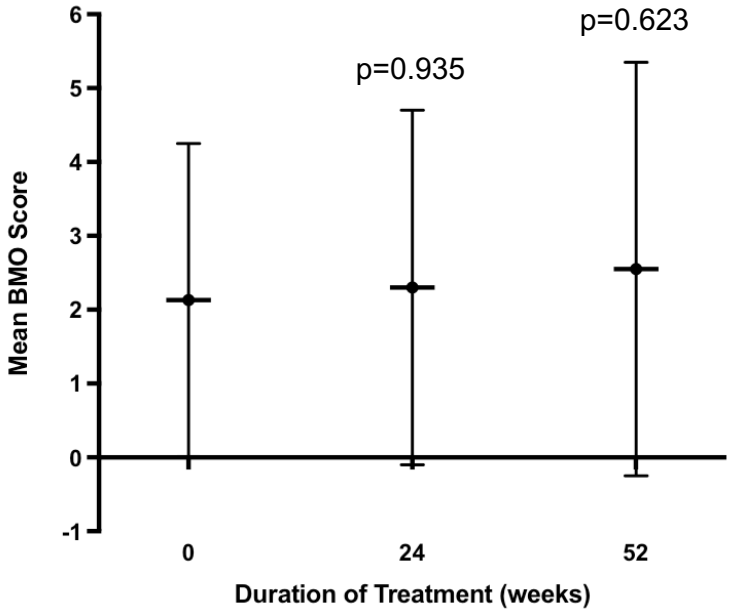


Figure 7.7. Mean (s.d.) overall BMO score at week 0 and after 24 and 52 weeks of ustekinumab therapy.

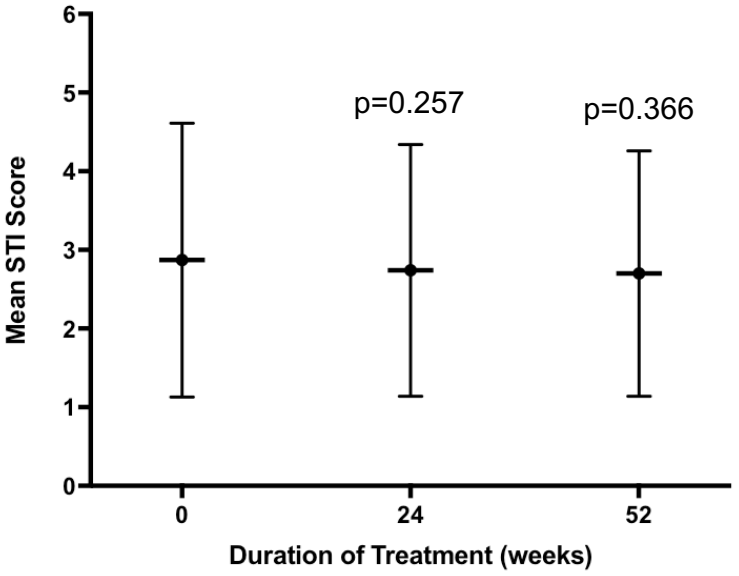


Figure 7.8. Mean (s.d.) overall STI score at week 0 and after 24 and 52 weeks of ustekinumab therapy.

7.4.6.1.2 Bursitis

Bursitis was assessed at 12 sites in each patient, at each time point. Bursitis was relatively common, with 17 of 23 (73.9%) patients having at least one area of bursitis at week 0, 17 of 23 (73.9%) at week 24 and 14 of 20 (70.0%) at week 52. In all patients, 49 of 272 (18.0%) bursae visualised (i.e. within FOV) exhibited inflammation prior to therapy at week 0. Despite ustekinumab therapy, there was little change in the burden of bursitis,

with 49 of 266 (18.4%) visible bursae showing features of inflammation at week 24, and 41 of 232 (17.7%) at week 52. Patients had between 0 and 5 areas of bursitis at each time point, with no significant change in the mean (±s.d.) number of lesions per patient between week 0 (2.26 ±1.66) and week 24 (2.57 ±1.81) (p=0.365), nor between week 0 and week 52 (2.45 ±1.79) (p=0.258).

Bursitis was seen at all anatomical sites assessed, but with greatest frequency (>54%) at the greater trochanteric bursae of the hips throughout the study (Figure 7.9). This is not an uncommon site for low grade bursitis in healthy individuals without psoriasis (Chapter 6), and it is therefore difficult to draw conclusions as to what extent these changes are pathological and what is within the accepted boundaries of normal physiology and aging. However, bursitis did frequently occur at sites of STI, which was present at a much lesser frequency in healthy individuals, supporting the concept of dissipation of inflammation throughout adjacent structures within the synovio-entheseal complex.

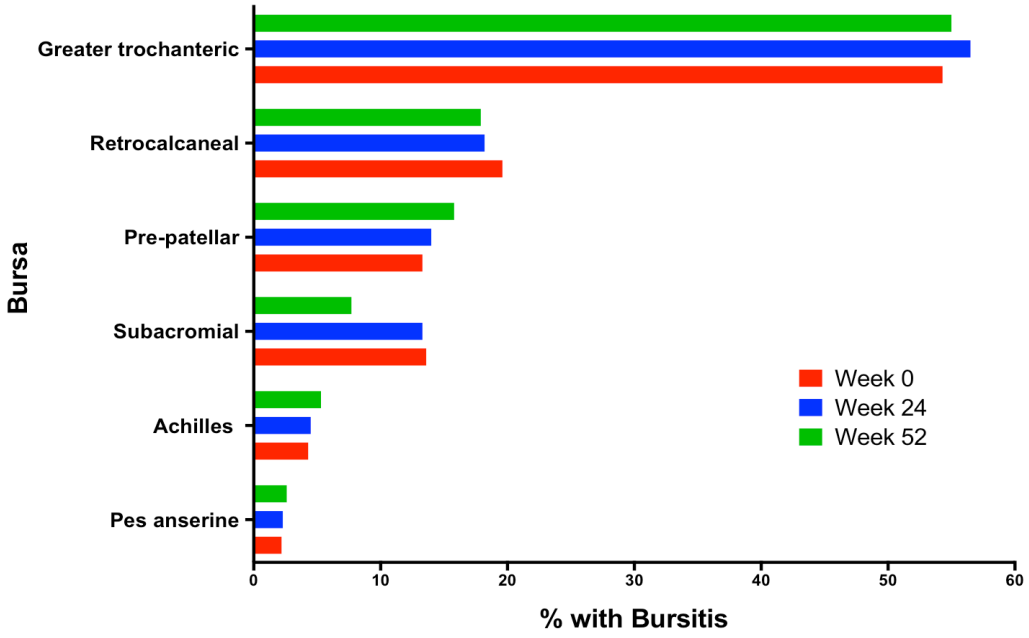


Figure 7.9. Comparison of percentage frequency of bursitis lesions at each site at each time point

No significant differences were seen in the percentage number of burseal lesions at any anatomical site from week 0 after 24 weeks (Table 7.9) and 52 weeks (Table 7.10) of ustekinumab treatment (all p>0.05).

	Burseal Level			Patient Level		
	No. of lesions (% of lesions within readable FOV)			No. of patients (% of patients with bursitis within readable FOV)		
	Week 0	Week 24	Group diff (p=)	Week 0	Week 24	Group diff (p=)
Subacromial bursae	6 (13.6)	6 (13.3)	0.967	4 (19.0)	4 (18.2)	0.928
Greater trochanteric bursae	25 (54.3)	26 (56.5)	0.834	14 (60.9)	14 (60.9)	1.000
Pre-patellar bursae	6 (13.3)	6 (14.0)	0.932	4 (18.2)	4 (19.0)	0.928
Pes anserine bursae	1 (2.2)	1 (2.3)	0.975	1 (4.3)	1 (4.5)	0.974
Achilles bursae	2 (4.3)	2 (4.5)	0.964	1 (4.3)	1 (4.5)	0.974
Retrocalcaneal bursae	9 (19.6)	8 (18.2)	0.867	6 (26.1)	6 (27.3)	0.897

Table 7.9. Comparison of the percentage frequency of readable bursitis lesions within FOV, in psoriasis patients at week 0 and after 24 weeks of therapy with ustekinumab. FOV: field of view.

	Burseal Level			Patient Level		
	No. of lesions (% of lesions within readable FOV)			No. of patients (% of patients with bursitis within readable FOV)		
	Week 0	Week 52	Group diff (p=)	Week 0	Week 52	Group diff (p=)
Subacromial bursae	6 (13.6)	3 (7.7)	0.385	4 (19.0)	2 (10.5)	0.639
Greater trochanteric bursae	25 (54.3)	22 (55.0)	0.952	14 (60.9)	12 (60.0)	0.954
Pre-patellar bursae	6 (13.3)	6 (15.8)	0.751	4 (18.2)	4 (22.2)	0.789
Pes anserine bursae	1 (2.2)	1 (2.6)	0.891	1 (4.3)	1 (5.3)	0.890
Achilles bursae	2 (4.3)	2 (5.3)	0.845	1 (4.3)	1 (5.3)	0.890
Retrocalcaneal bursae	9 (19.6)	7 (17.9)	0.849	6 (26.1)	5 (26.3)	0.983

Table 7.10. Comparison of the percentage frequency of readable bursitis lesions within FOV, in psoriasis patients at week 0 and after 52 weeks of therapy with ustekinumab. FOV: field of view.

Throughout the study, bursitis remained prevalent. The severity of bursitis was generally mild (grade 1), with less than 7% of all lesions being grade 2 (moderate), and the severity remained relatively unchanged with ustekinumab therapy. Few lesions resolved with treatment, but only one new area of bursitis developed by week 24 (Table 7.11) and no further new lesions or worsening of severity occurred by week 52 (Table 7.12). This suggests that progression of inflammation within the synovio-entheseal complex may have been limited, although histological analysis would be required to conclusively prove these observations.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Bursitis	All	1	0	258	0	1
	0			213		1
	1	1		45	0	
	2	0	0	3	0	
	3	0	0	0		

Table 7.11. Changes in the score assigned to individual bursitis lesions between baseline and week 24, where the bursa was in FOV and readable at both time points. 'New' lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had 'resolved'. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Bursitis	All	2	0	228	0	0
	0			187		0
	1	2		38	0	
	2	0	0	3	0	
	3	0	0	0		

Table 7.12. Changes in the score assigned to individual bursitis lesions between baseline and week 52, where the bursa was in FOV and readable at both time points. 'New' lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had 'resolved'. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Overall, mean bursitis scores (out of a possible maximum of 36) were low throughout the study, and as shown in Figure 7.10, there was no significant change with treatment in bursitis score between week 0 (mean score 2.26 $\pm$1.76) and week 24 (2.26 $\pm$1.71) (p=1.000), and between week 0 and week 52 (2.20 $\pm$1.82) (p=0.157).

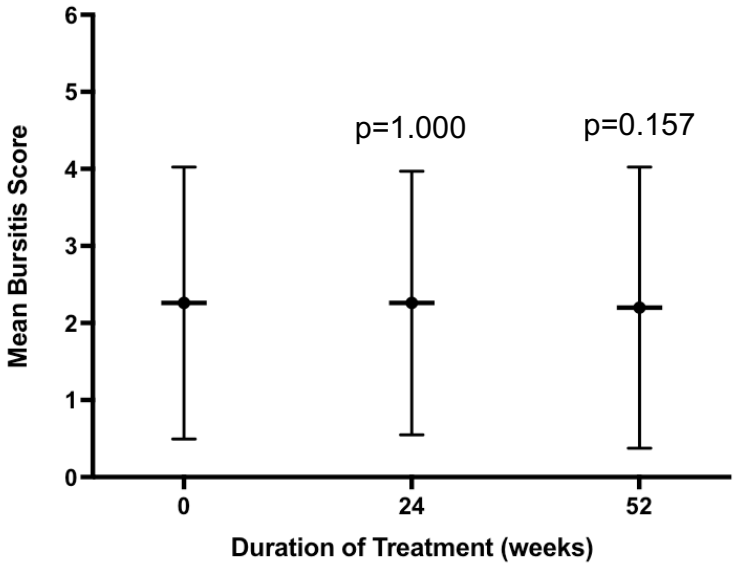


Figure 7.10. Mean (s.d.) overall bursitis score at week 0 and after 24 and 52 weeks of ustekinumab therapy.

7.4.6.1.3 Synovitis

An assessment of synovial joint fluid volume, as a surrogate marker of potential synovitis, was made at 16 joints in each patient at each time point. The presence of increased synovial fluid was common amongst all participants, with 21 of 23 (91.3%) patients having at least one area of increased fluid suggestive of inflammation at week 0 and at week 24, and 18 of 20 (90.0%) patients at week 52. Assessment of true synovial thickening was limited by the absence of contrast enhancement.

