Modification of midfoot bone stress with functional foot orthoses

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Submitted in accordance with the requirements for the degree

of Doctor of Philosophy

The University of Leeds

School of Medicine

Leeds Institute of Rheumatic and Musculoskeletal Medicine

March 2013

Intellectual Property and Publication Statements

The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others.

Publications and Presentations

The following presentations have resulted directly from this thesis. There are no publications resulting from this thesis. Please see table below for the publication plan.

Jill Halstead, A.M. Keenan, D. McGonagle, P.G. Conaghan, A.C. Redmond
Can functional foot orthoses modify foot motion and bone structure? Society of Chiropodists and Podiatrists Annual Conference 11th to 13th October 2012 (Invited speaker).

Jill Halstead, A.M. Keenan, D. McGonagle, P.G. Conaghan, A.C. Redmond
The development of a gait shoe for multi-segment foot motion analysis. Society of Chiropodists and Podiatrists Annual Conference 21st to 23rd October 2010, Bournemouth UK (accepted for podium presentation).

Jill Halstead, A.M. Keenan, A.C. Redmond, D. McGonagle
Bone marrow oedema changes: A possible precursor to osteoarthritis in the ankle. Society of Chiropodists and Podiatrists Annual Conference 23rd to 25th 2008 Bournemouth, UK (accepted for podium presentation).

Jill Halstead, A.M. Keenan, D. McGonagle, P.G. Conaghan, A.C. Redmond
Insights into mechanical foot pain combining state of the art motion analysis with 3D MR imaging. Staffordshire conference of clinical biomechanics, 16th April 2010 Staffordshire, UK (accepted for podium presentation).

Jill Halstead, A.M. Keenan, D. McGonagle, P.G. Conaghan, A.C. Redmond
An in-shoe comparison of foot kinematics in normals versus mechanical foot pain. i-FAB 2010 Congress September 16th to 18th 2010, Seattle USA (accepted for podium presentation).

This table provides an overview of the chapters and the publication plan.

Chapter and Aims	**Overview**	**Publications Plan**
Chapter Three: i - To identify a method to quantify bone marrow lesion volume in the midfoot bones.	This chapter included multiple studies to test the reliability of image segmentation and BML volume measurement methods.	Quantification of bone marrow lesions in the foot. **Oral abstract at SCP 2008**
Chapter Four: ii - To identify patterns of bone marrow lesions, which are observed with magnetic resonance imaging, in patients with mechanical medial midfoot pain. Iii - To explore the association between mechanical medial midfoot pain and distribution of bone marrow lesions. iv - To explore the effect of in-shoe foot orthoses on patterns of bone marrow lesions in the medial midfoot region. v - To explore the effect of in-shoe foot orthoses on foot pain and Impairment.	This chapter included a clinical study. Two interventions were randomly allocated over a three month period; an active intervention of functional foot orthoses and a control cushioning (sham) insole. Outcomes in pain, impairment and volume of bone marrow lesions were compared from baseline to follow-up. The differences between the two interventions were then compared.	The relationship between midfoot pain and MR imaging. **Oral abstract at SCCB 2010** The modification of midfoot pain and bone marrow lesions with foot orthoses. **Invited speaker BSR 2012**
Chapter Five: vi - To explore the effect of in-shoe foot orthoses on gait parameters and foot kinematics.	This chapter included two studies, firstly to compare multi-segment foot kinematics during barefoot and shod walking. Secondly to explore whether insoles can alter in-shoe gait parameters and foot kinematics	The development of a gait shoe for multi-segment foot motion analysis. **Oral abstract at i-FAB 2010 and SCP 2010** Foot orthoses intervention, the effect on multi-segment kinematics.

Acknowledgements

This thesis would not have been possible without the doctoral funding gratefully received from Arthritis Research UK and the many participants who gave their time to the research project.

I would like to thank those who have assisted with the research in this thesis:

The imaging team at LMBRU and in particular Richard Hodgson, Peter Wright, Robert Evans, Carol Burnett were responsible for development and acquisition of the magnetic resonance images.

The project would not have been possible without all the clinical departments supporting the study. I would like to thank all the staff at the musculoskeletal service, foot health department, and all the podiatrists, physiotherapists and rheumatologists for their time and support of this study.

I would like to thank Clare Skinner at the University of Leeds for providing advice in regards to the ethical application and hospital permissions.

Dr Elizabeth Hensor (department statistician) and doctoral supervisor Dr Anthony Redmond provided guidance and advice in regards to the data handling strategy and data analyses throughout the thesis.

I would like to thank Jude Muo who contributed to the phantom study (Section 3.5.1). My contributions were the development of the research concept, the construction of the phantom, data collection and processing

that included reliability of phantom measurements. Jude Muo contributed to the phantom study by undertaking the data collection for the field variance, field strength, and reliability phantom measurements. Data analysis in the phantom study was undertaken by Jude, supervised by myself and Dr Anthony Redmond. The work undertaken by Jude Muo was submitted for a Masters of Science in Medical Imaging submitted in September 2009 to the University of Leeds.

I would like to thank Dr Redmond, Dr Keenan, Professor McGonagle, Professor Conaghan - my supervision team for supporting me in writing the research grant and guiding me through my doctoral thesis. Each supervisor has played an important role in my clinical and academic career. I would like to thank Dr Redmond for his unwavering support, professional guidance and patience over the last ten years. Without Dr Redmond's support this thesis would not have been possible. Dr Keenan has been an excellent mentor throughout both the Masters and Doctoral research projects. I would like to particularly acknowledge her role in the development of my writing skills. Both Professor McGonagle and Professor Conaghan have been excellent clinical and academic mentors. Both were always patient with my endless questions, their advice and guidance was greatly appreciated.

I have been very lucky over the last four years to be supported by all the students and staff at the academic department (Leeds Institute of Rheumatic and Musculoskeletal Medicine). My special thanks go out to Dr Michael Backhouse, Dr Philip Helliwell, Dr Heidi Siddle, Begonya Alcacer-Pitarch, Dr Derrick White, Brian Whitham, Dr Christine Comer, Robin Waxman and Richard Wilkins for their advice and support.

Finally I would like to thank my husband, Jason Rastrick, for his unwavering love and moral support throughout the last four years of the PhD. In particular Jason provided assisted in the formatting and presentation of this thesis.

Abstract

Modification of Midfoot Bone Stress with Functional Foot Orthoses

Studies of foot orthoses suggest that they can improve foot pain and function, although the precise mode of action of foot orthoses is poorly understood. It is proposed that they may act through the modification of abnormal stresses or motions occurring within the foot. The central aim of this thesis is to explore whether functional foot orthoses can systematically modify bone stress in the midfoot as measured on magnetic resonance imaging.

Bone marrow lesion patterns quantified on magnetic resonance imaging was proposed as a surrogate measure of bone stress in the foot. A reliable method of bone segmentation and BML volume measurement was developed and applied in this thesis. In the interventional study of this thesis, the effect of functional foot orthoses on mechanical medial midfoot pain, foot impairment, patterns of bone marrow lesions and foot kinematics were investigated. Thirty seven participants with mechanical midfoot pain and medial midfoot bone marrow lesions participated in the study and were allocated to wear either functional foot orthoses (n=21) or a cushioning insole (n=16). The effect of the orthosis intervention on foot pain, impairment and volumes of magnetic resonance bone marrow lesions was compared in each group. In addition, the gait parameters and foot kinematics were assessed in a subset of 20 participants (functional foot orthoses n=10 and cushioning insole n=10).

Foot pain and foot impairment outcomes improved more in the functional foot orthoses group than the control group wearing cushioning insoles. The results suggest that the volumes of bone marrow lesions in the medial foot bones were reduced systematically in the functional foot orthoses group. In comparison, those wearing the cushioning insole showed no change greater than measurement error. There was no evidence in the small subset of

participants, that foot kinematics were systematically altered when wearing either the cushioning insole or functional foot orthoses compared to in-shoe only analyses.

The results reported in this thesis suggest that the biomechanical mechanism of functional foot orthoses in treating foot pain could be the modification of internal forces rather than their systematically influencing magnitudes of foot motion. This new data indicates that functional foot orthoses appear to have the potential to reduce foot pain and alter patterns of bone marrow lesions (a surrogate measure of bone stress) in the medial midfoot bones and further work is now required to explore this formally in larger studies.

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Abbreviations

Abbreviation	Meaning
0.2T	0.2 Tesla (extremity magnetic resonance imaging)
1.5T	1.5 Tesla
1M	First Metatarsal
2D	Two dimensional
2M	Second Metatarsal
3M	Third Metatarsal
3D	Three dimensional
3T	3 Tesla
4M	Fourth Metatarsal
5M	Fifth Metatarsal
AOFAS	American Orthopaedic Foot and Ankle Scale
BLOCKS	Boston Leeds Osteoarthritis Knee Score
BMI	Body Mass Index
BMLs	Bone marrow lesions
CD	Compact disc
CI	Confidence interval
CMC	Coefficient of multiple correlation
CT	Computer tomography
CUB	Cuboid bone
CUSH	Cushioning insole
Diff	Difference
DMG	Professor Dennis McGonagle
FE	Finite element
FFO	Functional foot orthoses
FFI	Foot Function Index
FHS	Foot Health Status Questionnaire
FOV	Field of view
IC	Intermediate cuneiform bone
ICC	Intra class correlation coefficient
KOSS	Knee Osteoarthritis Scoring System
LC	Lateral cuneiform bone
JHR	Jill Halstead-Rastrick
JM	Jude Muo
Max	Maximum
MC	Medial cuneiform bone
MFPDI	Manchester foot pain and disability index
MR	Magnetic resonance
MSK	Musculoskeletal
MTPJ	Metatarso-phalangeal joint
NAV	Navicular
n=	Number equals
No.	Number
NEX	Number of excitations
OFM	Oxford foot model

Abbreviation	Meaning
OA	Osteoarthritis
RCT	Randomised controlled trial
RMSE	Root mean square error
ROI	Region of interest
ROM	Range of motion
SD	Standard deviation
STIR	Short tau inversion ratio
T1	Image created typically by using short TE and TR times whose contrast and brightness are predominately determined by T1 signal
T2	Image created typically by using longer TE and TR times whose contrast and brightness are predominately determined by T2 signals.
TE	Echo Time
TR	Repetition Time
USA	United states of America
UK	United Kingdom
VAS	Visual analogue scale
WOMAC	Western Ontario and McMaster Universities Arthritis Index
WORMS	Whole-organ evaluation of the knee in osteoarthritis

Chapter One:

Introduction

1.1 Background

Foot pain is a common musculoskeletal complaint that can be provoked and/or aggravated by intense physical stress and repetitive weight-bearing movements, for instance: running, walking, stair climbing, prolonged standing and sit-to-stand activities. This pattern of foot pain associated with weight-bearing activities is clinically termed “mechanical foot pain”.

Foot orthoses are a common treatment for mechanical foot pain. Trials of foot orthoses, suggest that they can improve foot pain, impairment and disability associated with some foot conditions. Although the precise mode of action of foot orthoses remains poorly understood, they have been proposed to act through the modification of abnormal stresses or motions occurring within the foot. Gait studies are limited, as they have historically relied on measuring the interaction of the foot with the external environment. Whether or how foot orthoses modify internal stress within the foot is therefore poorly understood.

The skeletal system is continually adapting to physical stress. The relationship between internal stress, external stress and pathological response is exemplified in the musculoskeletal system through the clinical presentation of bony stress response, and in severe cases, stress fractures. Using magnetic resonance (MR) imaging, patterns of stress response, known as bone marrow lesions (BMLs) are detected in the lower limb and foot. These BMLs can be associated with intense periods of mechanical

stress with activities such as running and/or in the presence of structural or functional abnormalities. The link between abnormal gait kinetics and kinematics and underlying bone pathology has been best explored in the knee. Bone marrow lesions associated with knee osteoarthritis (OA) have shown specific patterns associated with gait abnormalities such as varus knee alignment, pes planus foot type and increased medial knee loading. The use of foot orthoses and surgical operations to alter knee kinetics and kinematics, has also been shown to precipitate changes in the intra and extra articular knee structures, knee bone density and in the modification of BMLs in some participants. This suggests that in an OA knee model, altering knee stress can be reflected in changes of internal bone physiology in some people.

For people with foot pain, the effect of foot orthoses on internal foot stress is unclear. Studies have shown that foot orthoses may alter foot kinematics, kinetics and pain, however the effect of foot orthoses on internal distributions of foot loads and therefore the potential course of mechanical pathology is unknown. Estimation of internal foot forces can be achieved using finite element (FE) and *in-vitro* modelling, however these models are usually case specific, are difficult to validate and the results have limited clinical application. In this thesis it will be explored whether functional foot orthoses (FFO) can influence the internal distributions of forces in the foot bones, and that this can be quantified by measuring volumes and patterns of BMLs, which can provide a surrogate measure of bone stress.

1.2 Aims and Objectives

The central aim of this thesis is:

to explore whether functional foot orthoses can systematically modify loading of the midfoot as reflected in magnitude and patterns of associated bone marrow lesions, and foot kinematics.

The following objectives were identified to fulfil this main aim:

I. To devise a method for accurately quantifying bone marrow lesion volume in the midfoot bones.

II. To identify patterns of bone marrow lesions, which are observed with magnetic resonance imaging, in patients with mechanical medial midfoot pain.

III. To explore the association between mechanical medial midfoot pain and distribution of bone marrow lesions.

IV. To explore the effect of in-shoe foot orthoses on patterns of bone marrow lesions in the medial midfoot region.

V. To explore the effect of in-shoe foot orthoses on foot pain and impairment.

VI. To explore the effect of in-shoe foot orthoses on gait parameters and foot kinematics.

1.3 Innovation

This is the first study to explore the underlying bone abnormalities in relation to mechanical medial midfoot pain and impairment. The application of high resolution MR imaging and a multi-segment foot kinematic model may provide new insights into the mechanism of foot orthoses. This thesis will explore whether an orthotic device can influence patterns of midfoot pain and underlying bone stress through the quantification of bone marrow lesions.

1.4 Scope and Boundaries

This thesis was underpinned by a central aim and six clear objectives to explore the mechanism of foot orthoses on midfoot pain, patterns of bone stress and foot kinematics. The application of MR imaging to explore bone stress in a clinical cohort is a novel approach, however it was not within the scope of this thesis to fully explore the association between midfoot pain and MR imaging findings, for instance to determine the epidemiology or pathological mechanisms. It was the focus of this thesis to apply innovative methods (multi-segment foot kinematics and MR imaging) to understand whether foot orthoses can modify patient reported outcomes and MR imaging findings and foot kinematics in a selected clinical group. Although the data within this thesis further reinforces the need for a large scale study of the clinical efficacy of foot orthoses on midfoot pain, this would require a substantial randomised controlled clinical trial, which again falls beyond the scope of this specific programme of work.

1.5 Thesis Structure

This thesis has the following structure:

I. Chapter Two, background and review of the literature.
II. Chapter Three, the measurement of bone marrow lesions.
III. Chapter Four, the effect of orthoses on bone marrow lesions.
IV. Chapter Five, the effect orthoses have on gait parameters and foot kinematics.
V. Chapter Six, a discussion of the study findings.

An overview of the three main study chapters is summarised in Table 1.1.

Chapter Two

The review of the literature in Chapter Two will comprise of four main themes that underpin this thesis i) foot pain, ii) imaging of the foot, iii) biomechanical function and iv) foot orthoses. This chapter includes a detailed background to the prevalence, burden and factors affecting foot pain. The review then focuses on mechanical foot pain and pathology, with specific consideration of the midfoot. The review goes onto describe and critique the role of imaging in the diagnosis of midfoot pathology, in particular the identification and quantification of bone stress and its association with foot pain. In the next section the relationship between biomechanics and foot pain is explored, to understand the association between altered biomechanical, foot pain and pathology. Finally the evidence for the efficacy of foot orthoses to modify pain, impairment, biomechanics and bone pathology is reviewed.

Chapter Three

In Chapter Three, MR imaging detection of BMLs is proposed as a surrogate measure of bone stress. In this chapter four experimental studies of MR imaging signal quantification are outlined and discussed. The first is a phantom study to examine the challenges of signal quantification. In the next two studies, the reliability and face validity of BML measurements in a region of interest (ROI) with ill-defined signal boarders are presented. The advantages and limitations of the tracing and signal growth measurements in both studies are discussed. The final method that approached quantification through a novel method of signal subtraction is presented and its application in the main analysis is justified.