In patients with increased synovial fluid, the maximum number of lesions observed in any one patient was seven at every time point. No significant changes were observed between the mean (±s.d.) number of areas of synovitis per patient at week 0 (3.30 ±1.96) and week 24 (3.35 ±1.95) (p=0.982), nor between week 0 and week 52 (2.78 ±2.07) (p=0.678).

Synovitis was observed in all areas except for the tarsometatarsal joints, although the observed frequency was low in the metatarsophalangeal joints and in sternoclavicular joints at all time points (Figure 7.11).

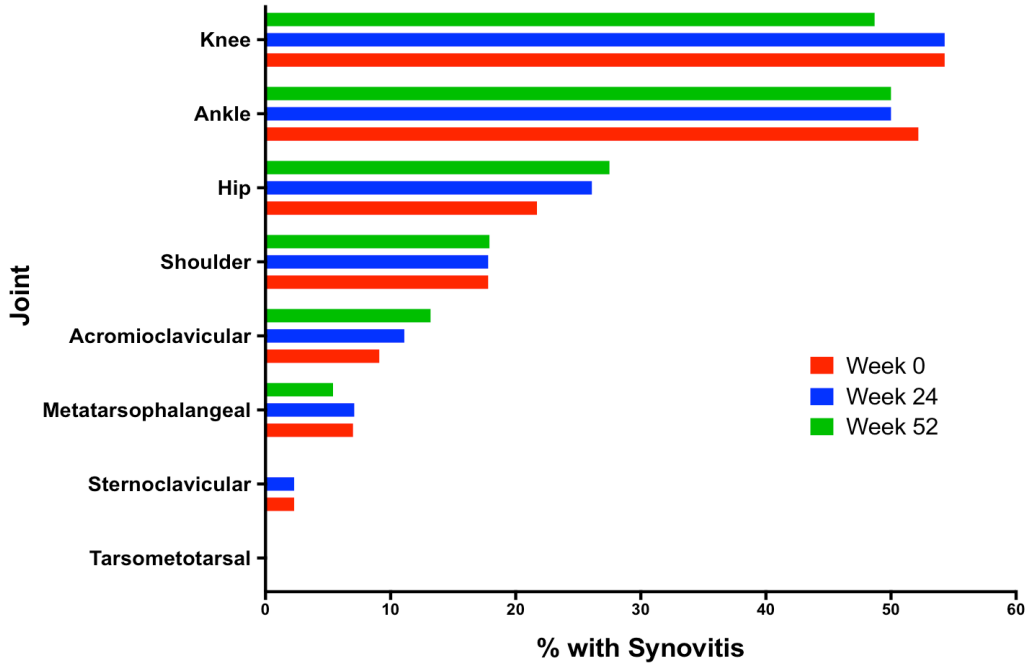


Figure 7.11. Comparison of percentage frequency of increased synovial volume at each site at each time point.

There were no significant differences in the percentage frequency of joints or patients with increased synovial fluid volumes at any site from week 0 after 24 weeks of treatment (Table 7.13) or 52 weeks of treatment (Table 7.14).

	Joint Level			Patient Level		
	No. of lesions (% of lesions within readable FOV)			No. of patients (% of patients with synovitis within readable FOV)		
	Week 0	Week 24	Group diff (p=)	Week 0	Week 24	Group diff (p=)
Sternoclavicular joints	1 (2.3)	1 (2.3)	1.000	1 (4.8)	1 (4.8)	1.000
Acromioclavicular joints	4 (9.1)	5 (11.1)	0.752	3 (14.3)	4 (18.2)	0.729
Shoulder joints	8 (17.8)	8 (17.8)	1.000	5 (22.7)	5 (22.7)	1.000
Hip joints	10 (21.7)	12 (26.1)	0.625	6 (26.1)	7 (30.4)	0.743
Knee joints	25 (54.3)	25 (54.3)	1.000	13 (56.5)	13 (56.5)	1.000
Ankle joints	24 (52.2)	23 (50.0)	0.835	13 (56.5)	13 (56.5)	1.000
Tarsometatarsal joints	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Metatarsophalangeal joints	3 (7.0)	3 (7.1)	0.976	2 (9.5)	2 (10.0)	0.959

Table 7.13. Comparison of the percentage frequency of readable synovitis lesions within FOV, in psoriasis patients at week 0 and after 24 weeks of therapy with ustekinumab. FOV: field of view.

	Joint Level			Patient Level		
	No. of lesions (% of lesions within readable FOV)			No. of patients (% of patients with synovitis within readable FOV)		
	Week 0	Week 52	Group diff (p=)	Week 0	Week 52	Group diff (p=)
Sternoclavicular joints	1 (2.3)	0 (0.0)	0.356	1 (4.8)	0 (0.0)	0.348
Acromioclavicular joints	4 (9.1)	5 (13.2)	0.557	3 (14.3)	4 (22.2)	0.520
Shoulder joints	8 (17.8)	7 (17.9)	0.984	5 (22.7)	5 (26.3)	0.790
Hip joints	10 (21.7)	11 (27.5)	0.535	6 (26.1)	6 (30.0)	0.775
Knee joints	25 (54.3)	19 (48.7)	0.605	13 (56.5)	10 (52.6)	0.801
Ankle joints	24 (52.2)	20 (50.0)	0.841	13 (56.5)	11 (55.0)	0.920
Tarsometatarsal joints	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Metatarsophalangeal joints	3 (7.0)	2 (5.4)	0.772	2 (9.5)	1 (5.6)	0.643

Table 7.14. Comparison of the percentage frequency of readable synovitis lesions within FOV, in psoriasis patients at week 0 and after 52 weeks of therapy with ustekinumab. FOV: field of view

All incidences of ‘synovitis’ documented at week 0 were grade 1, indicating only a mild increase in synovial fluid. As shown in Table 7.15 and Table 7.16, there was perceived worsening (grade 2) at one site in one patient at both weeks 24 and 52, and seven new lesions appeared on treatment (three by week 24 and four by week 52). Very few areas resolved throughout the study, which may indicate that the small increase in fluid documented was in fact within normal physiological limits, and assessment was inhibited by the lack of gadolinium contrast.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Synovitis	All	1	0	340	1	3
	0			267		3
	1	1		73	1	
	2	0	0	0	0	
	3	0	0	0		

Table 7.15. Changes in the score assigned to individual synovitis lesions between baseline and week 24, where the joint was in FOV and readable at both time points. ‘New’ lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had ‘resolved’. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Synovitis	All	4	0	292	1	4
	0			233		4
	1	4		59	1	
	2	0	0	0	0	
	3	0	0	0		

Table 7.16. Changes in the score assigned to individual synovitis lesions between baseline and week 52, where the joint was in FOV and readable at both time points. 'New' lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had 'resolved'. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

As shown for all other abnormalities (BMO, STI and bursitis), mean synovitis scores (out of possible maximum of 48) were low throughout (Figure 7.12) with virtually no change with treatment between week 0 (mean score 3.26 ±1.94) and week 24 (3.39 ±1.88) (*p*=0.180), and between week 0 and week 52 (3.30 ±1.92) (*p*=0.608).

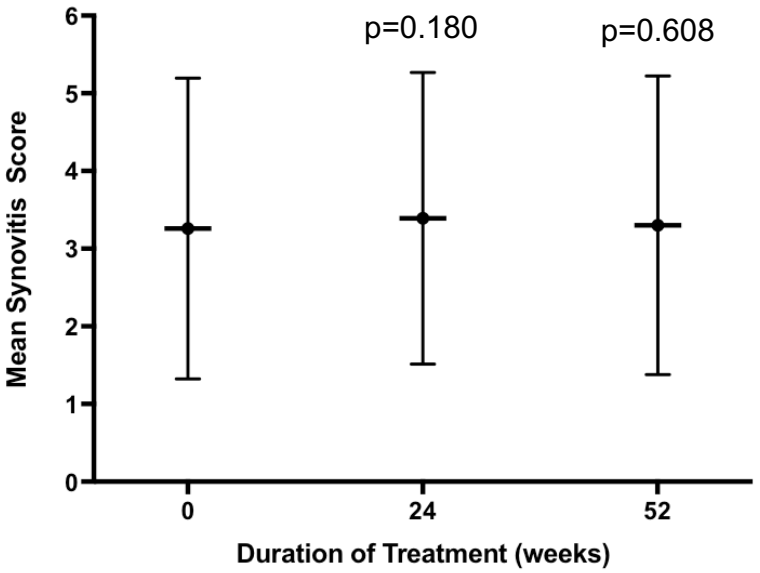


Figure 7.12. Mean (s.d.) overall synovitis score at week 0 and after 24 and 52 weeks of ustekinumab therapy.

7.4.6.1.4 Tenosynovitis

Tenosynovitis was assessed at four sites in each patient at each time point (medial and lateral tendons of the foot bilaterally). These serve as functional entheses, whereby these tendons run over bony surfaces and fibrocartilage on the under surfaces of the

tendons make contact with fibrocartilage on the underlying bone. It is hypothesised that these functional entheses have a similar tendency towards microdamage as true entheses in psoriatic arthritis, and in the absence of normal immune regulation, failure to repair can lead to persistent inflammation.

Tenosynovitis was uncommon in this cohort, affecting only 8.7% of lateral tendons and no medial tendons. With treatment, there was no change in the prevalence of lateral tenosynovitis by week 24 (Table 7.17) and a slight (but not significant) increase in lateral tenosynovitis by week 52 (Table 7.18).

	Tendon Level			Patient Level		
	No. of lesions (% of lesions within readable FOV)			No. of patients (% of patients with tenosynovitis within readable FOV)		
	Week 0	Week 24	Group diff. (p=)	Week 0	Week 24	Group diff. (p=)
Lateral tendons	4 (8.7)	4 (8.7)	1.000	2 (8.7)	2 (8.7)	1.000
Medial tendons	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA

Table 7.17. Comparison of the percentage frequency of readable tenosynovitis lesions within FOV, in psoriasis patients at week 0 and after 24 weeks of therapy with ustekinumab. FOV: field of view.

	Tendon Level			Patient Level		
	No. of lesions (% of lesions within readable FOV)			No. of patients (% of patients with tenosynovitis within readable FOV)		
	Week 0	Week 52	Group diff. (p=)	Week 0	Week 52	Group diff. (p=)
Lateral tendons	4 (8.7)	5 (12.5)	0.565	2 (8.7)	3 (15.0)	0.520
Medial tendons	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA

Table 7.18. Comparison of the percentage frequency of readable tenosynovitis lesions within FOV, in psoriasis patients at week 0 and after 52 weeks of therapy with ustekinumab. FOV: field of view.

As shown in Table 7.19, all lesions were mild (grade 1). Two lesions resolved after 52 weeks of treatment, although three new areas of mild tenosynovitis developed (Table 7.20).

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Tenosynovitis	All	0	0	92	0	0
	0			88		0
	1	0		4	0	
	2	0	0	0	0	
	3	0	0	0		

Table 7.19. Changes in the score assigned to individual tenosynovitis lesions between baseline and week 24, where the tendon was in FOV and readable at both time points. 'New' lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had 'resolved'. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Tenosynovitis	All	2	0	75	0	3
	0			73		3
	1	2		2	0	
	2	0	0	0	0	
	3	0	0	0		

Table 7.20. Changes in the score assigned to individual tenosynovitis lesions between baseline and week 52, where the tendon was in FOV and readable at both time points. 'New' lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had 'resolved'. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Mean tenosynovitis scores (out of possible maximum of 12) were very low throughout (Figure 7.13) with no change with treatment between week 0 (mean score 0.17 ±0.58) and week 24 (0.17 ±0.58) (p=1.000) and minimal deterioration between week 0 and week 52 (0.25 ±0.64) (p=0.785).

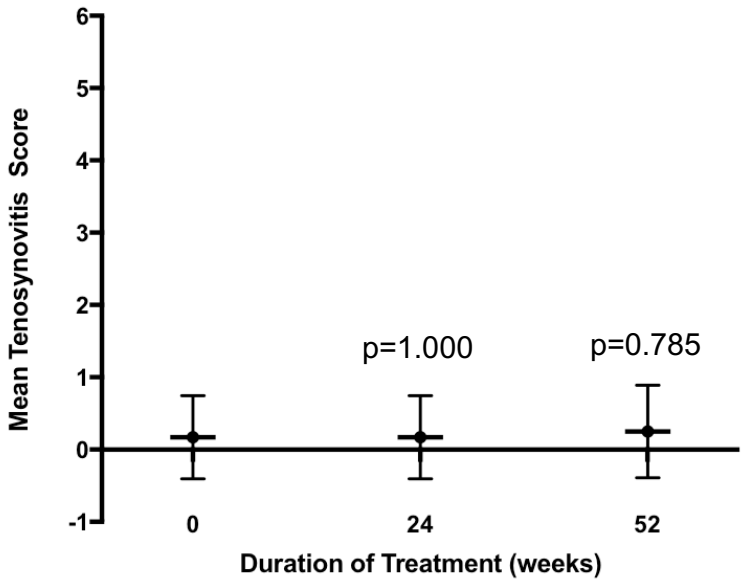


Figure 7.13. Mean (s.d.) overall tenosynovitis score at week 0 and after 24 and 52 weeks of ustekinumab therapy.

7.4.6.1.5 Structural Changes

Bone erosions (examined at four sites per patient) enthesophytes (examined at two sites per patient) were not identified at any locality at any stage throughout the study.

7.4.6.2 Axial Skeleton - Spine

7.4.6.2.1 Active Inflammation

In total, 15 of 23 patients (65.2%) of patients had at least one VU exhibiting active inflammation (BMO) within the spine at week 0, 14 of 23 patients (60.8%) after 24 weeks of ustekinumab therapy, and 13 of 20 patients (65.0%) after 52 weeks. The majority of abnormalities were found within the bone marrow of the vertebral corners, although in some more florid cases, BMO could be seen extending across the vertebral endplate (Figure 7.14).

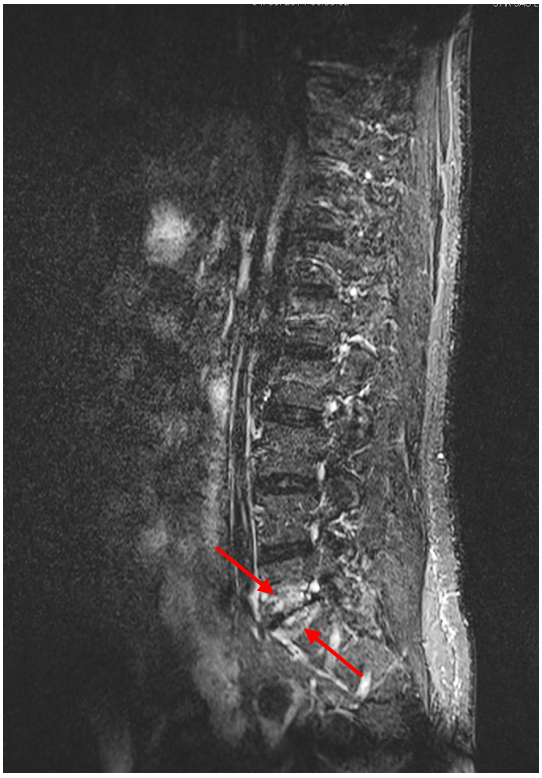


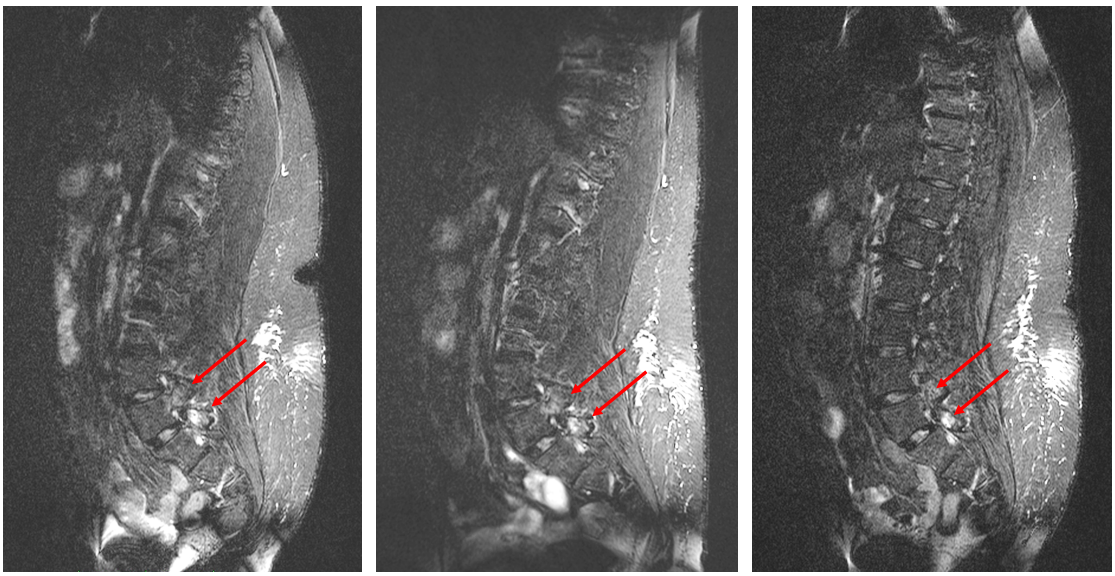
Figure 7.14. Saggital short τ inversion recovery (STIR) sequence showing vertebral endplate osteitis/BMO at L5/S1 (pre-treatment).

Of the 15 patients with spine BMO at week 0, 11 had BMO alone, and four showed BMO and structural changes. At week 24, 10 had BMO alone, and four had BMO and structural changes, and at week 52, 10 had BMO alone and three had BMO and structural changes. No individuals had isolated structural changes at any stage throughout the study.

Patients had between 0 and 6 BMO lesions each at week 0, the same at week 24, and between 0 and 5 lesions each at week 52. There were no significant differences in the mean number of lesions per patient at week 0 (1.43 ±1.75) and after 24 weeks of treatment with ustekinumab (1.39 ±1.88) (p=0.865), nor between week 0 and after 52 weeks of therapy (1.15 ±1.35) (p=0.270). Four patients at each time point had BMO lesions at three or more sites, which is highly suggestive of axial SpA (Hermann et al., 2012).

In terms of the location of BMO lesions, the majority were in the lumbar and lower thoracic spine at week 0 – L5/S1 (10/33 lesions), followed by L3/4 (4/33 lesions) and T8/9 (3/33 lesions).

Only one patient had active inflammation within the posterior elements (facet joints) at two sites (one area grade 1, one area grade 2), and this remained unchanged in severity from week 0 throughout treatment to week 52 (Figure 7.15).



Week 0 Week 24 Week 52

Figure 7.15. Saggital short τ inversion recovery (STIR) sequences showing grade 1 posterior element inflammation at L4 and L5, remain unchanged with ustekinumab treatment over 52 weeks.

The majority of abnormalities identified throughout the study were low grade. In total, 33 active inflammatory lesions were identified within all VUs assessed at baseline (grade 1: 24/33; grade 2: 8/33; grade 3: 1/33). At week 24, a total of 32 BMO lesions were identified (grade 1: 21/32; grade 2: 10/32; grade 3: 1/33) and at week 52, a total of 23 lesions were scored (grade 1: 16/23; grade 2: 6/23; grade 3: 1/23).

As a consequence, total scores for spine BMO were low. Spine BMO scores ranged from 0-9 (out of a possible maximum of 69) at week 0, with a mean (±s.d.) of 1.87±2.24. There was no significant change by week 24, with BMO scores ranging from 0-9 and a mean score of 1.91 ±2.64 (p=0.656). Similarly, at week 52, scores ranged from 0-8, with no significant change in mean BMO score (1.55 ±2.01) from week 0 (p=0.627) (Figure 7.16).

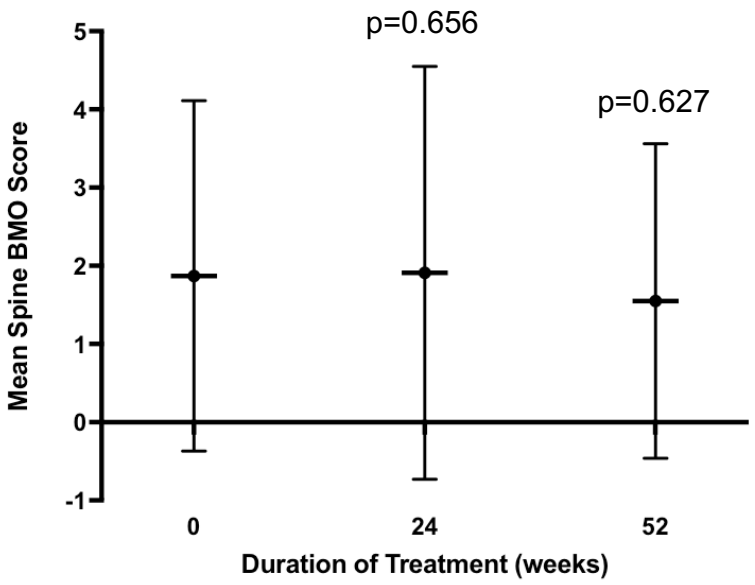


Figure 7.16. Mean (s.d.) overall spine BMO scores at week 0 and after 24 and 52 weeks of ustekinumab therapy.

The majority of lesions did not change in severity throughout the study, as shown in Table 7.21 and Table 7.22.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Bone Marrow Oedema	All	3	1	519	4	2
	0			494		2
	1	2		18	4	
	2	1	1	6	0	
	3	0	0	1		
Posterior Element Inflammation	All	0	0	529	0	0
	0			527		0
	1	0		1	0	
	2	0	0	1	0	
	3	0	0	0		

Table 7.21. Changes in the score assigned to individual spine vertebral body BMO lesions and spine posterior element inflammatory lesions between baseline and week 24. ‘New’ lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had ‘resolved’. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Bone Marrow Oedema	All	3	5	446	4	2
	0			432		2
	1	5		12	3	
	2	0	2	2	1	
	3	0	1	0		
Posterior Element Inflammation	All	0	0	460	0	0
	0			458		0
	1	0		1	0	
	2	0	0	1	0	
	3	0	0	0		

Table 7.22. Changes in the score assigned to individual spine vertebral body BMO lesions and spine posterior element inflammatory lesions between baseline and week 52. ‘New’ lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had ‘resolved’. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Despite the overall trend to no therapeutic response, there were cases where spine BMO appeared to improve significantly with ustekinumab therapy. These were cases where BMO was graded as moderate or severe at week 0, as shown in Figure 7.17. BMO can be seen extending from the corners to encompass the C5 inferior end plate (grade 3) and C6 superior end plate (grade 2) at week 0 and 24, and has reduced in severity (grade 1) after 52 weeks of ustekinumab therapy. Where deterioration occurred, it was generally subtle, from grade 0 to 1, or grade 1 to 2, as shown in Figure 7.18.

Week 0 Week 24 Week 52

Figure 7.17. Saggital T1w WBMRI sequences of the upper spine showing resolution of C5 inferior endplate BMO (grade 3 at weeks 0 and 24) and C6 superior end plate BMO (grade 2 weeks 0 and 24) with ustekinumab therapy for 52 weeks.

Week 0 Week 24 Week 52

Figure 7.18. Saggital T1w WBMRI sequences of the upper spine showing deterioration of L1 anterior superior corner BMO from grade 1 (at weeks 0 and 24) to grade 2 (at week 52) with ustekinumab therapy.

7.4.6.2.2 Structural Changes

Fatty infiltration of the bone marrow was an uncommon finding, with only four of 23 patients exhibiting low grade non-inflammatory changes at week 0 and 24, and three of 20 patients at week 52. In each instance, less than 50% of the vertebral body was affected, and fatty infiltration was localised to the corners, representative of the 'fatty romanus lesion' as described by Bennett et al, a diagnostic lesion specific for ax-SpA (Bennett et al., 2010). Only one patient had more than one corner lesion at week 0, and these five lesions persisted throughout the study, as shown in Figure 7.19. Saggital T1w WBMRI sequence of the lower spine showing persistence of vertebral corner fatty infiltration (Romanus lesions) in two difference slices at T6/7, T7/8, T9/10, T11/12 and L3/4, at weeks 0, 24 and 52.

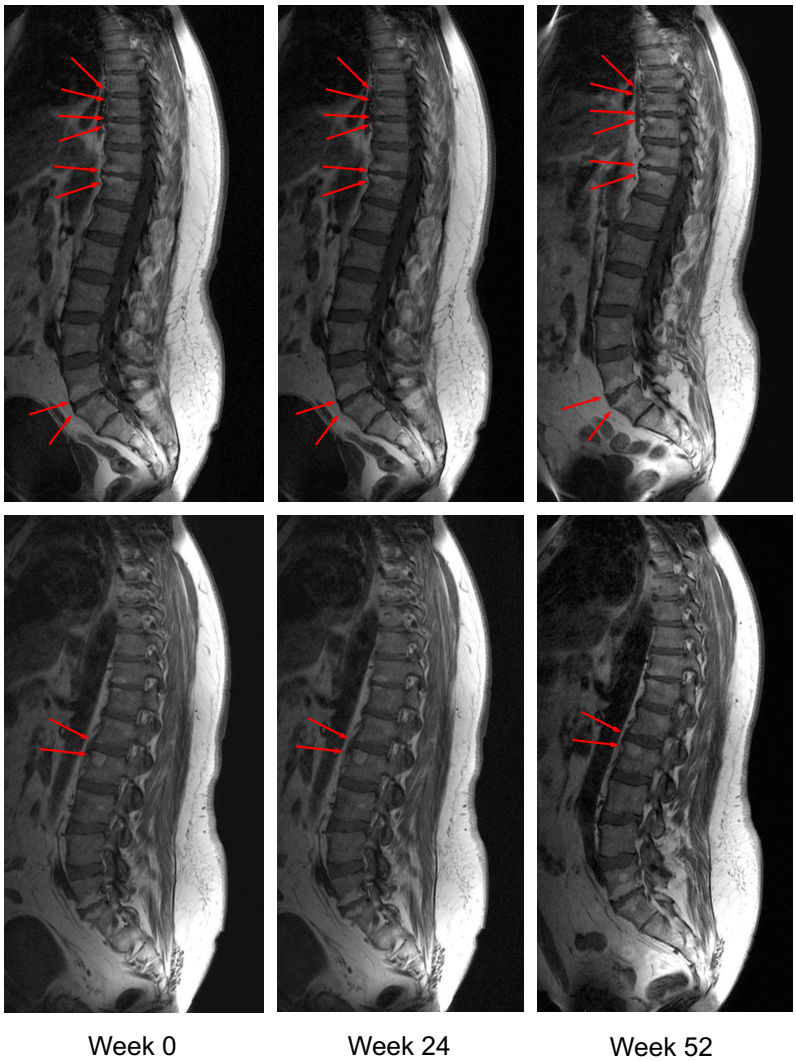


Figure 7.19. Saggital T1w WBMRI sequence of the lower spine showing persistence of vertebral corner fatty infiltration (Romanus lesions) in two difference slices at T6/7, T7/8, T9/10, T11/12 and L3/4, at weeks 0, 24 and 52.