Table 1.1: Summary of thesis studies

	Study Name	Aims	Participant Profile	Description
Chapter Three	Imaging segmentation and measurement of BMLs	To test the reliability of image segmentation and BML volume measurement.	n=20 Foot pain and BML group (1 time point)	Test the face validity and intra-rater reliability of segmentation of individual bones and BML volumes in the following sub-studies: I. Phantom study II. Manual and auto Tracing III. Signal growth IV. Signal subtraction
Chapter Four	Exploration of the effect of orthotic intervention on BMLs and patient reported outcomes	To compare pain, impairment and bone stress outcomes at baseline and follow-up. To compare the outcomes between the two insole groups.	n=42 Foot pain and BML group Randomised groups: Functional orthosis Cushioning insole	To compare baseline and follow-up: VAS MFPDI BML Volume To compare changes between insole groups: VAS MFPDI BML Volume
Chapter Five	The effect insoles have on gait parameters and foot kinematics	To compare multi-segment foot kinematics during barefoot and shod walking. To explore whether insoles can alter in-shoe gait parameters and foot kinematics. To compare foot kinematics between insole groups	n=15 Normal group n=15 Foot pain sub-group n=20 Foot pain group: n=10 Functional orthosis n=10 Cushioning insole	To compare gait kinematic variables: I. barefoot and shod II. between the foot pain and pain-free groups. To compare gait kinematic variables at follow-up between the insole groups

Chapter Four

In Chapter Four, the effect of foot orthoses on foot pain and patterns of bone stress is explored. In this chapter the image subtraction method of BML quantification (investigated in Chapter Three) is applied. Firstly, the clinical presentation of mechanical midfoot pain and associated patterns of BMLs are described and discussed in detail. In the main study, the effect of orthoses on changes in BML volume, foot pain and impairment are reported and discussed. Finally, the differences between the active functional foot orthoses and control cushioning insole intervention on the patient outcomes and imaging patterns are presented to investigate the mechanism of action of functional orthoses on bone physiology.

Chapter Five

In Chapter Five, the effects of foot orthoses on gait parameters and segmental foot kinematics are presented. In the main study of this chapter, foot kinematics were compared in-shoe and with and without functional foot orthoses, to better understand whether orthoses can systematically modify foot motions. This chapter also included a preliminary sub-study: the development and investigation of a novel gait shoe that can accommodate multi-segment markers and the foot orthoses.

Chapter Six

In Chapter Six, the main findings of the three experimental chapters are presented and discussed. The main findings of this thesis are compared to existing literature and the relevance to clinical practice considered. Finally, this thesis ends with conclusions and recommendations for future research in this field.

Chapter Two:

Literature Review

2.1 The Prevalence and Burden of Foot Pain

Prevalence of Musculoskeletal Foot Pain

Foot pain is a common problem in the UK affecting just over one in five people [1]. Similar prevalence figures in Europe (11%, 15%, and 22.5%) [2-4], USA (25%) [5] and Australia (17%) [6] suggest that foot pain is a global problem. The overall frequency of disabling foot pain in the UK is roughly equal between males and females, although some studies suggest more females suffer with foot pain in later years (aged 55 to 65 years) [1-3, 6, 7].

During adulthood, the prevalence of foot pain is strongly influenced by age: it is least frequent in early adulthood, and most frequent around age 50, often reducing in retirement years [1, 8, 9]. In addition, the location of pain within the foot can be influenced by age [1, 6, 10]. For instance, forefoot pain, is most prevalent in the older population associated with forefoot width and hallux valgus deformity [11, 12]. The midfoot has a similar prevalence of pain throughout adulthood and, hindfoot pain is more prevalent in younger age groups [1, 6].

Burden of Musculoskeletal Foot Pain

In the UK, foot pain associated with activity limitations can be highly disabling for one in twelve people [1, 8]. Foot pain, at any age, affects numerous facets of daily living, which frequently leads to disability. Daily activities affected by disabling foot pain include: standing time, sit-to-stand activities, stair climbing, walking ability and household activities [13-17]. In

the elderly, disabling foot pain is also associated with poor health and loss of social independence [13, 15, 18-21].

Not surprisingly, when foot pain occurs with other lower limb pain, there is greater pain and physical impairments than foot pain alone [17, 22, 23]. In particular, the combination of knee pain with foot pain has been strongly associated with increased severity of foot pain, greater activity impairments and walking difficulties [6, 17, 24]. The accumulation of multiple joint pain with foot pain can be associated with health deterioration and lifelong disability [8, 15, 25, 26].

Musculoskeletal joint pain consumes a range of health and social resources, including consultations, medication, rehabilitation, mobility aids and medical imaging [27-30]. In addition to the medical burden, foot pain disability can also lead to economic burden reflected in the high quantity of incapacity claims for musculoskeletal diseases [31-34]. For the foot, specific cost analyses of pain and associated disability are not available, however foot pain is a common reason to visit general practitioners [35]. While the contribution of foot pain to health economic data remains unknown, given the prevalence and burden estimates, it is likely to be notable.

2.2 Factors Associated with Foot Pain

Physical and Mental Health Factors

Foot pain is highly related to physical health and mental wellbeing [7, 36]. The interaction between depression and foot pain is related to movement and participation, as symptoms of depression are related to the fear of movement and pain severity [10, 37]. The relationship between foot pain and wellbeing is perhaps more complex than physical movement alone. There is a strong relationship between foot pain and multiple co-morbidities that may be linked with increasing age [6, 10, 17]. The combination of poor

physical and mental health with foot pain may indicate a poor prognosis and potentially long-term disability.

Body Weight

Not surprisingly, increased body weight has a substantial influence on the lower limb joints, often associated with long-term pain and disability [38, 39]. The foot is particularly sensitive to body weight changes, which often alters walking patterns [40], and with rising obesity rates this is likely to have a greater impact on foot disability in the future [41, 42]. A body mass index (BMI) of 28 and over can double the prevalence and severity of foot pain, though this impact can diminish in older age groups (over 75 years), possibly due to reduced mobility [6, 10, 14, 43]. Obesity-related ankle and foot pain responds positively to bariatric surgery, showing long-term improvements in pain and employment prospects [38, 44, 45].

Occupation

Foot pain has been associated with specific employment activities that involve physical strain [6, 46, 47]. Occupations that include lifting, for example in the farming industry, seem particularly susceptible [18, 47]. In addition, occupations that involve bending and squatting report more frequent and painful toe deformities, such as bunions, hammer and curled toes [18, 48].

Footwear

Poor-fitting footwear can cause temporary foot pain and increases the risk of foot problems developing, particularly in women [18, 49, 50]. Half of women report forefoot and hindfoot pain associated with a history of high heeled or poorly fitting shoes, in contrast men rarely report footwear related pain [12, 49, 50]. Older women with wider feet tend to experience predominantly forefoot pain associated with narrow and small footwear [12, 51, 52]. While there are some indications that footwear choice can be associated with foot

pain, it may also relate to the onset of foot deformity, such as hallux valgus [50].

In summary, foot pain is a common problem associated with impairment and disability. There are a number of health and lifestyle factors that are associated with foot pain. Some factors, such as chronic ill-health, obesity and occupation, may confound outcomes in foot pain treatments that are linked with long-term disability.

2.3 Mechanical Foot Pain

Foot pain that presents as a result of weight-bearing movement, such as walking and standing, is considered to be mechanically mediated [53]. This is referred to as mechanical foot pain. These pains are usually local to musculoskeletal and connective tissues in and around the joints, and are not associated with systemic inflammatory immune disease. Inflammatory musculoskeletal pain associated with auto-immune disease, such as rheumatoid arthritis, presents with diurnal variation and early morning stiffness of 30 minutes or over, and is not considered mechanical [54].

Most epidemiology studies have not attempted to define mechanical foot pain, preferring to divide the foot into regions rather than attribute a single aetiological cause. Rather, mechanical foot pain is a broad definition that encompasses a wide variety of specific pathologies that can cause pain. Due to the complex anatomy and function within the foot, localised pain syndromes are commonly used rather than specific diagnosis of foot pathologies: for example “metatarsalagia” including the forefoot and toes or “heel pain syndrome” including the hindfoot. Many clinical studies investigate a syndrome or regional pain due to a lack of diagnostic criteria or imaging to confirm the underlying diagnosis.

The underlying aetiological causes of mechanical foot pain are poorly understood. Common causes of mechanical foot pain such as plantar fasciitis and tendonitis are routinely diagnosed using clinical history and examination, possibly without a full understanding of the other possible underlying pathologies. For instance, histological studies have suggested that localised pain at the foot tendons and fascia may be a degenerative fibrotic process, rather than purely an inflammatory process, as previously thought [55-57]. The presentation of localised foot pain may well be degenerative or inflammatory and some may have both elements depending on the stage of disease [58].

Understanding the role of pathology in mechanical foot pain may enable streamlining of treatment and targeting specific mechanisms. For instance, steroid injections for foot pain may have greater efficacy if targeted to a pathological process identified using clinical or imaging indicators of inflammation. Equally, treatments that aim to modify foot mechanics such as foot orthoses may be better targeted, as it is not known the extent to which abnormal mechanics influence foot pain. A clear link between mechanics and foot pain may prove an important indicator for mechanical devices such as orthoses.

Mechanical foot pain can often result from a sudden single episode of major trauma or repetitive minor trauma with slow onset [1, 59]. Acute single trauma, such as sprains and strains, are frequently associated with short-term and long-term disabling foot pain [1]. Whereas, recurring minor trauma is thought to be related to local structural factors, such as foot deformity, lifestyle, weight-bearing movements can cause repetitive strain. Mechanical foot pain can also be associated with joint degeneration and structural foot deformity in adults of all ages.

The most common structural foot deformity is hallux valgus, which in severe cases is associated with joint pain, activity limitation and disability [11, 48,

52]. Planus or flat-foot deformity is another common structural deformity, often associated with foot pain in older adults [1, 10]. The prevalence of cavoid foot deformity is lower than hallux valgus and planus foot deformities, however it is highly associated with foot pain [6, 60]. Many cross-sectional epidemiology studies suggest a history of foot deformity can increase the likelihood of foot pain [6, 18, 60] but in the absence of prospective studies, this has not been confirmed.

Mechanical Midfoot Pain

This review of mechanical foot pain will be focused to the midfoot region as this is the focus of this thesis.

For the purpose of this thesis, mechanical midfoot pain was defined as a regional pain syndrome that includes a range of pathologies. The midfoot region starts from the neck of the talus medially and the peroneal sulcus of the cuboid laterally, extending distally to the mid shafts of the metatarsals. A distinction is made between the medial region including talus, navicular and the medial three tarso-metatarsal joints and the lateral region including the calcaneus, cuboid and the fourth and fifth tarso-metatarsal joints (see Figure 4.1).

The midfoot is a common region for foot pain associated with disability, nonetheless, little is understood about the potential multiple foot pathologies in this area [1, 6]. It includes a variety of conditions, including: posterior tibial tendon tears and ruptures, ligament disruption, degenerative inter-tarsal changes, fractures and dislocation of the tarsal joints [61-65]. Clinically midfoot pathologies that alter the movement and shape of the arch may be referred to as a “fallen arch” or pes planus deformity, rather than singular anatomical pathologies, possibly due to the complexity of midfoot anatomy [63].

Midfoot pain and pathology can affect normal walking and standing posture in daily living as these structures maintain the position and movement of the

foot [66]. Insights into foot pain may be provided by understanding the patterns of bone and soft tissue pathology using appropriate imaging modalities, which can provide a surrogate measure of pathology. The strengths and weaknesses of imaging, in particular MR imaging, to aid diagnosis and recognise pathological patterns of abnormality and morphology are discussed further in the next section.

2.4 Imaging of Foot Pathology

Medical imaging modalities are well established surrogate measures of pathology, with specific indications depending on the suspected underlying pathology and diagnosis. Plain radiographs, or X-rays, are the most common and long-standing imaging modality in rheumatology often used as the benchmark standard to aid diagnosis of bone pathology [67]. Plain radiographs are widely used to visualise fractures, alignment and bony deformities associated with trauma, infection, joint diseases and articular lesions [68-70].

Assessing the midfoot region, using the newly developed radiographic foot atlas for instance, has shown that mechanical midfoot pain may be more commonly associated with bone and joint pathology than previously suspected. Menz *et al.* (2010) found that radiographic OA was much more common than previously suspected in the midfoot region, with a prevalence of 60% in an elderly cohort [71]. The most common joints associated with foot pain were the navicular medial-cuneiform joint and the intermediate cuneiform-metatarsal joint [71]. In comparison, the first metatarso-phalangeal joint was less associated with self-reported arthritis pain [71].

Plain radiographs have been the standard measure of moderate to advanced arthritis, however they offer poor detection of non-radiolucent pathology in tendons, ligaments, capsular tissues and in particular acute physiological bone abnormalities [72, 73]. Sensitive imaging modalities,

such as MR imaging are used to aid diagnosis of soft tissues and joint pathology that may cause mechanical foot pain [74, 75].

Magnetic resonance imaging provides detailed visualisation of anatomical structures, in three dimensions, with signal intensity changes to highlight abnormal structures [76-80]. The interpretation of MR imaging is often used as a surrogate measure of pathology that can aid the clinical diagnosis of soft tissue, bone and joint pain [81, 82].

Magnetic resonance imaging can detect anatomy and bone contrast using varied field strengths. Conventional signal strength (1.5T or 3T) MR imaging scanners are very costly units that are required to detect central as well as peripheral abnormalities, requiring high field strength for all manner of pathologies. Lower field (0.2T) magnet strength MR imaging on the other hand was developed with a smaller bore specifically to scan musculoskeletal conditions in the joints of the extremities. The extremity magnets do not have the field strength for spectral water and fat differentiation, however signal contrast in the joints and tissues can be made using comparative sequences [83]. Comparison between abnormal imaging features using conventional 1.5T and extremity 0.2T shows good identification of connective tissues; menisci and ligament damage [83, 84]. Other imaging features such as cartilage damage has poor comparative detection rates *in-vitro* cartilage, although detection improved with greater lesion sizes [85, 86]. In terms of abnormal bone signal, extremity has good specificity (82.5%) of lesions, however extremity MR imaging lacks (65%) sensitivity of BML detection to conventional 1.5T MR imaging [87]. Most musculoskeletal research has been undertaken using conventional 1.5T MR imaging units.

In the foot, combined cadaveric and conventional MR imaging studies have shown a good visualisation of the complex midfoot anatomy, with the use of multi-planar imaging of oblique tissues and joints [88, 89]. In terms of midfoot pathology, MR imaging has been shown to be highly sensitive (94%)

of subtle and localised ligament and bone pathology, but lacks specificity (74%) compared to plain radiographs [64, 90, 91]. The main advantage of MR imaging over radiographs and ultrasound imaging is the concurrent depiction of bone pathology and physiology.

The relationship between mechanical foot pain and pathology, particularly at the midfoot, has not been examined fully. Using MR imaging, bone pathology in the foot can demonstrate patterns of abnormal contrast features within the bone, known as bone marrow lesions. Bone marrow lesions are a common and sensitive imaging feature associated with numerous musculoskeletal conditions. Bone marrow lesions may depict a spectrum of pathology (bone damage and repair) associated with weight-bearing stress. As the imaging feature (bone marrow lesions) is central to this thesis, it is discussed further, with particular focus on the foot.

Bone Marrow Lesions

The term bone marrow lesions (sometimes referred to as bone marrow oedema) are a contrast abnormality depicted exclusively on MR imaging. Bone marrow lesions (BMLs) are a benign region of heterogeneous signal intensity with ill-defined borders, situated within intramedullary bone. They are non-specific pathological findings on MR imaging associated with five main types of conditions: trauma, degeneration, infection, ischaemia and neoplasm (benign and malignant). Bone marrow lesions are also referred to as bone marrow oedema, however the term oedema implies an infiltrate of water, which does not reflect the variable pathological causes [79].

In musculoskeletal conditions, heterogeneous regions of BMLs, without a defined neoplastic lesion, are commonly associated with degenerative, traumatic, vascular and inflammatory conditions. Bone marrow lesions are a common finding with inflammatory conditions such as rheumatoid arthritis, spondyloarthropathies and represent infiltrate of fluid that can be erosive [87, 326]. In a consecutive sample of non-inflammatory musculoskeletal pain

(104 MR images taken to aid musculoskeletal diagnosis), the knee appears to be the most susceptible region of non-specific BMLs, followed by the talus and then the femoral head; the causes can be idiopathic, post-traumatic, mechanical stress and OA [92]. The occurrence and natural history of BMLs in the wider population is mainly limited to the knee joint due to the prevalence of knee pain and interest in understanding early onset of OA. Persistent BMLs in painless and painful knees can lead to cartilage defects in half of all cases [93-95]. Bone marrow lesions in the knee demonstrate a spectrum of pathology that in some cases may be associated with the onset of OA and those BMLs that resolve can represent a different histological profile.

There can be a range of histopathological findings associated with BMLs in different degenerative joint diseases. In OA, BMLs are commonly found, but the relative relationship between signal intensity and pathology appears more complex than in inflammatory joint diseases [96, 97]. In osteoarthritic knees and hips, histological studies report some oedema but mostly a mixture of necrosis, fibrosis and trabeculae micro-fractures [79, 98]. While there are no MR imaging or histological studies examining OA in the foot, radiological texts report similar pathological processes on plain radiographs.

Bone marrow lesions that are independent of neoplasm and degenerative joint diseases can reflect changes in bone physiology and pathology. Vascular metabolic disturbance for instance can manifest as diffuse patterns of BML (such as reflex sympathetic dystrophy syndrome), sometimes associated with necrosis (such as avascular necrosis) [99-101]. Both BML disorders are often found in the talus bone of the foot with typically distinct clinical presentations [102-104]. Within this spectrum of BML disorders, the least understood is transient osteoporosis, more recently described as bone marrow oedema syndrome. Histology studies of bone marrow oedema syndrome show reactive bone formation in the marrow spaces and oedema. This process of osteoclastic bone re-absorption, with little or no bone necrosis, reflects bone growth and increased bone vascularisation [105-

107]. Clinical and histological studies demonstrate that bone marrow oedema syndrome in the foot can be self-limiting (usually lasting 12 months) and a painful physiological bone disorder, that is characterised by alterations in bone density [104, 108].

Tentative new evidence suggests that BMLs may not be an entirely local pathophysiological process: it may also reflect systemic and age related changes. One small study showed bone marrow oedema syndrome in the foot was linked to concurrent osteoporosis and osteopenia associated with vitamin D deficiency [109]. In the knee, onset of BMLs in middle aged women was associated with increased circulating total cholesterol and triglycerides [110]. Although systemic factors may play a role in the onset and development of BMLs, the patterns of BMLs associated with foot pain may also be influenced by local mechanics.

Bone Marrow Lesions and Foot Pain

The link between foot pain and abnormal bone marrow was first identified with bone scintigraphy [111]. In the foot, metabolic bone changes associated with stress fractures, osteochondral defects, bruising, coalitions, and accessory bones found on scintigraphy were later confirmed with MR imaging as BMLs were found at concurrent sites [112, 113]. Some patterns of BMLs can present with mechanical trauma (triggered by minor stress) such as bone bruise or stress response, or severe trauma manifesting as a fracture [113]. A bone bruise has been identified as a histological mix of oedema, bleeding and micro-fractures within the bone; this can be difficult to distinguish between bone formation and early avascular necrosis [114]. The natural history of foot pain and associated BMLs in the foot is not widely understood.

Patterns of BMLs can be asymptomatic in the foot as well as the knee. this has been associated with intense mechanical movements, such as regular physical activity and endurance sports [115-117]. In these studies there are

no histology results to identify the bone pathology, and therefore a spectrum of abnormalities may be involved, including: bone formation, trabeculae damage and bruising. This questions the clinical significance of BML, particularly if they reflect a normal physiological process. The presence of BMLs may present a spectrum of physiological change that may lead to pathology and pain, however, there have been no histological studies to compare asymptomatic and symptomatic BMLs in athletes. The role of BML associated with foot pain has been investigated further in some MR imaging studies seen in Table 2.1.

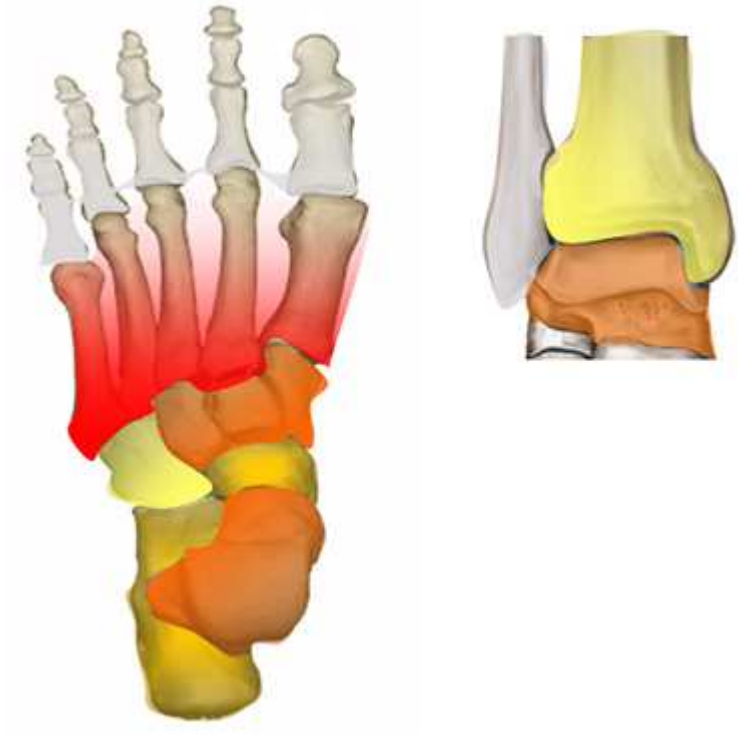
Mechanical overuse in daily activities, such as walking and standing, can be associated with foot pain and BMLs [118]. This pattern can present with chronic tendinopathy local to tendon and bone junctions at the cuboid, calcaneus and navicular [119, 120]. In the absence of soft issue and joint pathology, patterns of BML in the hindfoot and midfoot are usually described as bone marrow oedema syndrome or bone stress (a precursor to stress fractures) [121]. In many foot studies (see Table 2.1), multiple BMLs have been described in two or more bones of the foot, typically involving the talus and bones on the medial side of the foot [121-123]. Figure 2.1 illustrates the proportion of bones affected by stress by summarising the results of 10 foot studies. According to published research the metatarsals are proportionally the most commonly affected site, followed by the talus and the cuneiforms (see Table 2.1). This pattern may reflect a heterogeneous distribution of bone stress as some of the research studies were small in size or confined to military and sports personnel, no community studies have been undertaken to document the patterns of BMLs in the foot associated with pain.

Table 2.1: Summary of MR bone stress studies of the foot

Author	Sample Size	Bones	Frequency	Cause
Schweitzer & White 1996 [282]	12	Tibia Calcaneus Cuneiform Metatarsals Phalanx	3 2 1 4 8	Non-Radiographic Bone Stress Discomfort with exertion and pronation insole
Lazzarini *et al.* 1997 [127]	32	Tibia Talus Calcaneus Navicular Cuboid Cuneiform Metatarsals	3 10 16 11 5 5 11	Asymptomatic runners
Morrison *et al.* 2001 [121]	116	Tibia Fibula Calcaneus Cuboid	17 6 2 1	Mechanical Tendonopathy Pain with exertion
Radke *et al.* 2001 [105]	10	Talus Navicular Cuboid	8 1 1	Bone marrow oedema syndrome Pain with exertion
Zanetti *et al.* 2002 [122]	31	Tibia Fibula Talus Calcaneus Navicular Cuboid Cuneiform Metatarsals	5 2 11 11 11 6 12 11	Bone marrow oedema abnormalities Pain with exertion
Gigena *et al.* 2002 [123]	5	Talus	5	Transient Bone marrow oedema syndrome Pain with exertion
Fernandez-Canton *et al.* 2003 [124]	25	Tibia or Fibula Talus Calcaneus Navicular Cuboid Cuneiforms Metatarsals	10 16 13 16 15 18 10	Bone marrow oedema syndrome Pain with exertion
Trappeniers *et al.* 2003 [126]	10	Talus Calcaneus Navicular Cuboid Metatarsals	8 2 3 1 1	Asymptomatic Runners
Aigner *et al.* 2005 [288]	23	Talus Calcaneus Navicular Cuboid Cuneiforms Metatarsals	12 2 1 0 4 4	Bone marrow oedema syndrome Pain with exertion
Niva *et al.* 2006 [128]	131	Tibia Fibula Talus Calcaneus Navicular Cuboid Cuneiform Metatarsals Phalanx	8 5 55 33 33 18 79 124 2	Non-Radiographic Bone stress Military recruits Pain with exertion

Three studies have described imaging of foot BMLs in which patterns of lesions have been followed over a year. Around half of the BMLs associated with foot pain resolved over one year, irrespective of stress fractures [121]. Greater resolution (72%) of BMLs has been reported following a year of conservative therapy (non-steroidal anti-inflammatory drugs, calcium, calcitonin, physical therapy, massage - alone or in combination) [123]. The remaining BMLs showed patterns of stasis (8%), while others showed local migration into adjunctive bones of the same foot (20%) [123]. Longitudinal studies suggest foot pain persistence and intensity was associated with migration of BMLs in the other foot and the presence or development of associated pathological findings, for instance: necrosis zones, cysts, osteochondral defects and bone debris [121, 123, 124].

Figure 2.1: Bone stress map



Legend:

0-5%	6-10%	11-15%	16-20%	21-25%

Caption: This colour map (produced for this thesis) illustrates the pattern of bone stress in the foot bones as a proportion of the total bones (n=682) summarised in the 10 symptomatic and asymptomatic research studies shown in Table 2.1.

Biomechanics and Bone Marrow Lesions

Certain patterns of BMLs may occur following intense physical activities. Following excessive mechanical loading (in particular running), the presence of BMLs in conjunction with increased fluid in the joint and tendons has been found [115]. The foot is particularly susceptible site of bone stress injuries [117]. In runners, BMLs more frequently affect the talus, followed by the calcaneus, navicular, and finally the cuneiforms [117, 125, 126]. In military recruits, the most common area of bone stress was the metatarsals, followed by the tarsal bones in a similar pattern to runners [127, 128]. Reduced hindfoot motion in a rectus and cavus foot type showed greater proximal injuries (femur, tibia), while excessive motion in the pes planus type showed greater tarsal and metatarsal injuries [129]. It appears that the medial midfoot may be more susceptible to mechanical stress, as the navicular and cuneiforms were more commonly affected than the cuboid, which may be related to variants of foot type (see Table 2.1 and Figure 2.1).

In the knee (a common site of pain, pathology and disability) [130-132], the relationship between biomechanics, pain, and bone stress has been explored [133-135]. Painful knee OA has been associated with abnormal biomechanics: the incidence, location and progression of radiographic changes (in the medial or lateral surface) has been strongly associated with mal-alignment [136-138]. Further investigations using gait analysis of dynamic knee motion and ground reaction forces have shown knee adduction angular impulse and knee adduction moments were related to the severity of pain and stage of radiographic knee OA [139, 140].

These patterns of increased medial knee loading have also been associated with MR imaging detected knee pathology including the prospective increase of medial cartilage defects, an increase of medial tibial expansion and loss of cartilage volume [141, 142]. In relation to bone stress associated with knee OA, a varus alignment and increased medial knee forces (knee adduction moment and adduction angular impulse) were related to the presence of BMLs in the medial aspect of the tibia and femur bones [143, 144]. These

results indicate there may be a close biomechanical and biological relationship with knee pain and knee OA. Whether this also occurs in the foot is not clearly understood.

In summary, the clinical association and natural history of foot BMLs is poorly understood due to the lack of large cross-sectional or longitudinal MR imaging studies. In the knee, long-term MR imaging studies have shown an association between pain, specific patterns of bone pathology, and the biomechanical function of the knee. In comparison, less is known about the development of BMLs in specific foot pathologies in the foot. The available imaging studies suggest foot pain has been associated with specific patterns of BMLs in the foot, often in the medial midfoot bones. Exploratory studies suggest a link between biomechanics and the onset and resolution of foot BMLs, however the influence of mechanical treatments are limited to patterns of BMLs associated with acute stress or secondary to joint diseases. Larger clinical studies have been undertaken in the knee to understand the complex biological and mechanical interaction of bone and joint stress. In the foot, the relationship between biomechanical stress and bone pathology is not as clearly understood. Exploratory studies that measure foot biomechanics can provide insights into foot pain and dysfunction. In this next section the relationship between biomechanics and foot pain is discussed.

2.5 Biomechanics and Foot Pain

Measuring foot function can be undertaken using many methods. The simplest methods are motion-time studies that provide useful indicators of normal walking, from cadence to temporal and spatial characteristics of gait [145]. Contemporary gait analyses utilise a variety of gait laboratory equipment to measure kinetics (ground reaction force and plantar foot pressures) and kinematics (linear and angular motion). Clinical gait studies have shown foot pain can alter gait patterns in the foot and lower limb. Joint modelling of the lower limb has been utilized to investigate movement

patterns in daily activities such as walking, stair climbing and getting up from a chair [146-148]. Studies of lower limb motion have found a relationship between joint pains and lower limb biomechanics.

Relationship between Biomechanics and Foot Pain

In the last 20 years, research examining the relationship between biomechanics and foot pain has been growing. The relationship has been explored in both prospective studies and cross-sectional comparative studies. Prospective gait studies have identified specific kinetic and kinematic patterns associated with increased risk of injury, however they are most commonly found in sports participants and military personnel [149].

Specific biomechanical patterns have been associated with the onset of knee pain [150-153], shins splints [154], Achilles tendonitis [155] and ankle sprains [156, 157]. In the foot and ankle, the risk of Achilles tendon injuries and ankle inversion sprains in runners has been related to the transference of medial to lateral forefoot pressure during propulsion, increased foot contact time, increased knee flexion, greater tibial varum and calcaneal eversion range of motion (ROM) [155-157].

Biomechanical studies of musculoskeletal foot pain are mainly cross-sectional comparisons with normal groups that can be associated with global alteration in foot movements. These studies have illustrated the importance of ankle coupling mechanisms when walking [158], which can be affected by hindfoot and ankle pathology. Hindfoot coupling of the axial rotation of the tibia and frontal plane calcaneus movements is a normal patterns shown during walking and running [159, 160]. These coupling mechanisms are affected in rheumatoid arthritis, pes planus deformity and chronic ankle instability, where greater internal tibial rotation with prolonged and greater hindfoot eversion during stance has been noted [161-165]. The coupling mechanism between the tibia and calcaneus appears exaggerated in painful pathological complaints, with greater internal rotation and calcaneal eversion, also known clinically as a valgus heel.

This research highlights the relationship between proximal and distal segmental kinematics associated with joint pain. These relationships are widely reported for the knee and hip joints in motion analysis, as marker placement and model assumptions are relatively straightforward compared to the foot [166, 167]. In comparison, measuring changes in foot motion can be particularly challenging due to the complexity and subtle motion of the foot. There are now a number of biomechanical approaches to modelling the motions of the foot that will be discussed in the next section.

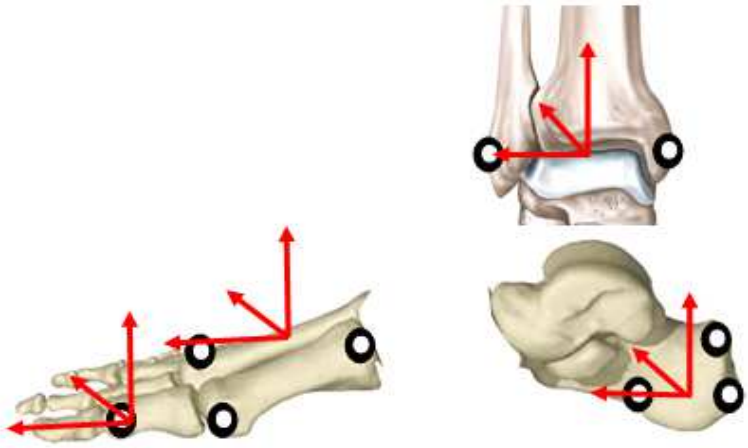
Biomechanical Foot Models to Measure Foot Kinematics

Measuring foot kinetics (either in-shoe or barefoot) can reliably be achieved using pressure insoles or force and pressure platforms. In contrast, measuring foot kinematics is far more challenging due to the complexity of the foot. Historically this has been overcome by measuring the foot as a single unit or confining kinematics to the hindfoot and ankle. Multi-segment foot models have attempted to solve this problem by partitioning the foot into separate segments. Multi-segment studies involving pathological and pain-free control groups have been undertaken, however there are difficulties in the understanding and interpretation of the kinematic outputs in the normal population due to the variability in segmental foot kinematics [168].