There was no pattern to the distribution of lesions seen in the four patients with fatty bone marrow infiltration. In patients with only one fatty vertebral corner lesion, inflammation was also present in the form of BMO. In the patient with five lesions, no BMO was seen, perhaps suggesting a longer duration of spinal disease resulting in fatty replacement of bone marrow and resolution of the inflammatory insult, as is seen in ax-SpA of more prolonged duration (Bennett et al., 2010). No sclerotic bone formation or erosions were seen in any patient throughout the study.

All fatty infiltration lesions were mild (grade 1), with the exception of one lesion in one patient, that persisted as grade 2 throughout, despite ustekinumab therapy. The static nature of observed fatty infiltration lesions at each time point is shown in Table 7.23 and Table 7.24.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Fatty Infiltration	All	0	0	529	0	0
	0			521		0
	1	0		7	0	
	2	0	0	1	0	
	3	0	0	0		

Table 7.23. Changes in the score assigned to individual spine fatty infiltration lesions between baseline and week 24. ‘New’ lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had ‘resolved’. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Fatty Infiltration	All	0	0	460	0	0
	0			453		0
	1	0		6	0	
	2	0	0	1	0	
	3	0	0	0		

Table 7.24. Changes in the score assigned to individual spine fatty infiltration lesions between baseline and week 24. ‘New’ lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had ‘resolved’. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Overall fatty infiltration scores ranged from 0-5 (out of a possible maximum of 69) at each time point. As shown in Figure 7.20, there were no significant changes in mean spine bone marrow fatty infiltration scores between week 0 (mean score 0.39 ±1.12) and week 24 (0.39 ±1.12) (*p*=1.000), or week 0 and week 52 (0.40 ±1.89) (*p*= 0.978).

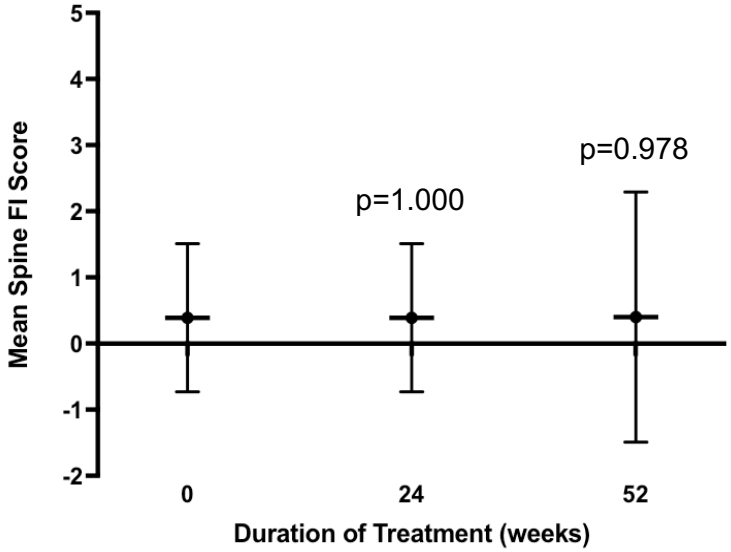


Figure 7.20. Mean (s.d.) overall spine fatty infiltration (FI) scores at week 0 and after 24 and 52 weeks of ustekinumab therapy.

There were no erosions or syndesmophytes seen in the spine in any patient throughout the study.

7.4.6.3 Axial Skeleton - Sacroiliac Joints

7.4.6.3.1 Active Inflammation

In total, 3 of 23 patients (17.4%) had at least one area of active inflammation within the SIJs at weeks 0 and 24, and 2 of 20 patients (10.0%) at week 52. One new lesion appeared in one patient at week 52, and two patients with BMO at weeks and 24 were lost to follow up by week 52. Patients had between 0 and 3 lesions each at weeks 0 and 24, and 0 and 1 lesion at week 52. Lesions were distributed throughout the SIJs (upper sacrum, upper ilium and lower ilium).

Overall, only six areas of BMO were identified in total (out of possible 184) at weeks 0 and 24, and all were grade 1 with the exception of one area (right upper sacrum) in one patient that worsened (grade 2) (Figure 7.21).

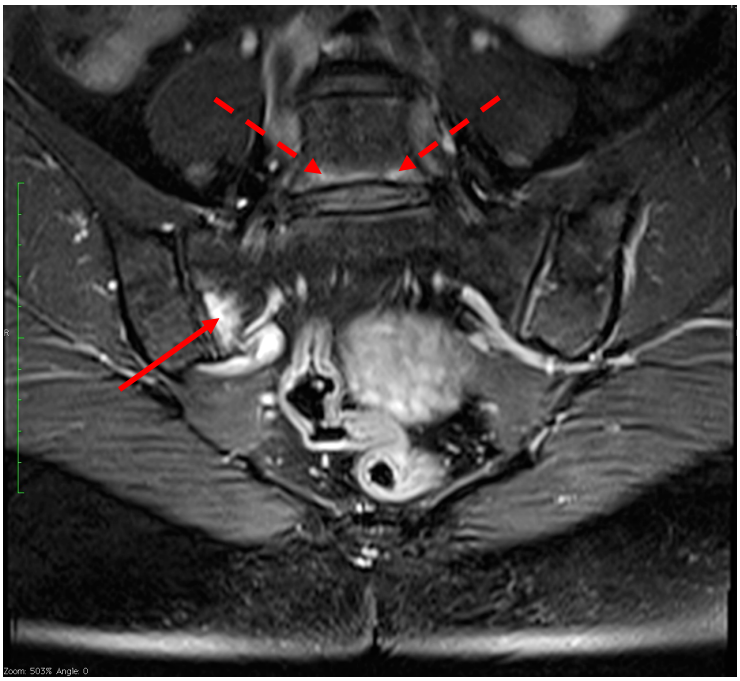


Figure 7.21. Coronal oblique T2w fat saturated sequence of the sacroiliac joints showing BMO within right sacrum (solid arrow) in one of three patients identified with SIJ BMO at week 0. BMO is also seen in the inferior corners of the L5 vertebrae (dashed arrows).

At week 52, only two areas of BMO (out of a possible 160) were identified. One area persisted in one patient from week 0 and one new area appeared in a different patient who did not have SIJ BMO at weeks 0 or 24. Two patients with BMO at weeks 0 and 24 were lost to follow up by week 52, which accounts for the reduction in lesions rather than being due to resolution on treatment.

Table 7.25 and Table 7.26 demonstrate the static nature of lesions between weeks 0 and 24, and weeks 0 and 52, respectively.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Bone Marrow Oedema	All	0	0	183	1	0
	0			178		0
	1	0		5	1	
	2	0	0	0	0	
	3	0	0	0		

Table 7.25. Changes in the score assigned to individual SIJ BMO lesions between baseline and week 24. ‘New’ lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had ‘resolved’. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
Bone Marrow Oedema	All	2	0	157	0	1
	0			156		1
	1	2		1	0	
	2	0	0	0	0	
	3	0	0	0		

Table 7.26. Changes in the score assigned to individual SIJ BMO lesions between baseline and week 52. 'New' lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had 'resolved'. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

Overall mean SIJ BMO scores were 0.26 ±0.75 at week 0, 0.30 ±0.88 at week 24 and 0.10 ±0.308. Statistical comparisons are not made as the numbers involved are inadequate, and compounded by two of three patients with BMO at week 0 being lost to follow up.

7.4.6.3.2 Structural Changes

Structural changes within the SIJs were rare, with no identifiable areas of fatty bone marrow infiltration, ankyloses or sclerosis seen in any patient throughout the study. Erosions were seen in two patients (lower ilium bilaterally in both, grade 1) at week 0, and remained unchanged despite treatment. No new erosions developed in any patient (Table 7.27). Overall mean erosion scores were 0.09 ±0.42 at each time point.

Abnormality scores	Score at baseline	Resolved	Improved	Unchanged	Worse	New
	All	0	0	2	0	0
	0			0		0
	1	0		2	0	
	2	0	0	0	0	
	3	0	0	0		

Table 7.27. Changes in the score assigned to individual SIJ erosions between baseline and week 24, and also between week 0 and week 52. 'New' lesions were those that scored 0 at baseline and >0 at follow-up. Conversely those that scored >0 at baseline and 0 at follow-up had 'resolved'. Scores of 1 or 2 could have worsened at follow-up, whilst scores of 2 or 3 could have improved.

7.5 Discussion

The results of this prospective, open-label, single-arm, proof-of-concept trial show that in asymptomatic patients with moderate to severe psoriasis, with a low burden of osteitis in both the peripheral and axial skeleton, no significant change is observed in inflammatory or chronic lesions following skin-directed treatment with ustekinumab for up to 52 weeks.

This is the first trial to use WBMRI to investigate the musculoskeletal response of any biologic therapy in patients with psoriasis and subclinical enthesopathy. There are no published data of the use of WBMRI to assess therapeutic response in established psoriatic arthritis (PsA) for comparison. Appel et al first reported the use of WBMRI to assess the response of widespread inflammatory lesions to Infliximab in one patient with established ankylosing spondylitis (AS) (BASDAI 7.5) after one year, and reported 'tremendous improvement' in both the axial and peripheral skeleton (Appel et al., 2007). Following this, three small published studies have used WBMRI to assess the response to biologic therapies in symptomatic patients with axial spondyloarthritis (ax-SpA) and AS, two using etanercept (Karpitschka et al., 2013, Song et al., 2011a, Song et al., 2011b, Song et al., 2015, Althoff et al., 2016) and one using ustekinumab (Poddubnyy et al., 2013, Poddubnyy et al., 2014a, Poddubnyy et al., 2014b). Change in WBMRI osteitis score was the primary endpoint of all studies with the exception of one, which reported WBMRI data as a secondary endpoint, with ASAS40 response as the primary outcome (Poddubnyy et al., 2014b).

Reflecting the fact that all published data relates to patients with axial spondyloarthritis, WBMRI assessments have focused primarily on the spine and SIJs. However, in two studies, peripheral skeleton data has been reported alongside data from the axial skeleton (Althoff et al., 2016, Karpitschka et al., 2013). Althoff and colleagues treated 41 patients with early ax-SpA with etanercept for up to three years, and WBMRI included the assessment of 21 sites bilaterally including the anterior chest wall, pelvis, knee and foot. The pre-treatment frequency of peripheral inflammatory lesions was slightly lower than in this study (2.6% entheses (in 9 of 41 patients) vs. 4.5% entheses), although this is to be expected given that patients had ax-SpA rather than a more predominantly peripheral pattern of spondyloarthropathy such as PsA. With treatment, peripheral enthesitis reduced by 31.8%, affecting just five patients with 0.8% of entheses reported as showing inflammation after 2 years of continuous treatment (Althoff et al., 2016). These data support the ultrasound, but not WBMRI findings from patients in this cohort of psoriasis patients, where a 42.1% decrease in the number of peripheral entheses with inflammatory abnormalities was observed after 24 weeks of ustekinumab therapy (Chapter 5.4.5.1.3.).

Further improvement is shown in a small prospective study of ten patients with established AS. Karpitschka and colleagues examined the entheses and synovio-entheseal complex surrounding the pubic symphysis, pelvis and hip (e.g. enthesitis ossis ischia, trochanteric bursitis), in addition to the synovium of the knee and upper ankle joints (synovitis) using WBMRI. Half of patients exhibited peripheral inflammatory lesions (pubic symphysis enthesitis: 3/10; right ischium enthesitis, 1/10; bilateral hip bursitis: 3/10; unilateral ankle synovitis: 1/10) before treatment. Again, using etanercept, peripheral inflammation lesion scores reduced by 60.6% by week 26, and 93.9% by week 52 (Karpitschka et al., 2013).