A method of modelling the foot has been proposed by grouping multiple joints into separate foot segments. *In-vitro* and *in-vivo* approaches to segmentation have been utilised, using either bone-pin models of individual joints, imaging models or pragmatic clinical models to derive segmental kinematics [169-171]. There are at least fifteen published multi-segment foot models in clinical and academic use that divide the foot from two to nine segments [172]. The positions of surface markers on a segment are used in conjunction with anatomical calibrations to determine the segment-fixed axes, about which segment rotation is described. The Euler angles approach or joint co-ordinate system are the most commonly applied mathematical methods to describe the motion of a rigid body in three

dimensions [173]. The joint co-ordinate system proposed by Grood and Suntay in 1983 [173] is widely recommended as it describes the joint and segmental motion (in all three planes) using clinically relevant terms and redefines the Euler angles independently of rotational sequence priority [174].

Figure 2.2: Illustration of a four-segment kinematic foot model



Caption: Anatomical marker placements and assumed location of segment co-ordinates (produced for this thesis).

The most common and basic multi-segment foot models consist of four-segments: tibial, hindfoot, mid/forefoot and hallux (see Figure 2.2). From 1996 to 2001, three academic gait laboratories independently developed the basis of this model, known as the Milwaukee [175], CAST [176] and Oxford [169] foot models. These four-segment models are widely accepted and utilised in clinical research, forming the basis of an industry standard. The Milwaukee model has been the most widely used clinical model in America (seven clinical studies), while in the UK the Oxford foot model is widely accepted (six clinical studies) and the Italian CAST model has been used in three clinical and three methodological studies [172]. The main limitations of the methodological and clinical multi-segment kinematic studies are the

small numbers of study participants (range 1 to 34 participants), limiting inference to the larger population [172].

The four-segment foot models (Milwaukee, CAST and Oxford) were derived from a logical division of foot anatomy in order to understand the hindfoot, midfoot and forefoot motions, since it was assumed that clinically these segments moved as a functional unit. These models showed good within-session and within-person reliability, although between-person and between-session reliability was lower. The Milwaukee model showed a coefficient of multiple correlation (CMC) intra-rater reliability of 0.72 to 0.99 and inter-reliability of 0.22 to 0.98 [177]. The CAST model was not as consistent, showing CMC intra-reliability of 0.64 to 0.91 and inter-rater reliability of 0.03 to 0.61 [176]. The Oxford model assessed the absolute differences of 0.7 to 2 degrees intra-rater variability and 1.1 to 6.4 degrees inter-rater variability [169]. Lower inter-rater reliability of segmental kinematics, shown in all foot models, possibly reflects the range of individual morphological and dynamic variability of the foot joints.

While it may appear that the Milwaukee model is the most reliable, each model had a different protocol and there have been no studies to compare the reliability of the models. The Milwaukee model utilises weight-bearing plain radiographs to identify the foot bones and a Eular description of rotation. The CAST model requires a virtual calibration of the foot bones (using a wand) and a joint co-ordinate system, whereas the Oxford model also utilised the joint co-ordinate system and relies on subjective skill to identify anatomical landmarks. The reliability statistics utilised in the validation of these models should be viewed with caution, due to the sample sizes. The size of the validation sample for the Milwaukee (n=6) [175] and CAST (n=9) [178] models was small for regression analyses. The reliability of the Oxford model was represented by more conservative statistics examining the absolute difference in kinematic traces with confidence intervals (CIs) in a comparatively larger group (n= 19) [169]. Due to the

small validation samples in all three models, one model is not considered to be superior over another as all three have methodological limitations.

As with all measurement systems, errors may occur at random or in a systematic manner. Systematic error in the multi-segment foot kinematics models can be local to individual segments. The four-segment kinematic foot models showed the highest reliability in the ankle and hindfoot segment (inter-reliability CMC 0.98, CMC 0.61, 1.1 degrees) and the least reliability in the forefoot segment (inter-reliability CMC 0.03, CMC 0.22 and 6.4 degrees) [169, 176, 177]. Forefoot segment rotations have good reliability within the same person and same session however, it is most susceptible to between day and between people variation [172]. The most commonly cited reason for variation between segment kinematics is the difficulties in repeated marker placement on the local foot anatomy.

The first reason for segmental variation may be poor knowledge of anatomical landmarks (for example: less pronounced joint margins and tubercles such as the sustentaculum tali or styloid process) and difficulty identifying landmarks, due to foot oedema or fat affecting precision. The midfoot and forefoot may be more susceptible than the hindfoot in these errors due to anatomical complexity and greater soft tissue volume. The second reason may be precision errors of marker placement, related to skin movement artefact. As recent cadaver studies have shown changes in skin movement artefact between three to eight degrees were more commonly found in the tarsal bones, with comparatively less artefact of one to two degrees at the tibial or calcaneus bones [170, 179]. These marker precision errors have been shown (*in-vitro* bone study of foot segments) to alter the alignment of the joint coordinate system, possibly altering segmental kinematics [179]. These cadaver models explain some of the error, other error may be the segmentation boundaries. A major drawback of clinical multi-segment models is that none of the marker placements or segmentations has been derived or validated using bone-mounted pins to examine the effect on segmental kinematics.

The results of three bone-pin multi-segment kinematic studies (two *in-vitro* cadaver and one *in-vivo* human) have shown variation in individual bone and segmental kinematics compared to the clinical models [170, 179, 180]. Lundgren *et al.* (2008) showed greater than expected motion of the calcaneus cuboid joint and fourth and fifth tarso-metatarsal joints in the frontal and transverse planes [180]. The variability of certain foot bone motions may add inherent error into the midfoot and forefoot segmental motions [179]. In particular, some bone-pin studies have shown that movement of the lateral forefoot joints were independent of the medial forefoot joints indicating a conflict in the traditional forefoot rigid segment. As a result, further segmentation of the foot has been proposed to divide the forefoot into a medial and lateral segments [181]. Testing the individual contributions of bone kinematics to segment kinematics in a cadaver study has shed light on this. Nester *et al.* (2007) found the greatest violation of the rigid body assumptions occurred with the inclusion of nine bones (navicular, cuneiforms and metatarsals) into the model [170]. A rigid body model was upheld when combining the navicular and cuboid into one segment. Models based on cadaver *in-vivo* bone research may derive new multi-segment foot models that maintain rigid body assumptions and possibly reducing sources of error.

Pragmatic clinical four-segment models are commonly used and the kinematic outputs are widely published, but there are some draw backs. The kinematic motion of the forefoot segment, for instance, is cautiously interpreted, as systematic sources of error are known. The understanding of bone-derived kinematics may inform the development of future segmental models, however the relative motions between the bones and segments in normal and pathological groups will need further investigations. For clinical studies using the four-segment model is the most pragmatic approach, and this improves on the previous hindfoot and ankle joint complex models. Clinical studies using the four-segment kinematic model or ankle joint

complex model, have shown altered patterns of movement in people with lower limb pain. This is reviewed further in the next section.

Relationship between Foot Kinematics and Foot Pain

Segmental motion patterns suggest there is a natural variance associated with foot posture (for instance pes planus). Normal patterns of foot kinematics suggest there are predictable patterns in the tibia and hindfoot segments with greater variability in the midfoot and forefoot segments [168, 170, 179]. Morphological alignment appears to account for some variability in foot motion, as anatomically high arched participants appear to be more inverted and internally rotated in the hindfoot and midfoot segments during walking, compared to low arched (pes planus) individuals [182]. In addition, comparative kinematics of 'normal' and pes planus foot types showed prolonged hindfoot eversion and midfoot adduction [183, 184].

Foot kinematics in groups of people with foot pain and pathology appear to be comparatively different to pain-free control groups. Posterior tibial tendon dysfunction can cause pain, walking difficulties and flat foot deformity associated with altered kinematics. In this foot disorder gait studies have reported reduced inversion and hindfoot dorsiflexion at heel strike, greater forefoot abduction in mid-stance and at toe-off, and greater hindfoot eversion throughout stance [185-189]. These alterations in segmental kinematics in posterior tibial tendon dysfunction are similar to those with pes planus foot type [183, 184], suggesting that foot deformity may lead to universal changes in foot segments.

Osteoarthritis is another common cause of foot pain and disability that can be associated with walking difficulties [190]. Painful OA of the ankle and first metatarso-phalangeal joint has been associated with the global alterations in the hindfoot, forefoot and hallux motion compared to a healthy group [191, 192]. In people with midfoot OA, reduced hallux motion was noted, however hindfoot and midfoot segments did not differ when compared to the normal

group [193]. This discrepancy between the midfoot and the forefoot and ankle OA studies may be due to walking speed. Reducing the walking speed of the normal comparative group (as in the midfoot OA study), can change kinematic patterns and potentially remove the group differences [194].

These small comparative studies show that pain local to the posterior tibial tendon and OA of the foot can be related to altered foot movements. All the studies above showed foot pain was associated with slower walking speed and less dynamic ROM in the hindfoot, forefoot and hallux. In addition, adverse patterns of hindfoot, forefoot and hallux motions were found, compared to healthy pain-free groups. Although altered foot movements are associated with painful foot pathologies (posterior tibial dysfunction and foot OA), it is unclear if it was an aggravating factor or a consequence of altered walking with foot pain.

In summary, transference of in the pattern of medial to lateral foot pressures and abnormal hindfoot eversion has been associated with the incidence of ankle pain. Local foot pain and foot pain as part of a pattern of multiple limb pain can show altered walking patterns and joint movements. Specific foot deformities and painful pathologies appear to alter segmental foot kinematics in comparison to pain-free participants. Pathology of the midfoot (posterior tibial tendon and midfoot OA) was associated with greater hindfoot eversion, forefoot abduction and reduced hallux dorsiflexion that was similar to abnormal pes planus foot types. The role of in-shoe foot orthoses in altering adverse foot kinematics associated with foot pain has been examined in a number of foot pathologies, this will be discussed in the next section.

2.6 Efficacy of Foot Orthoses for Improving Foot Pain and Biomechanics

Foot orthoses are widely used to treat a range of disorders that cause foot pain and foot deformity. Systematic reviews suggest the evidence for the efficacy of foot orthoses is strongest in systemic diseases, such as diabetes and rheumatoid arthritis, which can lead to chronic and progressive foot deformities [195-197].

The efficacy of orthoses has been explored using biomechanical measures in healthy pain-free controls and foot pain groups. Historically, clinical paradigms have suggested that excessive subtalar (hindfoot) pronation during walking and running may be detrimental. This has been supported by some foot posture measures and kinematic studies where healthy participants had less pronation than groups with foot pain. As a result the main aim of foot orthoses has been to reduce “adverse” hindfoot pronation.

There are many different types of foot orthoses that may alter foot pronation including commercial “off the shelf” products (known as pre-fabricated), which are contoured to support the arch and forefoot. In order to accommodate different foot types, prefabricated orthoses can be modified to change arch height, add cushioning or wedging (often referred to as semi-custom orthoses). Bespoke customised orthoses (known as cast foot orthoses) are made by taking an impression of the foot and making foot orthoses in a variety of materials. The type of material used to make the foot orthoses (softer cushioning or rigid orthoses) can have a different biomechanical effect [198]. All three types of foot orthoses, pre-fabricated, semi-custom, and bespoke are often prescribed for foot pain.

Effect of Foot Orthoses on Pain and Impairment

Foot orthoses have been shown to improve pain and impairment in the foot and lower limb across a range of disorders. Observational and clinical studies investigating the treatment of foot orthoses for a wide range of foot

disorders suggest that about half of people report improved foot pain and approximately one third report a prevention of re-occurrence or deterioration with continued use [199-201].

In specific foot pathologies, there is good randomised controlled trial evidence supporting the ability of foot orthoses to improve pain, function and disability [197]. A summary of randomised controlled trials for foot orthoses is provided in Table 2.2, trials of diabetes and rheumatoid arthritis have been specifically excluded. Plantar fasciitis has been the most researched (with three large randomised trials), in addition to two cross-over trials comparing different orthoses and night splints. The evidence suggests that foot orthoses (pre-fabricated and custom) can improve pain and function in people with plantar fasciitis from an eight to 52 week period [202-205]. The effect however was similar over one year compared to night splints, although orthoses compliance was greater [203, 206]. Only one randomised trial compared the orthoses to a non-functional flat sham insole, short-term improvements of heel pain and function were shown [204]. In addition, there is some evidence that when used in combination with rehabilitation (such as stretches), the orthoses may have a greater effect, although further large randomised controlled trials are needed [207].

In the treatment of painful pes planus foot disorders, associated with posterior tibial tendon dysfunction, there have been two orthoses trials. A pre and post orthoses intervention showed a 50% decrease in pain and disability [208]. When the orthoses treatment was randomised, a smaller effect on pain (-16%) and disability (-15%) was found [209]. Painful rigid foot deformity (pes cavus) can be associated with high foot pressures and treatment with foot orthoses compared to a flat sham insole showed a relative (-8%) reduction in pain and dysfunction (-10%) [210, 211].

Foot orthoses have also been shown to improve pain and function in patients with chronic degenerative foot deformities. Rheumatoid arthritis,

OA and juvenile arthritis can affect the joints of the feet often causing painful pes planus deformity [63, 212, 213]. Randomised trials of foot orthoses in rheumatoid and juvenile idiopathic arthritis have shown improvements in pain, function and disability compared to a control group [214, 215]. Long-term follow-up of people with rheumatoid arthritis has shown continued improvements in function and impairment [216]. Physiological changes in foot posture suggest that orthoses have a role to play in the stabilisation of foot deformities.

Osteoarthritis in the forefoot and knee can be treated with foot orthoses in order to modify abnormal foot forces, peak angle and pressure [139, 140, 217, 218]. Studies of foot orthoses for painful hallux valgus have shown moderate to good short-term pain reductions (-14% to -33.5%) over six months, however after 12 months, improvements in pain (-10%) lessened [219, 220]. In two high quality (double blind) randomised controlled trials of knee pain, the effect of the orthoses (compared to a sham insoles) showed only minor changes in pain (-1.1% & 0.4%) and knee function (-0.8% & 0.4%) over a one to two year period [221, 222]. These studies showed some short-term effect of foot orthoses in foot OA, however there was little effect in knee OA compared to a sham [221-224]. Biomechanical studies of orthoses in hallux valgus and knee OA conditions suggest there are variable biomechanical patterns, which may suggest a specific biomechanical profile of responders to orthoses treatment [141, 220, 225].

Table 2.2: Summary of randomised controlled trials of foot orthoses

Author	Participant Profile	Interventions	Change of Pain	Change of Function
Hirschmüller *et al.* 2011 [226]	RCT Symptomatic running injuries Total No. = 99 8 weeks	Custom Orthoses = 51 vs Control = 48 no orthoses	-6.6 mean difference	-3.2 Mean difference Pain Disability Index (0-70)
Bennell *et al.* 2011 [222]	Double Blind RCT Knee Osteoarthritis Total No. = 134 52 weeks	Lateral Wedge = 89	-0.9	3.1 Improved Knee Function (WOMAC 0-68)
		Sham Insole= 90	-1.3	4.0 Improved Knee Function (WOMAC 0-68)
Kulig *et al.* 2009 [209]	Double Blind RCT Posterior Tibial Tendon Dysfunction Total No. = 36 12 weeks	Custom Orthoses = 12	-16.3	-6.8 FFI (0-100)
		Exercise = 12 Concentric	-21.8	-3.3 FFI (0-100)
		Exercise = 12 Eccentric	-36.3	-8.0 FFI (0-100)
Baldassin *et al.* 2009 [223]	Double Blind RCT Plantar fasciitis Total No. = 105 8 weeks	Prefabricated Orthoses = 54	-23.2	-24.5 FFI (0-100)
		Customised Orthoses =51	-29.4	-25.7 FFI (0-100)
Landorf *et al.* 2006 [204]	Single Blind RCT Plantar fasciitis Total No. = 135 12 weeks	Custom Orthoses = 46	-23.4	-21.9 FHS (0-100)
		Pre-fabricated Arch support = 44	-29.3	-25.7 FHS (0-100)
		Sham Insole= 45	+18.3	-11.5 FHS (0-100)
Burns *et al.* 2006 [210]	Double Blind RCT Symptomatic Pes Cavus Total No. = 159 12 weeks	Custom Orthoses = 75 vs Sham Insole = 79	-8.3 mean difference	-9.5 Mean difference FHS (0-100)
Powell *et al.* 2005 [214]	Single Blind RCT Juvenile Idiopathic Arthritis Total No. = 40 12 weeks	Custom-Orthoses = 15	-3.9	-17.6 FFI (0-100)
		Sham Insole = 12	-0.7	-3.7 FFI (0-100)
		Athletic shoes (n = 13).	-1.9	-3.7 FFI (0-100)
Pham *et al.* 2004 [221]	Double Blind RCT Knee Osteoarthritis Total No. = 110 104 weeks	Lateral Wedge = 55	-5.8	1.2 Improved Knee Function (WOMAC 0-100)
		Sham Insole = 55	-4.7	0.4 Improved Knee Function (WOMAC 0-100)
Woodburn *et al.* 2002 [215]	RCT Rheumatoid Arthritis Total No. = 101 52 weeks	Custom Orthoses = 50 Vs Usual Care = 48 (n=3 with orthoses)	-19.1% mean difference	-13.5% Mean difference FFI
Martin *et al*. 2001 [203]	RCT Plantar fasciitis Total No. = 255 12 weeks	Custom Orthoses = 72	-34	N/A
		Pre-fabricated Arch supports = 62	-32	N/A
		Night Splints = 60	-30	N/A
Torkki *et al.* 2001 [219]	RCT Hallux Valgus Total No. = 134 52 weeks	Custom Orthoses = 69 vs Control = 69 no orthoses	-5% mean difference	+2 5% Mean Improvement Hallux Valgus Function (AOFAS 0-100)

The potential benefits of foot orthoses may be variable, possibly reflecting a wide range of baseline static and dynamic biomechanical characteristics. Only two published orthoses studies of people with patellofemoral pain syndrome and painful knee OA have examined the prospective biomechanical effect. Participants with patellofemoral syndrome who showed greater peak forefoot dorsiflexion, forefoot abduction and hindfoot eversion kinematics were predicted to be the best responders to the foot orthoses [227]. Participants with painful knee OA, who showed an immediate improvement of walking pain and a reduced initial-peak adduction moment when wearing the foot orthoses, were also predictive of clinical improvement at three months [228]. Furthermore greater body weight was predictive of poor response to foot orthoses to treat painful knee OA [229]. Foot orthoses that improve foot pain and impairment also have the potential to alter gait parameters, kinetics and kinematics, although there is emerging evidence that some people respond better than others [230]. The literature surrounding the biomechanical efficacy of orthoses will be reviewed in the next section.

Effect of Foot Orthoses on Kinematics

The main measureable component of pronation is the frontal plane movement of the hindfoot, known as the calcaneal or hindfoot eversion. Therefore the biomechanical outcome measures of choice to examine orthoses have been maximum angle, velocity or coupling of internal tibial rotation and calcaneal eversion during walking. Table 2.3 illustrates a selection of gait studies that show a variety of foot orthoses from soft to rigid, some with arch supporting properties or some with simple medial wedging, aimed at altering the movement of the hindfoot eversion (also referred to as pronation).

The results of these orthoses studies show there was a variable kinematic response. Some studies showed consistent reductions of two to five degrees in hindfoot eversion and internal tibial rotation (grey cells in Table 2.3) in healthy and foot pain studies [231-236]. Most of these studies were

small (range of nine to 15 participants), while the largest study of 60 participants showed the most consistent results [234]. In the six orthoses studies, a range of devices were tested, and there was no consistent pattern to suggest that one type of device was more effective at reducing hindfoot kinematics. In a direct comparison of medial wedge heights, a greater wedge of 10° to 25° reduced hindfoot eversion more consistently, whereas a lower wedge increased and decreased hindfoot eversion by +1.5° to -3.3° [237, 238].

In comparison, other studies showed variable increases and decreases of hindfoot eversion and tibial rotation from -0.8° to 1° across a range of orthotic devices [239-243]. These studies consisted of healthy groups with slightly larger sizes than the other studies (range of 12 to 24 participants). Variation between these five kinematic studies may be due to i) heterogeneous sampling (for example groups of young or physically active healthy volunteers), ii) variable biomechanical response to the orthoses especially in pain-free healthy groups, and iii) an unknown biomechanical effect of the shoe with the orthoses. More importantly, not all studies controlled or reported walking speeds between baseline and orthoses groups, which can have a substantial affect on foot biomechanics [244]. In this review of foot kinematic studies, foot orthoses seem to have a greater effect in pathological hindfoot kinematics than in normal healthy pain-free groups.

Effect of Foot Orthoses on Pressure and Force

In-shoe functional foot orthoses can alter detrimental foot forces as well as foot kinematics. Foot forces are usually measured by a force plate that is situated into the floor, which captures the ground reaction force as the foot strikes the floor-plate interface. Measuring the effect of orthoses using this equipment also includes the effect of the footwear, if placed in-shoe. In-shoe pressure sensors can measure force interaction directly between the foot and the orthoses, however there can be differences between foot forces

measured by pressure sensors compared to external force plates, at the 1st peak and mid-stance [245, 403].

Foot impact forces have been widely studied in runners with the aim of reducing overuse running injuries. This research has been applied to the manufacture of running shoes to reduced running injuries. Alterations of heel thickness, inclination and midsole hardness have been shown to reduce vertical impact forces and loading rates of the hindfoot and midfoot [198, 246, 247]. In kinetic analyses, the role of different types of orthoses to alter foot forces has been tested in walking and running states in small studies of healthy pain-free individuals.

Gait studies where hindfoot wedges were applied in asymptomatic feet have been shown to alter walking forces at the hindfoot by reducing the net ankle inversion moment, increasing the peak external rotation moment and increasing the peak adduction moment with medial wedges and vice versa for lateral wedges [237, 243]. Of these two studies only Nester *et al.* (2003) showed consistent kinetic and kinematic changes [237]. Similar changes in frontal plane kinetics were found with the application of medial wedged and contoured orthoses during running, reducing the foot peak eversion moment, and reducing the peak ankle inversion moment [159]. As these studies were conducted on healthy, pain-free participants, the extrapolation of the findings to a patient population may be limited. In a study of eight (pain-free) participants with pes planus feet, a soft wedged orthoses did not perform as well as the contoured and wedged orthoses [238]. The contoured and wedged orthoses reduced peak eversion motion, peak eversion moments and peak internal tibial moment [238].

Table 2.3: Summary of kinematic studies of foot orthoses

Author	Participants and number	Orthoses	Biomechanical Measure	Difference from in-shoe
Ferber *et al.* 2011 [241]	Healthy group n=20	Semi-custom	Max calcaneus eversion Medial arch angle	- 0.3° - 0.1°
		Arch support	Max calcaneus eversion Medial arch angle	+ 0.2° + 0.2°
Huerta *et al.* 2009 [243]	Healthy group n=12	7°Medial wedge	Max internal tibial rotation Foot abduction	+ 0.7 -1.6
		7°Lateral wedge	Max internal tibial rotation Foot abduction	+ 0.2 - 0.4
Davis *et al.* 2008 [240]	Healthy group n=19	Bespoke rigid cast	Max calcaneus eversion	- 0.8°
		Semi-custom	Max calcaneus eversion	- 0.7°
Zifchock *et al.* 2008 [242]	Healthy group n=19 low arch	Bespoke rigid cast	Max calcaneus eversion Calcaneus eversion velocity	+1° - 20°/s
		Semi-custom matched to arch height	Max calcaneus eversion Calcaneus eversion velocity	+0.2° - 20°/s
Stacoff *et al.* 2007 [238]	Symptomatic pes planus n=8	Medial wedge	Max calcaneus eversion	+1.5°
		Semi-custom	Max calcaneus eversion	- 1.8°
		Proprioceptive orthoses.	Max calcaneus eversion	+ 0.6°
Ferber *et al.* 2005 [248]	Foot & leg pain n=11	Semi-custom 4°wedge	Terminal stance coupling angle	+3.3°
		Semi-custom 15°or 25°wedges	Terminal stance coupling angle	- 2.5
Branthwait *et al*. 2004 [236]	Healthy group n= 9	Semi-custom	Max calcaneus eversion	- 2.1°
		Medial wedge	Max calcaneus eversion	- 3.1°
Nester *et al.* 2003 [237]	Healthy group n=15	10°Medial wedge	Max internal tibial rotation	- 3°
McPoil *et al.* 2000 [231]	Healthy group n=10	Semi-custom	Max internal tibial rotation	- 2.9°
		Arch support	Max internal tibial rotation	- 3.3°
Genova *et al.* 2000 [233]	Symptomatic pes planus n=13	Semi-custom n=10 & soft orthoses n=3	Max calcaneus eversion	- 2.2°
Stell *et al.* 1998 [234]	Symptomatic n=60	Bespoke rigid cast	Max calcaneus eversion Calcaneus eversion velocity	- 2° - 40°/s
		Semi-custom arch support & medial wedge	Max calcaneus eversion Calcaneus eversion velocity	- 5° - 100°/s
Brown *et al.* 1995 [239]	Health group n=24	Bespoke rigid cast	Max calcaneus eversion	- 0.4°
		Arch support	Max calcaneus eversion	- 0.2°
McCulloch *et al.* 1993 [235]	Symptomatic n=10	Rigid Cast n=7 & Semi-Rigid Cast n=3	Inversion at heel strike Max calcaneus eversion	- 3.3° - 3.3°

Caption: Grey cells indicate studies where systematic reductions of hindfoot eversion were shown.

These studies suggest that certain orthoses may have a systematic effect on foot forces. Measuring the forces in the foot has been limited to the hindfoot and ankle, therefore the effect of foot orthoses on the midfoot or forefoot is not fully understood. To overcome this in-shoe and floor mounted pressure platforms are often used to examine the foot forces and the effect of foot orthoses.

Modifying foot pressure rather than motion may be one aim of foot orthoses. The structure and function of the foot can account for up to 50% variance of plantar foot pressures [249]. Pes planus (low arch) foot types demonstrate higher medial midfoot and lower lateral forefoot pressures [250, 251]. Testing the interaction of the foot at the interface with the orthoses can be investigated by pressure sensors placed inside the shoe. Studies show that orthoses appear to be much more systematic in altering pressure, rather than kinematics, possibly due to the direct effect of the materials to change pressure. For example, non-contoured flat cushioning (foam) insoles reduce total peak pressures [252].

Functional foot orthoses (whether bespoke or pre-fabricated) have been shown to alter in-shoe foot pressures in a similar action, often, increasing medial arch pressure, medial heel pressure and reducing forefoot pressures [253-256]. A contoured orthotic device can reduce total plantar pressures in the forefoot region, however pressure in the medial heel and midfoot increased relative to the size of the wedging and height of the arch support [254, 256-259]. The alteration of foot pressures has been shown in observational clinical studies to improve heel pain, symptomatic pes cavus and symptomatic rheumatoid arthritis deformity [210, 260, 261]. The alterations in foot pressure and symptoms with orthoses suggest a biomechanical link between walking function and pain perception that can be mediated with orthoses [262]. Whether a reduction of pressure at the surface interface also reduces internal foot forces associated with pathology is poorly understood.

In summary, there are observational studies and randomised controlled trials of foot orthoses for a variety of disorders. Large randomised controlled trials suggest foot orthoses can improve pain, function and deformity for painful foot disorders, although the evidence for knee pain is not as clear. Further long-term randomised trials are needed (ideally with a sham or placebo control) to examine the efficacy of orthoses for a wider range of musculoskeletal foot disorders. Foot orthoses appear to have a biomechanical effect that systematically alters foot pressure and foot forces but the effect on foot kinematics is variable. There appears to be some indication that foot orthoses may affect foot kinematics systematically in pathological groups, however many of the studies were small and further investigations are needed. Different types of orthoses such as pre-fabricated arch supports and custom orthoses do not seem to alter foot kinematics systematically; with the exception of hindfoot medial wedges over 10°.

Outside of systemic diseases such as diabetes and rheumatoid arthritis, the mechanism of the foot orthoses requires further understanding. It is unclear if the improvements noted in the clinical trials and biomechanical studies also correlate with an improvement in the pathological structures associated with underlying stress. This will be discussed in the next section.

2.7 Foot Orthoses and Bone Stress

There is some evidence that the underlying mechanism of foot orthoses may be the modification of pressure, forces and kinematics, which has a mechanical impact on bone activity. It is unclear whether foot orthoses can alter internal foot forces as this is very difficult to measure *in-vivo*. A combined investigation using gait analyses and imaging provides a novel approach by combining surrogate measures of motion, morphology and pathology. This approach of using gait analyses and imaging has been explored in the knee and, to some extent in the foot.

Foot Orthoses and Bone Stress in the Knee

Knee pain and knee OA can be associated with varus mal-alignment of the leg, pes planus foot posture, abnormal foot kinematics, increased knee adduction impulse and increased knee adduction moment, indicating there may be a close mechanical and biological relationship with pain [136, 138-141, 263, 264].

Bone marrow lesions in the knee are histologically recognised as a mixture of oedema, blood, necrosis and fibrosis associated with trabecular remodelling and in some cases change of bone density [79, 265-267]. Prospective studies suggest the incidence of BMLs is related to the onset of knee pain and around 50% of people with BMLs go on to develop arthritic changes [96, 268]. Bone marrow lesions can be related to underlying stress such as body weight [269] intense physical activity [115] and increased biomechanical knee loading [143]. This is supported by surgical interventions to change the knee alignment, which can alter the pattern of BMLs [270, 271]. These alterations in patterns of BMLs associated with alignment and specific activity suggest they can reflect underlying bone stress and forces [266, 272, 273].

Orthoses (specifically lateral wedges placed in the shoe) have been shown to reduce abnormal knee forces (knee adduction moment and angular adduction impulse) in people with medial knee OA [274-278]. Some studies of foot orthoses in people with knee OA have also collected imaging data to understand the effect of the intervention on pathology. Studies suggest lateral wedge foot orthoses did not alter radiographic progression after 24 months of use, however, varus alignment improved [221, 279]. This may be because the mechanical affect of the lateral wedges has shown better efficacy in early arthritis [276].

Increased medial adduction loads at the knee have been associated with the presence of BMLs. A large (n=200) randomised (sham insole controlled) trial of lateral wedged orthoses, which altered knee loading after three months, did not show any significant median change of BMLs over 12 months [222, 228]. This is the first randomised trial to include biomechanical and MR imaging analyses, the results suggest a large change would be required using a three point scale to detect changes (where 0 = no change, 1 = up to 25% change and 2 = 26% or more). This BML scale lacks responsiveness and is biased towards BML resolution as opposed to BML reduction, which may not be feasible in an OA trial [280].

In a smaller randomised study of knee structure in OA, subchondral size of necrosis was measured prior to and following lateral wedges. A reduction of radiographic necrosis size of $1cm^2$ (mean difference between groups of (-15%) was related to improved symptoms over three years [281]. It is unclear if a larger sham-controlled trial would have yielded the same results. This study demonstrated that using maximal area measurement rather than a semi-quantitative scale provided detectable differences. Both imaging and biomechanical studies did not suggest that lateral wedged foot orthoses can systematically modify bone structure. Further knee studies are needed with sensitive measures of bone structure to detect change associated with orthoses interventions.

Foot Orthoses and Bone Stress in the Foot

Specific alignments of the foot (in particular extremes of dynamic foot posture) can be associated with the incidence of exercise-induced bone stress injuries, suggesting a link between biomechanics and patterns of injury. In addition the mechanism of foot orthoses appears to have an effect on bone stress as prospective studies show fewer radiographic bone injuries in the foot orthoses treatment arm [282].

The effect of foot orthoses has also been explored in observational MR imaging studies, which have shown orthoses may induce and alter patterns of BMLs. One exploratory study investigated the effect of a medial arch pad, made from compressed wool felt, which was inserted under the lateral column of the foot in eleven volunteers [283]. Wool pads have been shown to deflect around 30% of foot pressures, however, the effect on foot kinematics are not known [284]. In this study, wearing the pad constantly for two weeks during recreational activities caused discomfort and induced non-specific diffuse heterogeneous BMLs in the foot bones [283]. The onset and spontaneous resolution of BMLs (following removal of the pad) suggests the lateral wool pad may have altered foot biomechanics. This is plausible as non-contoured (thermoplastic) lateral wedges are known to alter ankle and knee kinematics and kinetics [285]. Placing an arch beneath the lateral column of the foot seemed to induce a mechanical response in the lateral bones (six out of 11 volunteers), followed by the tibia (two out of 11), and in one case the femur. In two cases this increased the forces on the foot quite dramatically and stress fractures were suspected. This study demonstrated that the introduction of a mechanical device may also have an adverse affect on bone physiology.