The response of peripheral psoriatic arthritis specifically to biologic therapy has only been assessed using conventional MRI and no data are published relating to ustekinumab or other non-TNF inhibitors. Most studies have used the PsAMRIS method to score images of the hands, which were not included in our MRI protocol, although responses at the knee (Anandarajah et al., 2010, Marzo-Ortega et al., 2007, Marzo-Ortega et al., 2001), foot (Yanaba et al., 2015) and hips (Marzo-Ortega et al., 2001) have been reported.

In contrast to the findings in this study, favourable improvements in inflammatory entheseal lesions have been observed in all other published studies and case series following biologic therapy, but these studies only included patients with known inflammatory arthritis. No data are available for subclinical inflammation. Following six months of etanercept, improvement in enthesitis and osteitis was observed at the knee, hips and hands of five patients with PsA (mean disease duration 12 years) (Marzo-Ortega et al., 2001). Yanaba and colleagues describe clearance of BMO and STI in the hands and feet of four patients with PsA (mean disease duration 12.0 $\pm$7.7 years) following 32 weeks of continuous adalimumab therapy. Tenosynovitis responded less well, with complete clearance in two, an improvement in one and no change in the fourth. Bone erosions remained unchanged as seen in this study (Yanaba et al., 2015).

Anandarajah et al reported the effect of adalimumab on BMO, synovitis, joint effusion and erosions detected by MRI at the knee and wrist in 11 PsA patients (mean disease duration 5.9 years) after 24 weeks of therapy. BMO and effusion scores improved markedly (by 65% and 44%, respectively). Tenosynovitis scores, which remained unchanged in this study, decreased by 12% with adalimumab. No changes were observed in erosion scores, and in further similarity to this study, there was a lack of meaningful improvement in mean synovitis score (3% decrease) (Anandarajah et al., 2010).

Synovitis also remained problematic in the hands and feet of five patients treated with adalimumab for 32 weeks, with an increase in scores in two of five patients, no change in one patient and a reduction in two patients (Yanaba et al., 2015). However, discrepancy exists with the findings of Marzo-Ortega and colleagues in two studies. In

the first, synovitis was observed in the knee joints of three patients and following six months of etanercept therapy, a ‘marked improvement ‘was seen in all patients (Marzo-Ortega et al., 2001). The reduction in synovitis scores was quantified in the second study, where a 37.8% to 91.9% decrease was observed in the knees of four patients treated with infliximab for 20 weeks. In this cohort, two patients had BMO at the knee, of which one resolved and one remained unchanged (Marzo-Ortega et al., 2007).

Only one longitudinal study has assessed damage progression in patients with PsA treated with biologic therapy, using conventional MRI of the hands. MRI signs of inflammation were found to decrease, but not disappear during adalimumab therapy, but as seen in this study (and the others described above), no overall changes in bone erosions or proliferations were observed after 48 weeks of treatment (Poggenborg et al., 2014c).

In similar contrast to the findings in this chapter, published data have also shown encouraging improvements in active inflammation in the axial skeleton with biologic therapy using WBMRI, but again, these data are for patients with established inflammatory arthritis. In patients with AS, a significant reduction in osteitis (using the Berlin Scoring Method) was observed after 24 weeks of ustekinumab therapy as compared with baseline in both the SIJs (BMO change score -2.2 ±3.8, corresponding to a 41% reduction from 5.4 ±4.9) and spine (-1.2 ±2.3 corresponding to a 31% reduction from 4.1 ±3.6), with even greater improvements seen in those who responded better clinically (Poddubnyy et al., 2014b, Poddubnyy et al., 2013). In contrast, in this study, increases in spine BMO score (2.1% increase from 1.87 ±2.24) and SIJ BMO score (15.4% increase from 0.26 ±0.75) were observed after 24 weeks of ustekinumab therapy, although these changes failed to reach statistical significance. Interestingly, the manufacturers of ustekinumab (Janssen Pharmaceuticals) have terminated a phase III, multicentre, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of ustekinumab in the treatment of patients with active non-radiographic axial spondyloarthritis (ClinicalTrials.gov identifier NCT02407223) because ustekinumab did not achieve key endpoints in a related study, although no data is published to clarify if patients worsened. The safety profile was reported to be consistent with past ustekinumab studies.

Further explanation for the trends observed in this chapter in the spine and SIJs may be that due to the comparatively very low mean osteitis scores in patients with subclinical disease (as oppose to patients with symptomatic AS), overall mean scores could be disproportionately influenced by any new positive finding or changes, and this is compounded by the difficulty in interpreting very subtle abnormalities on WBMRI which may or may not be truly pathological. In addition, as shown by Song et al, osteitis can fluctuate in severity, with up to 5% of axial BMO lesions resolving intermittently but returning in their cohort (Song et al., 2015). This could have a significant influence on

low overall mean scores depending on at what stage the WBMRI is performed within a study.

Improvements in spine and SIJ active inflammation scores have been achieved through the use of TNF inhibitors, namely etanercept, and reflect those improvements seen in the peripheral skeleton (Karpitschka et al., 2013, Song et al., 2011a, Song et al., 2015). Karpitschka et al observed a striking improvement from baseline in osteitis scores both in the spine and SIJs, with almost complete clearance of inflammation (93.6% (spine) and 100% (SIJs) reduction) in ten patients with early AS (mean baseline BASDAI 5.5) treated for 52 weeks. Patients were permitted to continue DMARD therapy or prednisolone (>7.5mg/day) throughout the study which may have influenced this outcome (Karpitschka et al., 2013). In contrast, these concomitant treatments had to be discontinued at least four weeks prior to participation in the ESTHER trial (Song et al., 2011a, Song et al., 2015). This may, in part, explain why the results at the end of week 48, although impressive, are not as substantial as those from Karpitschka and colleagues. At baseline, mean SIJ osteitis scores (assessed using the Berlin Scoring Method) were 7.8 ±6.3 (out of a possible maximum of 24) and reduced with treatment by 69.2% to 2.4 ±3.2, and mean spine osteitis scores (out of a possible maximum of 6) reduced by 56.5% from 2.3 ±3.5 to 1.0 ±2.1 (Song et al., 2011a). Of the 76 patients reported at week 48, 41 patients remained on treatment and were followed up at the end of year two and three. In this cohort, the reduction in mean SIJ osteitis score was maintained, with a 71.8% reduction (to 2.0 ±2.2) and 69.0% reduction (to 2.2 ±2.5) from baseline after two and three years of therapy respectively. Mean spine osteitis score reduction was also maintained, with a 58.8% reduction (to 0.7 ±1.4) at the end of year two and 47.1% reduction (0.9 ±1.8) at the end of year three (Song et al., 2015).

One positive finding from this investigation was the low rates of new BMO appearing during treatment. In the peripheral skeleton, only seven new areas of osteitis had developed over 52 weeks (0.9%), and two areas worsened (out of a total number of 790 lesions observed at week 52). In the axial skeleton, two areas of osteitis had developed over 52 weeks (0.4%), and four areas worsened (out of a total number of 450 lesions observed at week 52). Similarly, very low rates of new-onset osteitis were also observed during three years of continuous treatment with etanercept in the ESTHER trial (Song et al., 2015). The development of new osteitis in sites that were free of osteitis at baseline only occurred in 1.5% SIJ quadrants and in 0.4% of spine VUs in both year two and three. In another study, using conventional MRI, patients with very early ax-SpA (disease duration <3 years) were treated with infliximab versus placebo for 16 weeks (Barkham et al., 2009). Although the duration of treatment was much shorter, the low rate of new development of osteitis (3.8%) was similar to that of this study and data from Song et al (Song et al., 2015). Interestingly, the spontaneous rate of new BMO development in the placebo group was reported at 12%. These observations support the concept that early

introduction of biologic therapy in patients with (or destined to develop) spondyloarthritis could prevent the development and/or progression of inflammatory arthritis.

Inflammation in the posterior segment and facet joints of the spine is a recognised feature of axial spondyloarthritis, including in patients with psoriatic arthritis. In this cohort, posterior element inflammation was minimal, seen in the facet joints of only one patient (4.3%) at two sites which persisted, unchanged in severity, despite treatment. This is less than the findings reported in other WBMRI studies, but is expected given the primacy of enthesitis in this cohort compared to those including patients with early, but symptomatic ax-SpA of up to 5 years duration. For example, Karpitschka and colleagues found a mean of 2.4 ±1.5 facet joint inflammatory lesions per patient (mean BASADI 5.5) at baseline, and like VU osteitis, these decreased significantly after 52 weeks of etanercept therapy (0.2 ±0.2) (Karpitschka et al., 2013), In the ESTHER trial (mean BASDAI 5.5), 17.1% of patients had at least one site at baseline, compared to just 5% after 48 weeks of etanercept (Song et al., 2011a). Given the almost complete absence of posterior element inflammation in patients within this cohort, it is not possible to determine if the effects of ustekinumab are the same as those seen with etanercept in patients with more advance spondyloarthritis, although it is reassuring to not observe the development of any new facet joint inflammation during the study, which clearly develop as a later phenomenon in ax-SpA.

A common pathophysiological development in ax-SpA is that the initial osteitis is followed by fatty replacement of the bone marrow, and subsequently new bone formation. It is therefore thought that ‘fatty corners’ (fatty Romanus lesions) represent the post inflammatory phase of SpA, and are a relatively permanent phenomenon once developed (Bennett et al., 2010). In a cohort of 174 patients with back pain from which the specificity of three or more fatty romanus lesions for ax-SpA was described, those with a diagnosis of ax-SpA and fatty romanus lesions on MRI had a disease duration of 8.3 years (Bennett et al., 2010). Given that patients in this cohort were asymptomatic and without a diagnosis of PsA, it is therefore not unexpected that only four patients had areas of fatty infiltration. In three patients, this was limited to just one site, and while it could be a sign of previous inflammation and evolving ax-SpA, it may also be a sign of degenerative arthritis of the spine, especially as the fatty corners were found in the L5/S1 vertebrae, a common site for degenerative disease, in two patients. However, in one patient, five areas of fatty corners were seen. This patient may have had previous bouts of now burnt-out inflammation, which can occur without pain. It would have been interesting to have observed this patient in the longer term to see if he developed further inflammatory lesions or other chronic damage lesions such as syndesmophytes. Vertebral corner inflammation followed by fat deposition is shown to be the best contributor to the development of new bone at the same vertebral corner (Machado et al., 2016).

The fatty corners seen at baseline in this cohort remained stable during 52 weeks of treatment with ustekinumab, with no deterioration in the severity of lesions and no syndesmophyte formation. Ustekinumab could have intervened in the natural progression of these lesions, although the differentiation from mechanical or degenerative-related arthropathy cannot be confirmed with the data available. For the TNF inhibitors at the very least, emerging data support the concept of a 'window of opportunity' in AS disease modification, whereby intervention when a combination of inflammation and fatty changes are detected by MRI can potentially prevent the development of future new bone formation (Maksymowych et al., 2009a). Whether this is the case for ustekinumab and psoriatic arthritis remains to be confirmed in much larger longitudinal studies, and the termination of the phase III study of ustekinumab in non-radiographic axial spondyloarthritis is discouraging.

Aside from fatty bone marrow infiltration, other chronic lesions (bone erosions, spine syndesmophytes, SIJ ankylosis and SIJ sclerosis) were assessed in the axial skeleton in two published studies and one abstract (Song et al., 2011b, Karpitschka et al., 2013, Poddubnyy et al., 2014a), and found to be present at baseline in two (Song et al., 2011b, Poddubnyy et al., 2014a). In agreement with the findings in this study, both found no progression in chronic non-inflammatory lesions with biologic therapy. In 17 patients with established AS (mean disease duration 13.3 years), 24 weeks of ustekinumab therapy resulted in no change in SIJ erosion, sclerosis, fatty lesion and ankylosis scores, or spine erosion, fatty lesion and bone proliferation scores. WBMRI were assessed using the same Berlin Scoring Method as used in this study. Given the duration of disease symptoms, it is not surprising that many more chronic abnormalities were detected at baseline, and scores were higher (e.g. mean SIJ erosion score: 4.0 $\pm$2.4 vs. 0.09 $\pm$0.42 in this study; mean spine fatty lesion score 5.9 $\pm$4.8 vs. 0.39 $\pm$1.12 in this study) (Poddubnyy et al., 2014a). Likewise, in a study of 65 patients with early ax-SpA (mean symptomatic disease duration 2.6 years), the frequency of spine and SIJ chronic abnormalities at baseline were greater than in this study (spine erosions 0.4% and ankylosis 0.7%; SIJ erosions 73.1% and ankylosis 6.9%), but no significant change was reported after 48 weeks of etanercept therapy (Song et al., 2011b).