Orthotic devices may also have a beneficial effect on BMLs. Immobilisation of the foot is a common treatment for foot pain associated with BMLs and stress fractures. Immobilisation devices such as a walking cast or ankle boot are preferable to the use of crutches and have been shown to alter foot pressures according to the design of the sole, such as a heel lift or rocker [286, 287]. These offloading devices are used to treat acute bone pathologies, often stress injuries in sports and military personnel. A systematic review of immobilisation for bone stress injuries showed reduced pain and an earlier return to activities compared to controls, however no confirmation with follow-up MR imaging was performed [282]. The presumption that immobilisation may alter bone physiology is based on a small case series of 18 patients following foot trauma. In-situ MR imaging showed immobilisation altered BML patterns (present BML resolved and new signal in the sub-cortical bone regions was reported after two weeks)

that was resolved in most cases six months after immobilisation ceased [288].

In a study where follow-up MR imaging of BMLs was used as an outcome measure, the combination of immobilisation and Iloprost treatments were reported. This single intervention trial of three months duration showed resolution rates of foot BML (15 out of 23 cases), and smaller BMLs in eight cases [289]. Critically, no control group was reported but the results are favourable compared to a BML case series by Zanetti *et al.* (2002) [121]. It is unclear which therapy provided the added benefit (immobilisation or Iloprost), as single trials of Iloprost have also shown good improvement in BML over four months [92]. The underlying cause of BML may provide some clues as persistent foot pain was associated with BMLs secondary to mechanical stress and OA. Bone marrow lesions secondary to degenerative disease have been commonly identified in OA and neuropathic joint disease [92, 290]. Immobilisation in early neuropathic joint disease has been shown to improve resolution rates of BMLs [291, 292]. These studies demonstrate that there may be a biochemical reaction to mechanical stress that may precipitate or perpetuate bone pathology, manifesting as BMLs in the foot.

Perhaps the only method to directly measure the effect of orthoses on bone stress is through bone-mounted gauges and tissue modelling using FE models. Modelling of the foot bones and underlying trabeculae formation has shown, for instance, that the second and fifth metatarsals have different metatarsal cavities and bone formations compared to the remaining metatarsals [293]. Variation in the capability of the bones to absorb stress is suggested, as greater bone stress has been modelled in the medial column bones: navicular, medial and intermediate cuneiform, and second, third and forth metatarsals [294]. This modelling confirms the patterns of bone stress reported in imaging studies (see Table 2.1 and Figure 2.1). Modelling the stress of the foot dynamically has shown at foot push-off, the third metatarsal was most susceptible to sagittal stress, however torsional stresses varied in each of the metatarsals. The second metatarsal was

more susceptible to torsion (pronation) stress and most protected against sagittal stress [294, 295].

Using dynamic cadaver modelling (with an implanted strain-gauge) in eight specimens, the effects of both pre-fabricated and custom orthoses were investigated on the strain of the second metatarsal. Custom orthoses reduced the peak and rate of: compression, tension and shear strain, whereas the semi-custom orthoses only affected the shear strain rate and tension strain [296]. The contact area of the custom devices may be one explanation of the systematic reduction of internal bone forces. This study suggests that foot orthoses can potentially modify second metatarsal bone stress in a small sample of cadavers. This research supports the results of prospective studies, which show a reduction in the incidence of bone injuries using foot orthoses [281]. The clinical mechanism by which orthoses modify bone stress associated with midfoot pain remains poorly understood.

The role of foot orthoses to manage and prevent chronic foot deformity in degenerative, musculoskeletal and inflammatory foot pathology has been well documented in systematic reviews [196, 197, 297]. There are several high quality randomised controlled trials that show foot orthoses can systematically reduce foot pressures and alter hindfoot kinematics in conjunction with improved clinical outcomes [197, 204, 210, 216, 298]. The biomechanical evidence for the efficacy of foot orthoses has been focused on common complains such as plantar fasciitis [299, 300], further research is needed in a wider range of musculoskeletal foot disorders.

Exploratory studies suggest a link between biomechanics and the onset and resolution of foot BMLs, however the influence of mechanical treatments is limited to patterns of BMLs associated with acute stress or secondary to joint diseases. Larger clinical studies are needed to understand the complex biological and mechanical interaction of BMLs, and in particular exploratory studies that include BML measurements prior to and following foot orthoses

treatment. This addition of imaging with orthoses studies may provide an understanding of bone physiology as a surrogate measure of bone stress.

2.8 Summary and Rationale

The relationship between pain, structure and function in mechanical foot pain is not well understood. Mechanical foot pain is common and typically associated with abnormal foot posture, foot pressure and kinematics of the foot and lower limb. It is thought that mechanical musculoskeletal foot pain may behave in a similar manner to musculoskeletal knee pain, given the function of locomotion, weight-bearing stresses and movement adaptations. The relationship between pain, function and pathology of the knee has been explored. Knee pain, bone and joint pathology are more likely to be found with varus mal-alignment of the leg and hindfoot and an increased knee adduction moment, indicating there may be a close mechanical and biological relationship.

It is thought that the mechanism by which foot orthoses improve pain and impairment is through the modification of the internal stress on the body structure. Specific mal-alignments and movements of the knee have been associated with an increased risk of pain and patterns of BMLs in mechanical and degenerative knee pain. Patterns of BMLs in the foot have been identified and are associated with weight-bearing stress but it is unclear how these relate to medial midfoot pain. The possibility of orthoses modifying bone stress has been proposed in part and it is this mechanism that will be explored in this thesis through the novel application MR imaging. Whether that foot orthoses can modify midfoot BMLs as a surrogate measure of bone stress will be investigated in this thesis, in order to explore the possible biomechanical and biological mechanisms of foot orthoses.

This thesis sets out to explore the mechanism of functional foot orthoses on mechanical medial midfoot pain, impairment and patterns of BMLs, using

MR imaging. The first study of this thesis (Chapter Three) will identify and test different methods to reliability quantify BMLs. The second study (Chapter Four) will explore the baseline and change of foot pain, impairment and patterns of BML over a three month period with the intervention of foot orthoses. The final study (Chapter Five) will investigate the effect of orthoses on gait parameters and foot kinematics.

Chapter Three:

Imaging segmentation and measurement of bone marrow lesions

3.1 Overview

The literature discussed in Chapter Two reports how foot orthoses can provide clinical benefits, reducing foot pain and improving function in a number of foot disorders. The mechanism through which functional orthoses achieve these clinical benefits remains unclear. Some studies suggest that the underlying mechanism of foot orthoses may be modification of foot motions or perhaps the redistribution of internal forces in the foot. The direct effect of foot orthoses on internal foot forces is not fully understood as all current techniques that might provide direct measurements of the internal joint forces require invasive procedures.

Surrogate measures of foot forces are therefore required, and the options will be discussed in this chapter. Magnetic resonance imaging signal abnormalities in the bone, known as BMLs, are signal abnormalities associated with underlying pathological changes that can be mechanically induced. Patterns of BMLs, not associated with inflammatory disease or infection, are recognised as a bone response and can be a precursor to bone stress injuries. In this chapter, measurements of the physiological changes occurring within bone will be assessed using MR imaging to evaluate using BML measurement as a surrogate method. This approach is presented as BMLs have been shown to represent a continuum of damage and repair process of mechanical bone stress [115, 283] and can therefore be used as a surrogate marker for mechanical stress distributions.

The central aim of this thesis is that foot orthoses may alter stress distributions within the foot, and that the effect of this can be evaluated by exploring the response of bone physiology to the mechanical stress. As precise measurement of bone stress response is fundamental to the thesis, the current state of the art in bone stress measurement will be discussed. Finally, the measurement of MR imaging BMLs volumes, as a surrogate measure of bone stress, will be presented.

There are a number of approaches to quantifying BMLs, from semi-quantitative scoring to quantitative measurement. There are no MR imaging outcome measures validated in the foot to quantify BMLs either using semi-quantitative scoring or segmentation methods. To address this a phantom study and three methods of quantitative BML measurement were developed using an iterative process in this chapter. The final method of BML measurement will be described in detail and used in Chapter Four to investigate the effect of foot orthoses through bone physiological response to altered mechanics.

3.2 Research Aims

The specific aims of this chapter are to:

I. Investigate the accuracy and measurement error associated with auto tracing segmentation techniques in measuring water signal in a study of an MR imaging phantom.
II. Investigate the face validity of two different techniques to measure BML volume and the intra-measurement reliability of tracing and thresholding segmentation.
III. Investigate the face validity and intra-measurement reliability of signal growth segmentation techniques to measure BML volume.
IV. Investigate the face validity and intra-measurement reliability of tracing segmentation and bone signal subtraction.

3.3 Introduction

Bone stress can be measured either directly or indirectly. Direct measures are theoretically preferable but are invasive and resulting models are limited to small human and cadaver studies. Indirect measures of bone stress using state-of-the-art imaging of BML measurement may offer a surrogate approach more applicable in clinical studies.

Measurement of Bone Stress

In the foot, measurement of bone stress has been of historical interest due to the relatively high prevalence of second metatarsal stress injuries and fractures. Direct measurement of bone stress can be achieved using a bone-mounted strain-gauge, which is a method often applied to dynamic cadaver models and in small (human, *in-vivo*) studies.

Dynamic cadaveric studies use bone-mounted strain-gauges, coupled with bone tracking, to measure internal bone motions and joint forces during simulated foot contact. Strain-gauges can provide direct measures of tensile and compressive changes in a single bone. This method is limited somewhat by the number of bones measured, as strain-gauges cannot be mounted onto multiple small foot bones without a loss of foot integrity. Strain-gauge studies have therefore concentrated on one or two bones, often the second metatarsal. These studies suggest that metatarsal morphology is well adapted for locomotion, as the metatarsals have the greatest tolerance for vertical loading [301, 302]. Comparisons of stress across the metatarsals show good predictive validity for models of bone fracture sites, particularly for modelling horizontal and torsional stress in the second metatarsal [301-303]. Peak-stress and deformation patterns in the second metatarsal can be increased with load and muscle fatigue *in-vivo*, suggesting that anatomical and mechanical factors play a role in internal foot forces [304, 305]. These models can provide accurate experimental data, however the results are generated using small numbers of cadaveric and human *in-vivo* measurements due to ethical and technical issues of bone-

mounted devices (from 1 to 15 feet). This small pool of data limits applicability, as individual bone motions have been shown to be highly variable [306].

An alternative and non-invasive approach to developing an indirect understanding of bone stress is through mathematical estimations, typically using FE modelling. These state-of-the-art techniques can model foot motions by importing data from bone morphology, strength tests and segmentation from computer tomography (CT) imaging, and using this information to predict bone stress patterns and response. Finite element models are in some ways more useful than implanted strain-gauges as they can model the multiple bones and joints in the entire foot simultaneously, and in multiple scenarios such as joint surgery [307, 308]. There are limitations imposed by the quality of the input data, but using FE modelling Chen *et al*. (2001) was able to show that the distribution pattern of bone stress was greatest in the medial column bones and joints during walking motion in mid-stance and push-off [294]. This model matches patterns of bone pathology associated with midfoot arthritis and pathological bone stress, helping to validate the models and suggesting that internal foot forces can be related to bone pathology [133, 309]. Direct measures and models of internal bone forces are limited in their size and application due to their invasive nature or the complexity of the input data. In the broader population, surrogate methods that use external measures of foot forces are more widely used.

The most widely used measures of lower limb force are external, floor mounted force and pressure plates, which measure the interaction of the foot with the contact surface during locomotion. This method can be applied to large numbers of participants as it is non–invasive and data acquisition is relatively practical. Using force plates and mathematical principles of inverse dynamics and related approaches, joint forces, moments and powers can be calculated. This type of approach is widely applied in joints with a single point of application of force such as the knee and the hip. In

the foot however, the modelling is more complicated due to the multitude of small bones and joints and multiple points of contact with the supporting surface, which yield significant complexities in the models and a resulting low signal to noise ratio. Force plates studies have contributed minimally therefore to our understanding of how forces are distributed within the foot.

The direct and indirect methods used to measure forces have clear limitations associated with their application in the foot. As a consequence, kinematic effects of mechanical devices such as orthoses have been studied in detail, while the effect of foot orthoses on modifying internal foot forces is not well understood. One cadaveric study using strain-gauges to measure forces at the second metatarsal has examined the effect of foot orthoses on metatarsal bone strain, shear and compression and concluded that both custom and semi-custom devices had the potential to reduce forces [296]. This study suggested that foot orthoses have the potential to modify internal foot forces, however measurements were based on a single bone from eight cadaver feet in simulated dynamic gait assessment. The effect of foot orthoses on internal foot stress across multiple bones *in-vivo* merits further investigation.

Bone Marrow Lesions as a Surrogate Measure of Bone Stress

In order to assess the effect of foot orthoses on internal foot forces in a larger sample, an alternative surrogate method was proposed: patterns of bone marrow signal. Patterns of bone repair and bone pathology (visualised using MR imaging) show as abnormal bone marrow signal or BMLs [114, 121], and in this chapter it is hypothesized that measurement of BML volume in foot bones may offer a surrogate measure of bone stress using non-invasive imaging.

Bone marrow lesions are visualised as ill-defined areas of increased (bright) signal intensity on T2 weighted, or fat-suppressed images, occurring in the cancellous bone and typically extending away from the articular surface over

a variable distance [310]. Bone marrow lesions can represent a wide range of pathological abnormalities (as discussed in Section 2.4.1). In common musculoskeletal conditions BMLs are associated with mechanical pain and physical activity and can represent abnormal bone physiology and stress [311]. This is most widely shown in sports, military and osteoarthritic knee studies, where patterns of bone stress are mechanically driven, and the bone adapts to altered loads by remodelling to meet demand.

As discussed in Chapter Two, functional foot orthoses have been shown both to reduce the incidence of exercise-induced bone injuries in the foot medial midfoot [282]. In addition, in cases where a harmful device was placed inside the shoe new BMLs were formed [283]. In this thesis, I sought to explore the effect of foot orthoses on patterns of BML signal in the midfoot, and to seek a reliable method of measurement that can sensitively detect changes in the size and distribution.

Quantification of Bone Marrow Lesions

To measure BMLs, semi-quantitative scores are used in clinical trials to establish severity and progression, while descriptive terms are used by radiologists for diagnostic purposes. A number of interval semi-quantitative scoring systems have been developed to examine the effect of clinical interventions on BMLs associated with OA. The reliability of these visualised scores is limited by reader's ability to detect subtle changes and consequently, these scoring methods use large percentage intervals of change (25% to 30%).

Semi-quantitative estimates of BML volumes, as a percentage of bone, are included in some well established outcome measures of knee OA: Boston Leeds Osteoarthritis Knee Score (BLOKS) and Whole-Organ evaluation of the knee in Osteoarthritis (WORMS) [312, 313]. These types of measures have tended to use a three point ordinal scale to define the size of a lesion at a given location: for instance with a score of zero indicating no BML, one

indicating mild BML (up to 25%), two indicating moderate BML (25% to 50%) and three indicating severe BML (occupying over 50% of bone volume) [312, 313]. As an outcome measure, BML scoring has been used in some observational and interventional knee studies, however the responsiveness of the scoring change has not been fully explored [95, 222, 280, 314].

Using the BML interval scale of 0 to 3 can bias the treatment effect for smaller BMLs at baseline. For larger volumes at baseline, a greater reduction of BMLs would be required to detect change. The use of BML scores (0 to 3) in knee trials has been criticised for failing to report the small differences in BML volume, suggesting scoring can lack responsiveness [280]. Measurement over time is also confounded by the naturally variable history of BMLs, which are known to migrate, resolve and form new lesions in knee OA [95, 315]. Intervention studies for knee OA that have used these ordinal scales have not shown a treatment effect [222, 280, 316].

More recently, manual measurements of the absolute BML area on individual scan slices have become more popular. One semi-quantitative score, the Knee Osteoarthritis Scoring System (KOSS), has combined interval scales and manual measurements of BMLs (where: 0 =none, 1 = minimal <5 mm diameter, 2 = moderate 5 mm to 2 cm diameter, 3 = severe >2 cm diameter) or included both area measurements and subjective interval scales [317]. In clinical OA studies, BML area measurements have been limited to quantifying the single largest lesion in the knee, and demonstrated good reliability [271, 318]. There is however, disagreement regarding what constitutes a meaningful change in BML area, and not all studies have accounted for measurement error or predicted changes in the natural course of BMLs. For instance, based on natural history of BMLs associated with knee pain, a change of 140mm^2 in BML area has been proposed as the smallest detectable difference, which may not be represented in the KOSS interval scale and may not be comparative across different sizes of knees [315, 317]. As an alternative, volumes of BMLs as a percentage of bone may offer the potential for reliable and comparative measures of change that

can document multiple lesions and changing patterns of BMLs in bones of variable size.

Quantitative Measurements of Bone Marrow Lesions

Volumes of BMLs may be assessed by segmentation of signal intensity using a desired threshold from a greyscale within ROI. Segmentation of MR images is a method that has been well described for identifying and measuring anatomical volumes differentiated by different signal intensities. In musculoskeletal diseases this is mainly undertaken for cartilage morphology where there are reasonably clear margins depending on the MR sequences used for acquisition [319]. To identify the BML volume is more challenging, as BMLs are heterogeneous regions of signal with ambiguous edges due to border fade out and small signal and may be over or under estimated (partial volume effects). This can affect the measurement of BML volume, as the boundary definition can be subjective [320]. Segmentation of BMLs using a reader-defined manual outline in the wrists of people with rheumatoid arthritis has shown good agreement and intra-measurement reliability (ICC 0.6 to 0.99), however the agreement between different researchers was poor (ICC 0.46) [321, 322]. Although studies suggest training and calibration of manual outlining techniques can improve inter-reader reliability [323].

To try to improve the repeatability and reduce error associated with BML volume measurement, a variety of computer assisted techniques have been developed. These techniques aim to automate or semi-automate the process of separating normal and abnormal bone marrow signal by defining the boundaries of the BMLs. Calculating optimal thresholds of signal intensity of the BML within the boundary of the bone removes subjective decisions and reduces the reliance on a human operator [324, 325]. Such techniques can reduce error but they rely on homogenous grey-scale signal intensity throughout the bone volume. This may be problematic in the foot as multiple bones may be susceptible to inconsistent fat-suppression, which would misrepresent pathological signal. Further validation work is needed,

as previous computer assisted studies have used small samples (a range of 10 to 20). Larger studies are needed to evaluate between-reader and between-session reliability using single and multiple images (at two time points) to understand if these methods can offer advantages over manual outlining segmentation, particularly in the foot.

3.4 Rationale for using BML Volume in Bone Stress Measurement

Volumes of BMLs have been used in clinical studies as an outcome measure, although any formal evaluation of the associated reliability is rarely published. This calls in to question whether the clinical effect of the intervention may be confounded by measurement error [326]. Computer assisted methods offer objective approaches to defining the margins of the BML with potential for improved inter-measurement reliability. In the next section we present a coordinated series of BML volume measurement studies, conducted to find a reliable method for quantifying the change of BML volume in response to an orthotic intervention.

The main scope of this chapter was to investigate the method of segmentation and measurement of BML signal derived from MR imaging. This was explored through four studies. The first study investigated measurement techniques applied to known volumes of water signal in a phantom. The following three studies explored multiple measurement techniques of BMLs *in-vivo* to examine face validity and intra-measurement reliability. The first *in-vivo* study used a tracing method, the second study examined a signal growth method and the third employed a segmentation and signal subtraction method. The research questions, results, and limitations of each method are presented per study and briefly discussed.

3.5 Methods

Phantom Study

The phantom was created and scanned with different sequences and at different time points in two field strengths (Section 3.6). The phantom was scanned in an extremity 0.2T MR image and a large bore 3T MR image scanner using a standard knee coil in both scanners. The images produced were then measured and the results were compared to the known volumes of water contained in the vials in the phantom. The inter-measurement, intra-measurement reliability and accuracy calculations were undertaken, and the results presented in Section 3.6.

Recruitment

People with mechanical medial midfoot pains were recruited as part of a clinical study. This included participants with midfoot pain that was thought to be of a mechanical origin. A single foot from each participant was scanned using a MR imaging scanner (Magnetom Verio, three Tesla, MR imaging scanner, Siemens Medical Solutions, USA). In the event of bilateral foot pain, either the most painful foot was imaged or if equal pain was present in both feet, the dominant foot was identified using a first step technique.

Imaging Protocol

All images were acquired using an eight channel foot and ankle coil (Magnetom Verio, Siemens), with the foot placed perpendicular to the ankle and magnetic field (β0). To minimize positional error, all images were measured manually from the scout image to ensure that the foot was perpendicular to the ankle in the sagittal plane prior to sequential imaging. The optimal field of view (FOV) was designated as the distal third of the talus to the head of the metatarsals, although this FOV was reduced slightly for larger feet.

All foot images were acquired using water-sensitive sequences: a short tau inversion ratio (STIR) sequence and an optimized T2 weighted fat saturated sequence. To identify the optimal contrast of signal in the T2 weighted sequence, the echo time was manipulated and a fat saturated sequence was chosen as the main protocol from which to analyse the BML volume. A 3D water-sensitive sequence would have offered the potential for true isotropic evaluation, however this sequence had not been optimised in the foot at the time of the study due to problems with fat saturation failure.

Another approach to 3D quantification of BMLs may have been the use of the contrast agent gadolinium. Gadolinium uptake into BMLs has shown potential to improve enhancement especially when associated with inflammatory diseases [327]. The potential benefits of gadolinium enhanced imaging in volumetric quantification in BMLs associated with mechanical pathology and OA has not however been fully determined. Two studies that have compared BML volumes in gadolinium contrast T1 weighted fat saturated images and water-sensitive sequences have shown that gadolinium consistently increases the signal contrast. The size of the BML volume however did not alter consistently when using the gadolinium contrast, compared to water-sensitive sequences across multiple scanners and sequences [118, 320, 328]. This may be due to the mixed pathology of mechanical BML where fluid infiltrate is not the sole determinant of the image abnormality [79, 311]. Nonetheless, in this study the use of gadolinium contrast was not felt to be sufficiently well justified in the quantification of BMLs to warrant the extra risk and inconvenience to participating patients and all sequences were obtained without administration of contrast.

All foot images were acquired using the same protocol, a T2 weighted fat saturated sequence (*TR = 3000-3600 ms, TE69, flip angle = 155-160º, 2mm slices and 0.4mm inter-slice gap, Matrix 256*256*) and a short tau inversion ratio sequence or STIR *(TR =4500 ms, TE33, NEX 2, TI 200, flip angle 90°, 3mm slices and 0.6mm inter-slice gap, Matrix 192*144)* in all three planes.

Two water-sensitive sequences were chosen as the foot is susceptible to fat saturation failure at the margins of the foot due to the heterogeneous shape of the foot in the magnetic field. The ROI was identified as the medial column of the midfoot, within which areas of hyper-intense signal with ill-defined borders were identified in the bones. The regions of BML signal in the bones of the foot were confirmed by a rheumatologist as greater than one slice and in two planes.

The images were anonymised and allocated an image number by a member of the radiology research department, external to the research team. These anonymised images were measured by a single researcher (JHR) using multiple techniques.

To examine the reliability and face validity of BML volumetric measurement, BML volumes were measured using visualisation and analysis software Analyze (BIR Mayo clinic Inc. USA). The Analyze software allows the measurement of a specified signal range in a pre-identified region, using multiple tools and approaches that will be described the methods section pertaining to the three four studies.

3.6 Volumetric Measurement in a Phantom

In the main study an extremity 0.2T and a large bore 3T MR imaging scanner was used to investigate the presence and volumes of BMLs in the foot. To understand the possible sources of error, this phantom sub-study aimed to determine the accuracy and reliability of known water volumes in a phantom, using MR imaging scans taken using different time points, using two different scanners and multiple researchers.

3.6.1 Procedure

To test the technical accuracy of the measurement techniques, a cylindrical phantom containing oil and vials of water was created to imitate BMLs that comprise small regions of water-dense tissue infiltrating into fatty marrow. The phantom consisted of three stable vials of distilled water measuring 0.502ml (502mm^3), 0.602ml (602mm^3) and 0.611ml (611mm^3) contained in an oil-filled cylindrical plastic container. To test the constancy of the water volumes, the vials of distilled water were measured using a calibrated electronic micro-balance that has sensitivity of 0.001g and a reproducibility error of 0.0005g (Mettler PM200, Mettler-Toledo International Inc Leicester UK). Measurements were taken over a two-week period and no loss of volume was detected in the process. The stable vials were fixed to a plastic base and then affixed to the base of the cylinder with sealant. After a period of drying, the cylinder was filled with 400ml of vegetable oil and the whole container was sealed with sealant and tape to stabilise the phantom and prevent escape of the oil.

This phantom was scanned using MR imaging in a number of scenarios, using different field strengths, different time points. The MR images were then measured using the following auto tracing method. The auto tracing tool (Analyze version 3.1, BIR MAYO Clinic US 1996-2001) uses a single seed-point placed within signal intensity, which is judged by the researcher to represent the ROI. This range of signal intensities grows the seed-point within the image to define the edge of the ROI within the phantom. This

semi-automated tracing technique was used to define an area of pixels within the ROI per slice. Analyze software then calculates the signal volume with the additional information of slice thickness and the slice gap.

Inter and Intra Measurement Reliability Tests

Two researchers (JHR and JM) traced and measured a single water vial, 20 times per slice, on the same MR images of the phantom. The first researcher (JM) acclimatised to the Analyze software for five hours using an alternative vial on the phantom images. The results of both researchers measuring the same vial were compared to the true volume to determine agreement and absolute error.

Field Strength Tests

Two matched sequences were used to scan the phantom in the extremity 0.2T and large bore 3T MR imaging scanner to compare the effect of field strength on the resulting phantom volume measurements. The 3T MR imaging protocol replicated as far as possible the scan sequences used in the 0.2T extremity MR scanner. Each slice of a single water vial was measured 20 times by a single researcher (JM) on the sequences obtained from the extremity 0.2T and large bore 3T MR image scanners.

Field Variance Tests

The same sequence was used to scan the phantom three times in the extremity 0.2T scanner on the same day. The researcher (JM) measured the same water vial five times in all three images. These measures were further compared with the results of a scan of the same vial on a different day.

Analysis

For each slice the ROI was defined and the number of pixels within the ROI was calculated within the Analyze software to yield an area measurement. The volume of the water signal was then derived using the formula:

Water Vial Volume = ∑ Area of vial water x (Slice Thickness + Inter-slice Gap)

Where the water vial volume is the sum of the water vial area, multiplied by the combination of slice thickness and inter-slice gap. This volume calculation has been used to identify volumes of erosion and synovitis reliably [329, 330].

The total volume for the phantom ROI was then calculated and tabulated for the difference of the measured volume from the known volume (Diff), and the resulting root mean square error (RMSE). The consistency of tracing and measuring the ROI in each slice was obtained by calculating the standard deviation (SD) of the difference.

3.6.2 Results

Inter and Intra Measurement Reliability Tests

A specific sequence was optimised on the extremity 0.2T MR imaging scanner with the following coronal (short axis) T1 weighted spin echo sequence (*TE 26, TR 840, NEX 2, FOV 170x170mm, 0 slice gap, Matrix 256x192*). Two researchers (JHR and JM) traced and measured a single water vial, 20 times per slice, on the same MR images of the phantom. The results of both researchers' were compared to the true volume to determine difference.

Table 3.1: First researcher (JM) 20 measurements of phantom water vial

Slice 1 (mm^3)	Slice 2 (mm^3)	Slice 3 (mm^3)	Measured volume (mm^3)	Actual volume (mm^3)	Diff (mm^3)	RMSE (mm^3)
148.17	198.44	246.07	592.68	502	90.68	90.68
132.29	210.35	212.99	555.63	502	53.63	53.63
145.52	201.09	146.85	493.46	502	-8.54	8.54
144.20	201.09	202.41	547.70	502	45.70	45.70
138.91	201.09	195.79	535.79	502	33.79	33.79
145.52	198.44	190.50	534.46	502	32.46	32.46
145.52	197.12	190.50	533.14	502	31.14	31.14
141.55	197.12	197.12	535.79	502	33.79	33.79
141.55	197.12	202.41	541.08	502	39.08	39.08
141.55	195.79	202.41	539.75	502	37.75	37.75
136.26	193.15	197.12	526.53	502	24.53	24.53
145.52	195.79	202.41	543.72	502	41.72	41.72
149.49	190.50	246.07	586.06	502	84.06	84.06
138.91	199.76	222.25	560.92	502	58.92	58.92
144.20	209.02	223.58	576.80	502	74.80	74.80
144.20	199.76	201.09	545.05	502	43.05	43.05
149.49	199.76	222.25	571.50	502	69.50	69.50
138.91	209.02	222.25	570.18	502	68.18	68.18
138.91	199.76	209.02	547.69	502	45.69	45.69
138.91	202.41	215.64	556.96	502	54.96	54.96
Mean					**47.74**	**48.60**
SD					**22.76**	

The accuracy of the first researcher (JM) to quantify the water vial in the phantom shows a systematic error of 47.74mm^3 (SD of 22.76mm^3) or an absolute percentage error of 9.7% relative to the true volume (see Table 3.1). The second researcher (JHR) did not initially have the same experience of segmentation using the software first researcher (JM) and this showed a greater systematic error of 155.67mm^3, absolute percentage error of 31.01%, and double the SD (42.02mm^3) compared to the first researcher (JM) (see Table 3.2).

Table 3.2: Second researcher (JHR) 20 measurements of phantom water vial (pre-training)

Slice 1 (mm^3)	Slice 2 (mm^3)	Slice 3 (mm^3)	Measured volume (mm^3)	Actual volume (mm^3)	Diff (mm^3)	RMSE (mm^3)
199.76	306.92	234.16	740.84	502	238.84	238.84
202.41	305.60	272.52	780.53	502	278.53	278.53
197.12	216.96	238.13	652.21	502	150.21	150.21
146.85	215.64	293.69	656.18	502	154.18	154.18
199.76	215.64	224.90	640.30	502	138.30	138.30
158.75	216.96	252.68	628.39	502	126.39	126.39
171.98	222.25	293.69	687.92	502	185.92	185.92
197.12	220.93	251.36	669.41	502	167.41	167.41
173.31	220.93	261.94	656.18	502	154.18	154.18
144.20	222.25	264.59	631.04	502	129.04	129.04
173.31	215.64	271.20	660.15	502	158.15	158.15
199.76	218.29	252.68	670.73	502	168.73	168.73
198.44	216.96	256.65	672.05	502	170.05	170.05
170.66	220.93	232.84	624.43	502	122.43	122.43
165.37	220.93	256.65	642.95	502	140.95	140.95
198.44	216.96	251.36	666.76	502	164.76	164.76
160.08	218.29	236.81	615.18	502	113.18	113.18
165.37	215.64	251.36	632.37	502	130.37	130.37
162.72	215.64	248.71	627.07	502	125.07	125.07
162.72	210.35	226.22	599.29	502	97.29	97.29
Mean					**155.70**	**155.70**
SD					**42.02**	

After a further training period and consulting on the semi-automated tracing method between the two researchers (JM and JHR) the measurements of the second researcher were repeated (see Table 3.3). The results show the measurement error (31.61mm^3) and SD (11.55mm^3) and a smaller absolute percentage error (6.3%).