This study was not without limitations. As a proof-of-concept study, the numbers were small, but the aim to provide a 'snapshot' of the prevalence of subclinical disease principally within the axial skeleton and observe the trends in disease following treatment with ustekinumab have been met. Overall, the number of abnormalities identified were generally low prior to treatment, especially in the axial skeleton, which will account for why much less dramatic changes following treatment were found in this study compared to those described in patients with symptomatic ax-SpA, where it is much easier to interpret more pronounced abnormalities as pathological. Further limitations included the omission of a second trained musculoskeletal radiologist or rheumatologist with

expertise in scoring enthesitis on ultrasound, which prohibited any assessment of interobserver agreement. High rates of 'synovitis' on WBMRI were found in this study, and in part, this could have been a sensitivity issue on behalf of the scorer, although there is no means of clarifying this without a second observer.

In this study, WBMRI has allowed the visualisation of peripheral entheseal sites that are not readily accessible by ultrasound, such as the shoulders, costochondral joints, pubic symphysis and pelvis, and has shown areas of inflammation at sites not previously reported in patients with psoriasis. Only selected tendon entheses, joints and bursa in the knee, ankle and foot were visualised with both WBMRI and ultrasound in this study. There were contradictory responses to treatment using the two modalities – with ultrasound, significant decreases were seen in inflammatory lesions (e.g. patella tendon insertion thickening and hypoechogenicity reduced from 30.4% and 43.5% of entheses at week 0, respectively, to 17.5% and 15.0% after 52 weeks of therapy). In contrast, analysis of WBMRI revealed no significant change in inflammatory lesions (9.8% of entheses had BMO and 19.5% had STI at week 0, and 10.5% had BMO and 18.4% had STI at week 52). The same discrepancy exists for the quadriceps tendon, Achilles tendon and Plantar fascia insertions. There are two potential reasons for this discrepancy: (1) a lack of saggital views of the knee, foot and ankle and (2) a lack of gadolinium contrast. In addition, poor correlation between MRI and ultrasound findings has also been described previously. Aydin et al showed very low (10-26%) positive agreements between MRI and ultrasound findings for individual entheseal lesions at the knee, with low kappa values (0.06-0.18) and no correlation between MRI and ultrasound scores (r^2=0.059) (Aydin et al., 2013b).

Absence of saggital views had an impact on the ability to score the quadriceps and paella tendon insertions in the knee, and the Achilles tendon insertion in the ankle, in addition to analysis of joint synovitis and enthesophytes. These were excluded to try limit the duration of the scan in addition to the number of times a patient had to be repositioned. Ultrasound offers the advantage at peripheral sites of being viewed in real-time, with greater ease to visualise an entire joint to obtain a comprehensive assessment of any abnormalities. It also offers higher spatial resolution and is better suited to looking at the architecture of entheses and soft tissues, and is therefore perhaps more suited to the assessment of subtle subclinical disease.

Gadolinium contrast was not administered in this study due to the repeated number of investigations required (three WBMRI scans per patient) and the potential for gadolinium to cause nephrogenic systemic fibrosis. The lack of gadolinium contrast enhancement made visualisation of the entheses difficult and is likely to have resulted in under-reporting of abnormalities, especially where subtle changes in severity may have occurred. All images were scored by a rheumatologist with expertise in scoring WBMRI, but given the subtlety of abnormalities, where any uncertainty existed about the presence

of a lesion, the area was scored as zero. This negative bias may have been reduced if gadolinium was able to more clearly delineate subtle lesions and a second observed .

The lack of gadolinium contrast also had an impact on the ability to make a comprehensive assessment of synovitis, as synovial thickness could not be measured (Chapter 6.5). A surrogate assessment of synovial fluid volume was adopted which may not be a true representation of inflammation, nor may this be a sensitive marker to change with treatment. The lack of improvement in synovial fluid volumes following ustekinumab in this work argues against an inflammatory genesis for the fluid. Prior studies have aimed to simplify MRI protocols by eliminating gadolinium administration, but found that without contrast, specificity for synovitis and tenosynovitis was low in early arthritis (Stomp et al., 2015)

In summary, this is the first study to use WBMRI to assess the pattern of bone marrow oedema, perientheseal soft tissue inflammation and chronic damage abnormalities in asymptomatic patients with psoriasis and the response to treatment with ustekinumab. No significant change was seen in either inflammatory or structural damage lesions, influenced by the low burden of mild disease at the outset, coupled with difficulties in image interpretation due to lack of contrast enhancement and a tendency to under-report subtle abnormalities. However, in agreement with previous studies in ax-SpA and PsA, no progression in either inflammatory lesions or chronic damage abnormalities were observed. These findings suggest that early introduction of skin-directed therapy with ustekinumab in psoriasis patients that might be destined to develop spondyloarthritis (based on US enthesopathy score positivity) could limit the progression to symptomatic inflammatory arthritis and hopefully prevent future functional limitation and disability. Larger, prospective longitudinal studies, with refinement to the WBMRI protocol, are now required to confirm these observations.

7.6 Conclusion

This is the first study to use WBMRI to assess the change in active inflammatory lesions and structural abnormalities in the axial and peripheral skeleton following skin directed treatment with a biologic agent in asymptomatic patients with psoriasis and subclinical enthesitis. No significant changes were observed in terms of the severity and extent of bone marrow oedema, perientheseal soft tissue inflammation and chronic damage abnormalities by the primary endpoint of 24 weeks, or after 52 weeks of therapy. Factors influencing the ability to detect any change include a low burden of mild disease at the outset and difficulties in image interpretation due to lack of contrast enhancement. However, in agreement with previously published studies of patients with psoriatic arthritis and axial spondyloarthropathy, no progression of abnormalities occurred, suggesting that in those destined to develop PsA, ustekinumab may be able to limit

progression to symptomatic arthritis and prevent future disability. Larger scale, prospective longitudinal studies with WBMRI protocol refinement are now required to confirm these observations.

Conclusions and Future Directions

The incidence of psoriatic arthritis (PsA) is increasing, yet many patients remain uninformed about the link between musculoskeletal symptoms and psoriasis, and often are not adequately screened either in primary or secondary care. Increased recognition of the need for early therapeutic intervention has, in recent years, improved the collaboration between dermatologists and rheumatologists and lead to the development of several screening questionnaires to be used in patients with psoriasis. However, many patients with PsA continue to be diagnosed late, after the 'window of opportunity' where structural damage and functional limitation could potentially have been circumvented.

In this thesis, 10.1% of psoriasis patients screened in a variety of primary care settings had undiagnosed PsA, despite have signs and symptoms consistent with inflammatory arthritis. Several patients commented that receipt of the educational leaflet was the first time they were aware of the possibility of developing arthritis as part of their psoriatic disease, although the provision of an educational leaflet did not improve the response rate to the invitation for screening except for in the most deprived areas. Testing of a new candidate questionnaire (CONTEST), developed from the most discriminative items from the three most widely used PsA screening questionnaires, is shown to be effective at detecting PsA for the first time in a primary care setting. However, the CONTEST questionnaire did not outperform the Psoriasis Epidemiology Screening Test (PEST), which is currently recommended as the screening questionnaire of choice by the National Institute of Health and Clinical Excellence (NICE) in their psoriasis guidelines. These questionnaires had a reasonable sensitivity and specificity for PsA in this primary care cohort, but both had two patients with falsely negative questionnaires, demonstrating the need for additional methods of screening and identification of PsA amongst patients with psoriasis.

Within primary and secondary care cohorts of patients with psoriasis, the presence of subclinical enthesopathy has been consistently observed using grey scale and power Doppler ultrasound, ranging from 33-62.5% of patients examined depending on the population studied, the number of entheses scanned and the definition of enthesopathy used. In this thesis, amongst systemic immunosuppressant and biologic naïve patients presenting to secondary care with moderate-to-severe psoriasis (PASI$\geq$10), asymptomatic enthesopathy was identified in 60.3% of patients, of which 49.3% had potentially modifiable inflammatory enthesitis. Ultrasound examinations were, for the first time, based on the complete OMERACT definition of enthesopathy and included grey scale assessments of entheseal thickening, hypoechogenicity, calcifications, bone cortex irregularities, erosions and enthesophytes, in addition to power Doppler (PD)

signal. Where reference measurements have not previously been published, objective reference values for entheseal thickness were calculated using methods described in the literature. Thickening was by far the most common abnormality, but proportionally high numbers of entheses also demonstrated hypoechogenicity, calcifications and adjacent bone cortex irregularities and enthesophytes. Bone erosions, a later phenomenon of sustained entheseal inflammation, were infrequent.

Whereas earlier assessments have been limited, in this thesis, a broad range of entheseal sites were assessed to reflect the heterogeneous nature of PsA, and to test the feasibility of a screening ultrasound protocol for use in the research and clinical setting. In total,19 sites were scanned bilaterally, and enthesitis was seen in at least one patient at all sites. Most enthesitis occurred within the larger enthesis of the knee, elbow and ankle, with very few abnormalities seen in those joints that sustain the least microtrauma, such as the third, fourth and fifth digits of the hands. It is therefore advised that a screening protocol for use in the clinical setting should concentrate on the entheses of the knee (quadriceps, proximal patella, distal patella), ankle (Achilles tendon, plantar fascia) and elbow (common extensor, common flexor, distal brachial triceps), and to provide a more comprehensive assessment in clinical trials, could also include the thumb and index extensor and flexor tendons, and the peroneal brevis tendon at the ankle. In this thesis, a small number of healthy volunteers were also found to have abnormal ultrasound findings in a similar distribution to, but at a significantly lower frequency than, patients with psoriasis. Abnormalities were greater in older patients and those with a higher BMI. This supports the concept of degeneration occurring as a result of repeated microtrauma at weight-bearing sites, but with sustained and aberrant inflammation in genetically-primed individuals with psoriasis.

The ultrasound protocol also included analyses of the entire synovio-entheseal complex and identified subclinical abnormalities at sites remote, but in close association to the enthesis in patients with psoriasis. Synovitis was a common finding, in contrast with tenosynovitis and bursitis which were infrequent. Reflecting the early, pre-clinical stage of disease in these patients, power Doppler signal was only observed in just 0.2% of entheses. Given the higher rate of PD signal seen in patients with PsA (suggesting a later switch to a more vascular phenotype), longitudinal monitoring of PD signal may be one method of determine when to instigate therapy in patients with asymptomatic enthesopathy.

As a means of screening, there appears to be limited value in clinical entheseal assessments, with 47.8% of patients having clinically tender entheseal points but no evidence of inflammation (or any other abnormality on ultrasound). Similarly, in the real world setting, there appears to be no value in targeting screening for subclinical enthesitis depending on the distribution of psoriatic plaques. In this cohort, no correlation was observed between those with disease of the scalp or intergluteal cleft and

sonographic inflammation scores, although nail disease did appear to be a marker for subclinical enthesitis, and those with more severe nail disease (higher mNAPSI score) had more subclinical inflammatory enthesitis and synovitis. Longitudinal assessment of patients with nail psoriasis would be useful to determine if this could be a clinical biomarker for targeted ultrasound screening in asymptomatic patients.

Overall, very few data are available regarding the rates of evolution from subclinical enthesitis to clinical PsA, and future studies should include a prospective cohort of patients followed up over several years to ascertain further predictors of joint disease, although this is difficult due to patients requiring therapy for psoriasis. A cohort of patients with less severe psoriasis treated with topical medicaments and phototherapy could provide these data, although it is likely that a proportion of these patients would transition onto immunomodulatory anti-psoriatic therapy, which could influence the progression to PsA.

Aside from ultrasound, this prospective pilot data is the first to demonstrate the ability of whole body magnetic resonance imaging (WBMRI) to evaluate subclinical inflammatory and structural damage abnormalities in symptomatic patients with psoriasis in both the axial and peripheral skeleton. As an adjunct to ultrasound, inaccessible sites could be visualised including the shoulders, costochondral joints, pelvis, spine and sacroiliac joints (SIJs). Improvements in hardware and refined techniques of image acquisition resulted in significantly greater numbers of joints within field of view (FOV) and readable compared with the limited data already published (with a minimum of 86% of joints readable peripherally and 100% axially).

Subclinical axial disease is shown here to occur in patients with psoriasis, and WBMRI was able to demonstrate, for the first time, a significantly higher rate of osteitis and adjacent soft tissue inflammation throughout the entire spine of patients with psoriasis compared with healthy volunteers. Several psoriasis patients had bone marrow oedema (BMO) affecting the vertebral corners in keeping with changes recognised in spondyloarthritis (SpA). However, these abnormalities were generally limited to less than three sites and did not therefore fulfil the Assessment of Spondyloarthritis International Society (ASAS) diagnostic criteria, although longitudinal review of these patients is warranted to determine if they develop further lesions and symptomatic SpA. In keeping with the primacy of entheseal disease in this cohort, very few structural damage abnormalities were observed in the spine (syndesmophytes) with no erosions. Disease within the SIJs overall was limited and confirms the observation that spinal inflammation tends to develop first in SpA.

WBMRI was also able to identify asymptomatic inflammatory abnormalities at peripheral sites previously not described in patients with psoriasis, including the manubriosternal joint, shoulder entheses and pubic symphysis, complementing the widespread and

heterogeneous changes seen in WBMRI studies of patients with PsA. In similarity to ultrasound scores, the most consistent association was mNAPSI score, correlating with total WBMRI BMO score in both the peripheral and axial skeleton, suggesting that the presence of nail psoriasis should be included as a co-variable in future investigations.

One of the main objectives of this thesis was to evaluate the effect of biologic therapy on subclinical enthesitis in both the peripheral and axial skeleton. This is the first comprehensive longitudinal assessment using both ultrasound and WBMRI to evaluate the response of imaging abnormalities in treatment naïve patients who require skin-directed systemic therapy for moderate to severe psoriasis. Ultrasound evaluations of the peripheral skeleton demonstrated a significant effect on inflammatory enthesitis, with a 31.3% reduction in inflammation score after just 12 weeks, 42.4% reduction after 24 weeks and a 51.5% reduction after 52 weeks of therapy. No significant alterations were observed on ultrasound chronic damage score, prompting interest for future investigation to determine if IL-12/23p40 inhibition may have stemmed the progression of existing, and the development of new, structural abnormalities. In the axial skeleton, results were less impressive, with no significant change in spinal or SIJ lesions, although the frequency of inflammatory and chronic damage abnormalities did not increase.

These data were intended to inform a larger, prospective trial, and sample size calculations show this to be feasible. Alongside a group of untreated psoriasis patients (to determine the predictive value of subclinical enthesitis in the later development of PsA), groups of patients treated with different immunomodulatory therapies should be examined to determine whether these observations can be replicated or even superseded by other skin-directed immunomodulatory therapies. It is likely that the response to ustekinumab is due to suppression of IL-23, and future investigation should include patients treated with an IL23p19 inhibitor (which have been shown to have superior PASI responses to IL-12/23p40 inhibitors), in addition to molecules that target cytokines downstream from IL-23 (e.g. IL-17A inhibitors). Ideally, patients should be followed up for several years, and attend for annual screening using the ultrasound protocol described in this thesis. Larger numbers per group are necessary to confirm the observations seen with BMI, age and nail psoriasis, and therefore a multicentre approach would be favourable. Much like RA, early treatment is known to be beneficial in PsA, and the data in this thesis suggest, for the first time, that IL-12/23p40 inhibition appears to be valuable in subclinical enthesitis. However, the longer-term benefits of biologic therapies on the possible progression to PsA and the prevention of disability and functional limitation remain to be determined.

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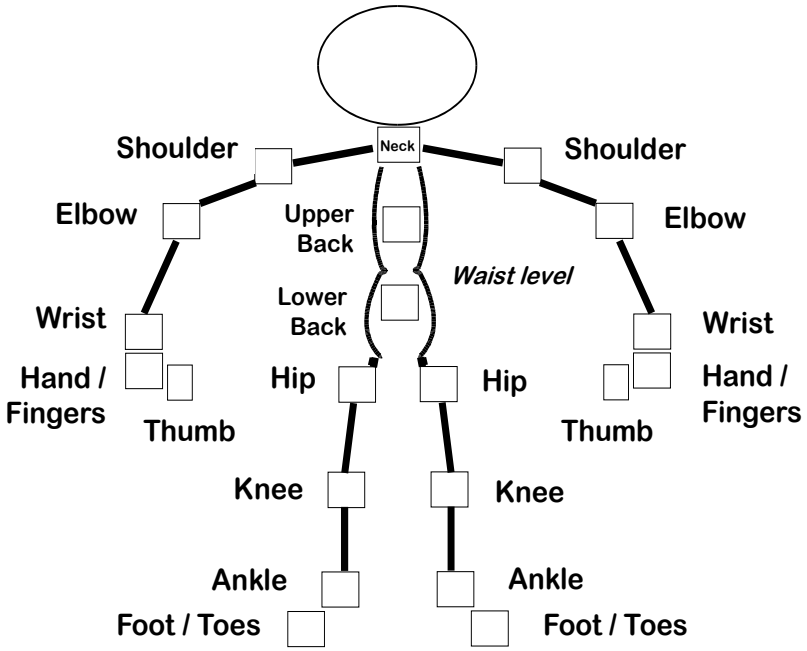
Appendix 1

Psoriasis Epidemiology Screening Tool (PEST)

In the drawing below, please tick the joints that have caused you discomfort (i.e. stiff, swollen or painful joints).



Reproduced with kind permission of Professor Philip Helliwell (University of Leeds)

Please answer the questions below and score 1 point for each question answered 'Yes'

		Yes	No
1.	Have you ever had a swollen joint (or joints)?	☐	☐
2.	Has a doctor ever told you that you have arthritis?	☐	☐
3.	Do your finger nails or toenails have holes or pits?	☐	☐
4.	Have you had pain in your heel?	☐	☐
5.	Have you had a finger or toe that was completely swollen and painful for no apparent reason?	☐	☐
	Total	**/ 5**	

A total score of 3 or more out of 5 is positive and indicates a referral to rheumatology should be considered

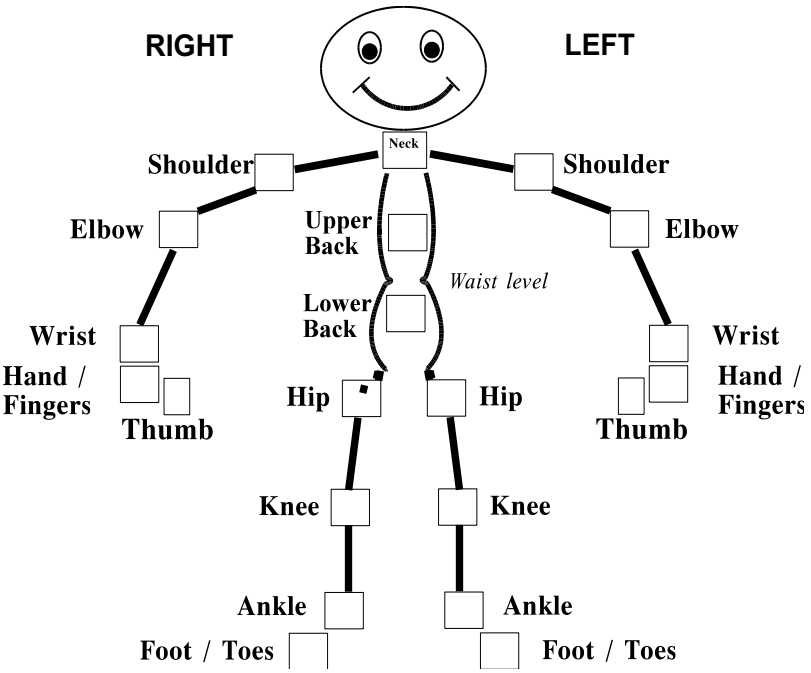
Appendix 2

CONTEST Questionnaire (with and without joint mannequin)

(please tick yes or no for each statement)

	YES	NO
Have you ever had a swollen joint (or joints)?		
Has a doctor ever told you that you have arthritis?		
Do your finger nails or toe nails have holes or pits?		
Have you had pain in your heel?		
Have you had a finger or toe that was completely swollen and painful for no apparent reason?		
Have you ever noticed any of these changes in your fingernails:		
Pits in the nails as shown in PICTURE 1		
Lifting of the nail from the nail bed as shown in PICTURE 2		
Have you ever had neck pain lasting at least 3 months that was not injury related?		
My back hurts.		
My joints become swollen.		
My joints feel “hot”.		

In the drawing below, please tick the joints that have caused you discomfort (i.e. stiff, swollen or painful joints):



PICTURE 1
Pits in the nail

PICTURE 2
Lifting of the nail

Appendix 3

Dermatology Life Quality Index (DLQI)

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant	❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒		
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒

Please check you have answered EVERY question. Thank you.

Appendix 4

The Psoriatic Arthritis Quality of Life (PsAQoL) Questionnaire

- I feel there is no enjoyment in my life
- I feel I am losing my independence
- I often get angry with myself
- I can’t do the things I want to do
- I feel older than my years
- I am unable to join in activities with my friends or family
- It limits the places I can go
- I have to push myself to do things
- I am easily irritated by other people
- I have to keep stopping what I am doing to rest
- I feel dependent upon others
- It takes me a long time to get going in the morning
- I take it out on people close to me
- I can’t do things on the spur of the moment
- I feel like a prisoner in my own home
- I have to limit what I do each day
- It puts a strain on my personal relationships

Appendix 5

Health Assessment Questionnaire

1. For each category, please check the **one** response that best describes your abilities over the **past week**.

Dressing and Grooming	**NO DIFFICULTY**	**SOME DIFFICULTY**	**MUCH DIFFICULTY**	**UNABLE TO DO**
Dress yourself, including tying shoelaces and doing buttons	☐	☐	☐	☐
Shampoo your hair	☐	☐	☐	☐
Rising				
Stand up from an armless chair	☐	☐	☐	☐
Get in and out of bed	☐	☐	☐	☐
Eating				
Cut your meat	☐	☐	☐	☐
Lift a full cup or glass to your mouth	☐	☐	☐	☐
Open a new carton of milk	☐	☐	☐	☐
Walking				
Walk outdoors on flat ground	☐	☐	☐	☐
Climb up five stairs	☐	☐	☐	☐
Hygiene				
Wash and dry your entire body	☐	☐	☐	☐
Take a bath	☐	☐	☐	☐
Get on and off the toilet	☐	☐	☐	☐
Reach				
Reach and get down a 5 lb object (for example, a bag of sugar from just above your head)	☐	☐	☐	☐
Bend down to pick up clothing from the floor	☐	☐	☐	☐
Grip				
Open car doors	☐	☐	☐	☐
Open jars which have been previously opened	☐	☐	☐	☐
Turn taps on and off	☐	☐	☐	☐
Activities				
Run errands and shop	☐	☐	☐	☐
Get in and out of a car	☐	☐	☐	☐
Do chores such as vacuuming, housework or light gardening	☐	☐	☐	☐

2. Do you **usually** (more than 50% of the time) use the following aids or devices for any of the activities listed on page 1? *Check all that apply.*
   - ☐ Canes
   - ☐ Walker
   - ☐ Crutches
   - ☐ Wheelchair/scooter
   - ☐ Raised toilet seat
   - ☐ Bath seat
   - ☐ Jar opener (for jars previously opened)
   - ☐ Special or built-up utensils
   - ☐ Special or built-up chair
   - ☐ Bath rail
   - ☐ Long-handled applicance for reach
   - ☐ Other (specify) _____

3. Do you **usually** (more than 50% of the time) need help from another person for any of the following? *Check all that apply.*
   - ☐ Errands and housework
   - ☐ Reaching
   - ☐ Dressing and grooming
   - ☐ Gripping and opening things
   - ☐ Eating
   - ☐ Walking
   - ☐ Rising
   - ☐ Hygiene

4. Please circle the number, from 0 to 10, which indicates how much pain you have had in the **past week because of your arthritis**, with 0 being "no pain" and 10 being "pain as bad as it could be".

PAIN SCALE RATING: **0 1 2 3 4 5 6 7 8 9 10**

Appendix 6

Contraindications to biologic therapy (Ustekinumab)

- Active infection, including open leg ulcers, HIV, hepatitis B or C carriers
- Active or latent tuberculosis
- Malignancy – current, or previous within the last ten years (except basal cell carcinoma)
- Severe heart failure (NYHA grade III or more)
- Demyelinating disorders
- Uncontrolled diabetes
- Chronic lung disease (pulmonary fibrosis or bronchiectasis)
- Previous PUVA phototherapy (>1000 joules)
- History of other significant medical conditions, including:
    - Severe pulmonary disease (defined as requiring previous hospital admission or supplemental oxygen)
    - Active or severe cardiovascular disorders: uncontrolled hypertension, myocardial infarction within the previous twelve months, unstable angina within the previous six months)
    - Any immunodeficiency disorder
    - Connective tissue diseases (e.g. primary Sjogrens syndrome, systemic sclerosis, systemic lupus erythematosus, polymyositis)
    - Renal impairment (creatinine clearance <45ml/min)
    - Abnormal liver function tests (alanine transferase >3x upper limit of normal)
    - Blood disorders, i.e. thrombocytopenia (platelets $<125x10^9$/l), neutropenia (neutrophils $<2.0x10^9$/l) or anaemia (Hb <8g/dl).

Appendix 7

Psoriasis Area and Severity Index (PASI)

LESION SCORE

Erythema (E) Induration (I) Scaling (S)	No Symptoms	Slight	Moderate	Marked	Very Marked
SCORE	0	1	2	3	4

AREA SCORE

AREA	0	1% - 9%	10% - 29%	30% - 49%	50% - 69%	70% - 89%	90% - 100%
SCORE	0	1	2	3	4	5	6

Lesion Score	Head (H)	Trunk (T)	Upper Limbs (UL)	Lower Limbs (LL) *including buttock*
Erythema (E)				
Induration (I) (thickness)				
Scaling (S)				
SUM: E + I + S				
Percentage of Affected Area				
Area Score				
SUBTOTAL: Sum x Area Score				
Body Area: Subtotal X amount indicated	x 0.1	x 0.3	x 0.2	x 0.4
TOTALS	H	T	UL	LL

PASI SCORE: H + T + UL + LL ☐

Appendix 8

Modified Nail Psoriasis Severity Index (mNAPSI)

Features		Right					Left				
		5	4	3	2	1	1	2	3	4	5
Onycholysis	0 = none	0	0	0	0	0	0	0	0	0	0
	1 = 1-10% of nail surface	1	1	1	1	1	1	1	1	1	1
	2 = 11-30% of nail surface	2	2	2	2	2	2	2	2	2	2
	3 = >30% of nail surface	3	3	3	3	3	3	3	3	3	3
Pitting	0 = none	0	0	0	0	0	0	0	0	0	0
	1 = 1-10 pits	1	1	1	1	1	1	1	1	1	1
	2 = 11-49 pits	2	2	2	2	2	2	2	2	2	2
	3 = >50 pits	3	3	3	3	3	3	3	3	3	3
Nail plate crumbling	0 = none	0	0	0	0	0	0	0	0	0	0
	1 = 1-25% of nail	1	1	1	1	1	1	1	1	1	1
	2 = 26-50% of nail	2	2	2	2	2	2	2	2	2	2
	3 = >50% of nail	3	3	3	3	3	3	3	3	3	3
Features (tick if present)		Right					Left				
Leukonychia											
Splinter haemorrhage											
Nail bed hyperkeratosis											
Red spots in lunula											
Oil spot dyschromia											

Appendix 9

MUSTEK Study RR12/10234

UNIVERSITY OF LEEDS

MUSTEK STUDY: ULTRASOUND CRF

Study ID: | | | |

Date: | | | |

USS Visit: | Week 0 | Week 12 | Week 24 | Week 52 |

Sonographer _____

SCALES:

Entheseal thickness to be recorded in millimetres (mm)

Grey Scale assessments:
0 = absence
1 = mild
2 = moderate
3 = marked/severe

Power Doppler assessments:
0 = absence
1 = mild (≤3 isolated signals)
2 = moderate (>3 isolated signals or confluent signal in <50% of synovial area)
3 = marked (signals in >50% of the synovial area)

Bony Erosions:
0 = absence
1 = <2mm
2 = 2-3mm
3 = ≥ 3mm

KEY:

Enth Thick	Entheseal Thickening
Enth Hypo Echo	Entheseal hypoechogenicity
Enth Calc	Calcification
Enth-phytes	Enthesophytes
Bony Eros	Bony Erosions
Bony Cort Irreg	Bony Cortex Irregularities
Enth PD	Entheseal Power Doppler Signal
PD	Power Doppler
Dors	Dorsal
Vol	Volar
TS	Tenosynovitis
Synov	Synovitis

UPPER LIMB

RIGHT												FINGER TENDONS & JOINTS (All 0-3 unless stated) Examine flexor tendons at thickest part			LEFT										
Enthesis							Teno-synovitis		Joint Synovitis						Enthesis							Teno-synovitis		Joint Synovitis	
Enth Thick (mm)	Enth Hypo echo	Enth Calc	Enth-phytes	Bony Eros	Bony Cort Irreg	Enth PD	GS	PD	GS	PD				Enth Thick (mm)	Enth Hypo echo	Enth Calc	Enth-phytes	Bony Eros	Bony Cort Irreg	Enth PD	GS	PD	GS	PD
											Thumb	Flex													
												Ext	IP												
													CMC												
											Index	Flex													
												Ext	DIP												
													PIP												
													MCP												
											Middle	Flex													
												Ext	DIP												
													PIP												
													MCP												
											Ring	Flex													
												Ext	DIP												
													PIP												
													MCP												
											Little	Flex													
												Ext	DIP												
													PIP												
													MCP												

SCAN THUMB + INDEX FINGERS IN ALL PATIENTS – PLUS ONE MORE DIGIT (EACH HAND) IF SIGNIFICANT NAIL DISEASE PRESENT (Dr Savage to indicate)

RIGHT				WRIST TENDONS & JOINTS (All 0-3 unless stated)	LEFT			
Teno-synovitis		Joint Synovitis			Teno-synovitis		Joint Synovitis	
GS	PD	GS	PD		GS	PD	GS	PD
				Wrist Joint				
				EXT Compartment 1				
				EXT Compartment 2				
				EXT Compartment 3				
				EXT Compartment 4				
				EXT Compartment 5				
				EXT Compartment 6				

RIGHT									ELBOW TENDONS & JOINTS (All 0-3 unless stated)	LEFT								
Enthesis							Joint synovitis			Enthesis							Joint synovitis	
Enth Thick (mm)	Enth Hypo echo	Enth Calc	Enth-phytes	Bony Eros	Bony Cort Irreg	Enth PD	GS	PD		Enth Thick (mm)	Enth Hypo echo	Enth Calc	Enth-phytes	Bony Eros	Bony Cort Irreg	Enth PD	GS	PD
									Common Extensor[1]									
									Common Flexor[2]									
									Distal Brachial Triceps									

[1]Common extensor tendon insertion on lateral epicondyle [2]Common flexor tendon insertion on medial epicondyle

RIGHT		ELBOW BURSAE (All yes/no)	LEFT	
Burseal Synovial Hypertrophy	Burseal PD		Burseal Synovial Hypertrophy	Burseal PD
		Olecranon		

LOWER LIMB

RIGHT											KNEE TENDONS & JOINTS (All 0-3 unless stated)	LEFT										
Enthesis							Teno-synovitis		Joint Synovitis			Enthesis							Teno-synovitis		Joint Synovitis	
Enth Thick (mm)	Enth Hypo echo	Enth Calc	Enth-phytes	Bony Eros	Bony Cort Irreg	Enth PD	GS	PD	GS	PD		Enth Thick (mm)	Enth Hypo echo	Enth Calc	Enth-phytes	Bony Eros	Bony Cort Irreg	Enth PD	GS	PD	GS	PD
											Knee Joint											
											Quadriceps[1]											
											Proximal Patellar[2]											
											Distal Patellar[3]											

1. Superior pole of patella – quadriceps tendon enthesis (tendon thickness ≥6.1mm)
2. Inferior pole of patella - proximal patella ligament enthesis (tendon thickness ≥4.0mm)
3. Tibial tuberosity – distal patella ligament enthesis (tendon thickness ≥4.0mm)

RIGHT		KNEE BURSAE (All yes/no)	LEFT	
Burseal Synovial Hypertrophy	Burseal PD		Burseal Synovial Hypertrophy	Burseal PD
		Pre-patellar		
		Superficial infrapatella		
		Deep infrapatella		

RIGHT											FOOT & ANKLE TENDONS & JOINTS (All 0-3 unless stated)	LEFT										
Enthesis							Teno-synovitis		Joint Synovitis			Enthesis							Teno-synovitis		Joint Synovitis	
Enth Thick (mm)	Enth Hypo echo	Enth Calc	Enth-phytes	Bony Eros	Bony Cort Irreg	Enth PD	GS	PD	GS	PD		Enth Thick (mm)	Enth Hypo echo	Enth Calc	Enth-phytes	Bony Eros	Bony Cort Irreg	Enth PD	GS	PD	GS	PD
											Ankle Joint (Midline)											
											Posterior tibialis											
											Flexor digitorum longus											
											Flexor hallucis longus											
											Anterior tibialis											
											Extensor hallucis longus											
											Extensor digitorum longus											
											Perineal longus											
											Peroneal brevis											
											Achilles Tendon[1]											
											Plantar Aponeurosis[2]											

[1] Superior pole of calcaneus – Achilles tendon entheses (tendon thickness ≥ 5.29mm) [2]Inferior pole of calcaneus – plantar aponeurosis (aponeurosis thickness ≥ 4.4mm)

RIGHT		ANKLE BURSAE (All yes/no)	LEFT	
Burseal Synovial Hypertrophy	Burseal PD		Burseal Synovial Hypertrophy	Burseal PD
		Retrocalcaneal		

Appendix 10

The Leeds Teaching Hospitals NHS
NHS Trust

MAGNETIC RESONANCE IMAGING (MRI) SCREENING FORM

NAME : _____ **DOB :** _____

ADDRESS : _____ **WEIGHT :** _____

Please answer the following questions (please tick) :	***YES***	***NO***	***UNSURE***
Do you have / have you ever had a cardiac / heart pacemaker?			
Do you have / have you ever had an implanted medical device e.g. drug infusion device, nerve or bone stimulator, cochlear implant etc.			
Have you ever had a bleed inside your head?			
Have you ever had any operations involving your head, eyes or heart?			
Have you had any other operations / surgery in the last six weeks?			
Have you ever worked as a machinist, metal worker or welder?			
Have you ever had any metallic fragments in your eyes?			
Have you ever had any metal in your head or body e.g. shrapnel?			
Do you suffer / have you suffered from a heart disorder / fits / blackouts / epilepsy or diabetes?			
Are you under the care of a kidney doctor for kidney failure and/or are you on dialysis?			
Do you have any allergy to any drug?			
Do you use an EpiPen or suffer from any of the following: asthma, hay fever, hives, seafood allergy?			
Do you take Beta Blockers?			

Do you have any of the following(please tick):	***YES***	***NO***	***UNSURE***
A prosthesis or implant (e.g. breast, eye, ear, hip/knee, penile, artificial limb)			
Shunts, lines, catheters, wires, stents, vascular clips			
Clips in the brain (e.g. Aneurysm clips)			
Dentures or plate, hearing aid			
Any medicine patches (e.g. HRT patches, etc.)			

As this is a teaching hospital, MR pictures are often used for education and research purposes. No personal details will accompany the images. Please tick the box if you DO NOT want your MR pictures being used for these purposes. ☐

Female patients only :

Is there any possibility of pregnancy? ***YES / NO*** *Are you breastfeeding?* ***YES / NO***

IMPORTANT - Please ensure that all removable loose objects e.g. watch, wallet, credit cards, keys, loose change, jewellery, hair clips, hearing aid, etc are left outside the scanning room in the lockers provided. If you have any questions feel free to ask.

Patient Signature :_____ Date : _____

Relationship to patient (if applicable) _____

To be filled in by MRI Staff

3 Point ID Checked : _____ Screening form checked and no contraindications : _____

Appendix 11

The Glasgow Ultrasound Enthesitis Scoring System (GUESS)

Superior pole of the patella—quadriceps tendon enthesis

- Quadriceps tendon thickness ≥6.1 mm
- Suprapatellar bursitis
- Superior pole of patella erosion
- Superior pole of patella enthesophyte

Inferior pole of the patella—proximal patellar ligament enthesis

- Patellar ligament thickness ≥4 mm
- Inferior pole of patella erosion
- Inferior pole of patella enthesophyte

Tibial tuberosity—distal patellar ligament enthesis

- Patellar ligament thickness ≥4 mm
- Infrapatellar bursitis
- Tibial tuberosity erosion
- Tibial tuberosity enthesophyte

Superior pole of the calcaneus—Achilles tendon enthesis

- Achilles tendon thickness ≥5.29 mm
- Retrocalcaneal bursitis
- Posterior pole of calcaneus erosion
- Posterior pole of calcaneus enthesophyte

Inferior pole of the calcaneus—plantar aponeurosis enthesis

- Plantar aponeurosis thickness ≥4.4 mm
- Inferior pole of calcaneus erosion
- Inferior pole of calcaneus enthesophyte

Each item scores one point. Total possible score on both lower limbs is 36.

Appendix 12

The Sonographic Enthesitis Index (SEI)

Entheseal areas	Signs of acute injury	Signs of chronic lesion
Quadriceps tendon enthesis (superior pole of the patella)	Thickening of tendon/aponeurosis	Tendon tear
Proximal insertion of the patellar tendon (inferior pole of the patella)	Hypoechogenicity of tendon/aponeurosis	Loss of thickness
Distal insertion of the patellar tendon (anterior tibial tuberosity)	Peritendinous/periaponeurotic oedema	Tendon calcification
Achilles tendon enthesis (superior pole of the calcaneous)	Bursitis*	Bone erosion
Plantar aponeurosis enthesis (plantar pole of the calcaneous)		
Total 76 points	SEI-A 0–36 points	SEI-C 0–40 points

SEI-A, Sonographic Entheseal Index of Acute injury; SEI-C, Sonographic Entheseal Index of Chronic lesion.

Each variable was scored as 0 (absence) or 1 (presence) and the SEI was the total sum of SEI-A and SEI-C.

The maximum SEI scoring was 76 points (36+40).

*Where applicable.