Table 3.3: Second researcher (JHR) 20 measurements of phantom water vial (post-training)

Slice 1 (mm^3)	Slice 2 (mm^3)	Slice 3 (mm^3)	Measured volume (mm^3)	Actual volume (mm^3)	Diff (mm^3)	RMSE (mm^3)
138.91	211.67	190.50	541.08	502	39.08	39.08
130.97	209.02	190.50	530.49	502	28.49	28.49
144.20	209.02	181.24	534.46	502	32.46	32.46
141.55	206.38	190.50	538.43	502	36.43	36.43
148.17	209.02	182.57	539.76	502	37.76	37.76
130.97	209.02	183.89	523.88	502	21.88	21.88
145.52	210.35	194.47	550.34	502	48.34	48.34
144.20	207.70	186.53	538.43	502	36.43	36.43
144.20	210.35	197.12	551.67	502	49.67	49.67
144.20	209.02	177.27	530.49	502	28.49	28.49
144.20	205.06	187.86	537.12	502	35.12	35.12
138.91	198.44	189.18	526.53	502	24.53	24.53
146.85	209.02	197.12	552.99	502	50.99	50.99
144.20	210.35	181.24	535.79	502	33.79	33.79
141.55	191.83	181.24	514.62	502	12.62	12.62
138.91	202.41	183.89	525.21	502	23.21	23.21
149.49	191.83	191.83	533.15	502	31.15	31.15
144.20	189.18	173.31	506.69	502	4.69	4.69
144.20	190.50	190.50	525.20	502	23.20	23.20
145.52	210.35	179.92	535.79	502	33.79	33.79
Mean					**31.61**	**31.61**
SD					**11.55**	

Field Strength Tests

The phantom was scanned in two MR imaging scanners, with matched sequences on the extremity 0.2T scanner (*TE 26, TR 840, NEX 2, FOV 170x170mm, 0 slice gap, Matrix 256x192*) and large bore 3T scanner (*TE 21, TR 840, NEX 2, FOV 170x170mm, 0 slice gap, Matrix 256x192*). The results of the 20 measurement tests can be seen in Table 3.1 for the extremity 0.2T results and Table 3.4 for the for the 3T results.

Table 3.4: The results of the water vial measurements taken from the T1 weighted spin echo images (T1 SE) on the 3T MR imaging

Slice 1 (mm^3)	Slice 2 (mm^3)	Slice 3 (mm^3)	Measured volume (mm^3)	Actual volume (mm^3)	Diff (mm^3)	RMSE (mm^3)
177.27	182.57	165.37	525.21	502	23.21	23.21
156.11	214.32	194.47	564.90	502	62.90	62.90
165.37	206.38	141.55	513.30	502	11.30	11.30
169.34	206.38	193.15	568.87	502	66.87	66.87
170.66	215.64	193.15	579.45	502	77.45	77.45
166.69	203.73	141.55	511.97	502	9.97	9.97
162.72	195.79	193.15	551.66	502	49.66	49.66
182.57	205.06	190.50	578.13	502	76.13	76.13
182.57	198.44	190.50	571.51	502	69.51	69.51
158.75	190.50	195.79	545.04	502	43.04	43.04
152.14	209.02	189.18	550.34	502	48.34	48.34
179.92	199.76	195.79	575.47	502	73.47	73.47
160.08	190.50	194.47	545.05	502	43.05	43.05
165.37	190.50	183.89	539.76	502	37.76	37.76
165.37	205.06	162.72	533.15	502	31.15	31.15
148.17	209.02	169.34	526.53	502	24.53	24.53
173.31	207.70	166.69	547.70	502	45.70	45.70
157.43	193.15	177.27	527.85	502	25.85	25.85
173.31	194.47	173.31	541.09	502	39.09	39.09
161.40	203.73	173.31	538.44	502	36.44	36.44
Mean					**44.77**	**44.77**
SD					**20.83**	

The measurement results on the 3T spin echo sequence were systematically overestimated by 44.8mm^3 or 8.92%. This was similar to the extremity measurement results from the 0.2T image sequence (Table 3.1), which showed a similar overestimation by 48.6mm^3 or 9.7%. The SD of the measurements was similar in the 0.2T extremity image measurements (22.76mm^3) and large bore 3T MR image measurement (20.83mm^3).

Field Variance Tests

Three MR imaging scans of the phantom (taken on the same day) in the extremity 0.2T scanner were measured by a single researcher (JM). The same sequence was used for all three scans: a coronal (short axis) T1 weighted spin echo sequence (*TE 26, TR 840, NEX 2, FOV 170x170mm, 0 slice gap, Matrix 256x192*). The fluid was measured in the water vial of the phantom, five times using the same semi-automated tracing technique as before (Tables 3.5, 3.6 and 3.7).

The results in the tables suggest the measurements of the water vial in the phantom taken in different scans all over-estimated the true volume. The accuracy of the researcher (JM) to quantify the water vial in scan one shows a systematic error of 87.94mm^3 (SD of 6.7mm^3) or an absolute percentage error of 17.5% (see Table 3.5).

Table 3.5: Scan One - Time 11:29am: The results of the water vial measurements taken from the T1 weighted spin echo images (T1 SE) on the 0.2T MR imaging.

Slice 1 (mm^3)	Slice 2 (mm^3)	Slice 3 (mm^3)	Measured volume (mm^3)	Actual volume (mm^3)	Diff (mm^3)	RMSE (mm^3)
176.82	181.14	222.87	580.83	502	78.83	78.83
186.09	190.05	219.60	595.74	502	93.74	93.74
179.82	195.45	218.28	593.55	502	91.55	91.55
181.05	195.45	218.28	594.78	502	92.78	92.78
179.82	188.01	216.96	584.79	502	82.79	82.79
Mean					**87.94**	**87.94**
SD					**6.70**	

The accuracy of the researcher (JM) to quantify the water vial in scan two shows a systematic error of 67.60mm^3 (SD of 14.96mm^3) or an absolute percentage error of 13.5% (see Table 3.6).

Table 3.6: Scan Two - Time 11:44am: The results of the water vial measurements taken from the T1 weighted spin echo images (T1 SE) on the 0.2T MR image

Slice 1 (mm^3)	Slice 2 (mm^3)	Slice 3 (mm^3)	Measured volume (mm^3)	Actual volume (mm^3)	Diff (mm^3)	RMSE (mm^3)
160.08	214.92	216.06	591.06	502	89.06	89.06
148.17	210.96	195.60	554.73	502	52.73	52.73
148.17	205.41	205.38	558.96	502	56.96	56.96
148.17	212.91	203.73	564.81	502	62.81	62.81
160.08	205.41	212.91	578.40	502	76.40	76.40
Mean					**67.60**	**67.60**
SD					**14.96**	

The accuracy of the researcher (JM) to quantify the water vial in scan three shows a systematic error of 56.04mm^3 (SD of 12.6mm^3) or an absolute percentage error of 11.2% (see Table 3.7).

Table 3.7: Scan Three - Time 11:59am: The results of the water vial measurements taken from the T1 weighted spin echo images (T1 SE) on the 0.2T MR images

Slice 1 (mm^3)	Slice 2 (mm^3)	Slice 3 (mm^3)	Measured volume (mm^3)	Actual volume (mm^3)	Diff (mm^3)	RMSE (mm^3)
145.53	223.59	186.45	555.57	502	53.57	53.57
145.53	218.28	197.64	561.45	502	59.45	59.45
145.53	210.36	189.09	544.98	502	42.98	42.98
154.77	213.00	210.00	577.77	502	75.77	75.77
151.08	211.68	187.68	550.44	502	48.44	48.44
Mean					**56.04**	**56.04**
SD					**12.60**	

The technical variance (within one day), produced an overestimation of 31.9mm^3 or an absolute percentage error of 6.4% between each of the three different scans. The between day variance on day one (47.74mm^3 or 9.7%), compared to day two (70.52mm^3 or 14.1%) showed a difference of 22.78mm^3 or 4.4%. The results suggest the greatest error may be as large as 17.5%.

3.6.3 Discussion

To compare the effect of MR imaging field strength on phantom volume measurements, the phantom was examined using matched sequences in an extremity 0.2T and large bore 3T MR image scanners. The accuracy of measuring the volume of water contained within a single water vial using auto tracing techniques was similar at both field strengths (0.2T extremity 44.8mm^3 or 8.9% and 3T large bore 48.6mm^3 or 9.7%).

The auto tracing measurement error was similar for the first (47.74mm^3 or 9.7%) and second researcher (31.61mm^3 or 6.3%) after training although prior to training, the measurement error was much greater (155.67mm^3 or 31.0%). These results suggest the measurement error can be substantially reduced with training and experience.

The measurement error between different scanning sessions suggested a within-day overestimation of the true volume of 31.9mm^3 or a percentage error of 6.4%. The between-day variance also showed an over-estimation of 22.78mm^3 or 4.4%. These results suggest the summation of technical variance of up to 54.68mm^3 or 10.8% that may reflect changes in images associated with field strength and pulse variations.

This phantom study suggests that there are many potential sources of error associated with repeatability measurement, arising from both the scanner itself and the researcher's judgement. The error in volume estimation was

around 10% regardless of the field strength (using a matched sequence). Variability in the positioning of the phantom and inherent magnetic field changes within the scanner suggests that this was the largest source, yielding an additional error of 7.5%.

3.7 *In-vivo* study: Intra-Measurement Reliability of Tracing Methods

The aim of this study was to examine the intra-measurement, between-session reliability and face validity of BML quantification on 3T images using two techniques: manual spline tracing and semi-automated tracing.

The MR images of two pilot participants and 13 consecutive participants who entered into the interventional study were analysed. Fifteen MR images of BMLs in the medial midfoot region, verified by a rheumatologist (DMG) on a water-sensitive STIR sequence, were chosen for analysis. The long axis (axial) of the foot was chosen as the slice plane as it was felt that this plane was most appropriate to visualise the tarsal bones within-plane [331]. Volumes were once again calculated using Analyze software version 3.1 (BIR MAYO Clinic US 1996-2001) and applying the formula described previously based on slice area, slice thickness and inter-slice gap.

3.7.1 Procedure

A pragmatic sub-group was identified from the main study and MR images from two pilot participants (with foot pain and OA related BMLs in the midfoot) and the first 13 participants were included for the reliability analysis. The presence of BML in the midfoot bones was initially identified by a rheumatologist who has experience with semi-quantitative scoring of BML (DMG). Fifteen STIR images were measured in a random order (generated using a computer-based random numbers table) twice, at baseline and after a one week interval.

The ROI was identified as an area of heterogeneous hyper-intense signal with ill-defined borders, which was distinct within the bone. One bone was identified per person in the medial midfoot region, and if there were BMLs in multiple foot bones, the researcher (JHR) identified the bone with the greatest signal volume (see Table 3.8). The specific image slices in the long axis were identified within the chosen midfoot bone.

For each measurement, the long axis image of the tarsal bones was maximized to the largest size possible to view the whole bone containing the BMLs as a complete ROI. The images were analyzed in a random order and the order of the technique (manual tracing and auto tracing) was also randomized.

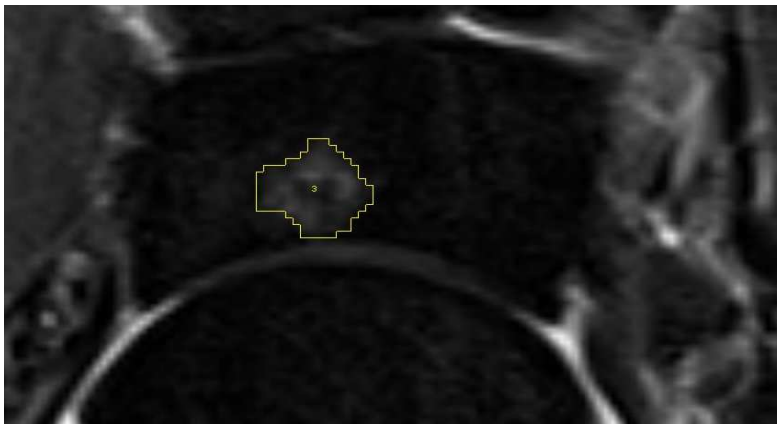
Table 3.8: Identifies the number of bones with BML and chosen study bone

No.	No. of bones with BML	BML Locations	Study Bone
P1	**2**	Medial Cuneiform, 1st Metatarsal	Medial Cuneiform
P2	**7**	Navicular, Medial Cuneiform, intermediate Cuneiform, Lateral Cuneiform, 1st Metatarsal, 2nd Metatarsal, 3rd Metatarsal	Intermediate Cuneiform
1	**5**	Navicular, Medial Cuneiform, Intermediate Cuneiform, Lateral Cuneiform, 3rd Metatarsal	Navicular
2	**2**	Lateral Cuneiform, 3rd Metatarsal	Lateral Cuneiform
3	**4**	Navicular, Medial Cuneiform, Intermediate Cuneiform, Lateral Cuneiform	Intermediate Cuneiform
4	**2**	Medial Cuneiform, Intermediate Cuneiform	Medial Cuneiform
5	**2**	Lateral Cuneiform, 3rd Metatarsal	3rd Metatarsal
6	**7**	Navicular, Medial Cuneiform, Lateral Cuneiform, 1st Metatarsal, 2nd Metatarsal, 3rd Metatarsal, 4th Metatarsal	Lateral Cuneiform
7	**2**	Intermediate Cuneiform, 2nd Metatarsal	Intermediate Cuneiform
8	**3**	Medial Cuneiform, Intermediate Cuneiform, 2nd Metatarsal	2nd Metatarsal
9	**5**	Navicular, Medial Cuneiform, Intermediate Cuneiform, Lateral Cuneiform, 2nd Metatarsal	Intermediate Cuneiform
10	**2**	Intermediate Cuneiform, 2nd Metatarsal	Intermediate Cuneiform
11	**1**	Medial Cuneiform	Medial Cuneiform
12	**2**	Intermediate Cuneiform, Medial Cuneiform	Medial Cuneiform
13	**2**	Intermediate Cuneiform, 2nd Metatarsal	Intermediate Cuneiform

Manual Tracing

Using Analyze software (version 3.1), a spline tracing tool was employed by a single researcher (JHR). The mouse pointer was used to identify the border of the BML by placing multiple points around the BML joined by spline (polynomial) curved lines that semi-automates the tracing process until the area of the ROI was defined per slice (see Figure 3.1).

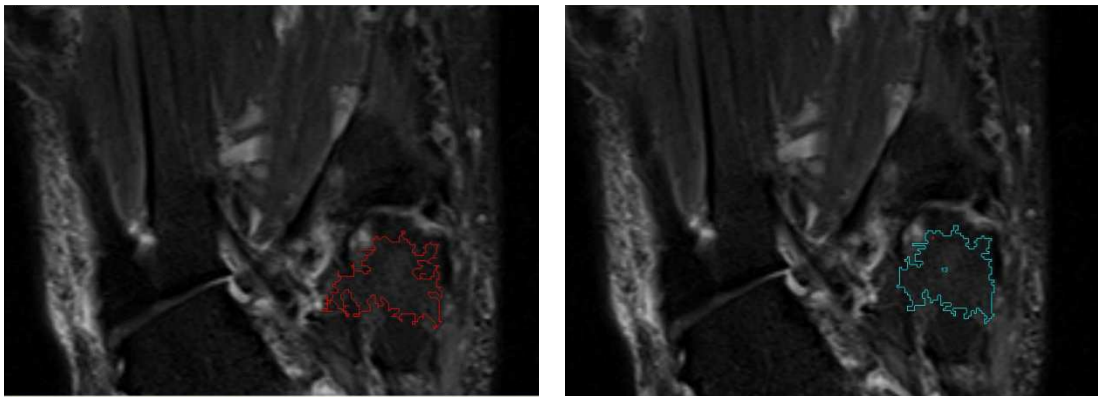
Figure 3.1: Manual tracing in the navicular bone of one participant



Auto Tracing

The Analyze software (version 3.1) semi-automated tracing tool uses a single seed-point placed within an area of high signal intensity, which the researcher (JHR) judged to represent the ROI. Within the ROI this signal was not uniform due to signal fade-out and therefore the boundaries of the grey-scale are manipulated to represent a connected region of hyper-intense signal that constitutes the BML. This range of signal intensities grows the seed-point within the bone to define the edge of the ROI within the bone. Where signal is linked outside the chosen bone (by joint fluid or ligaments) the ROI was edited to maintain the ROI within the bone borders (see Figure 3.2).

Figure 3.2: Auto tracing tool pre and post editing



1	2

Caption: The ROI signal identified at the base of the medial cuneiform in image 1. Image 2 shows post editing of ROI, where the signal beyond bone limits into soft tissues was removed.

Analysis

Each ROI area was defined per slice, with the volumes per person and per bone defined using the following formula.

$$\text{BML Volume} = \sum \text{Area BML} \times (\text{Slice Thickness} + \text{Inter-slice Gap})$$

Where the BML volume is the sum of the BML area, again multiplied by the combination of slice thickness and inter-slice gap.

The total volume for the BML ROI was then calculated and tabulated for the mean, difference and RMSE. In addition, the mean-difference was plotted for the two measurements after Bland and Altman and the distribution pattern examined for bias [332].

3.7.2 Results

The results comparing the two techniques for each participant are shown in Tables 3.9 and 3.10 respectively. Firstly the manual tracing results will be discussed, followed by the semi-automated tracing. Finally both techniques will be compared and discussed.

Manual Tracing

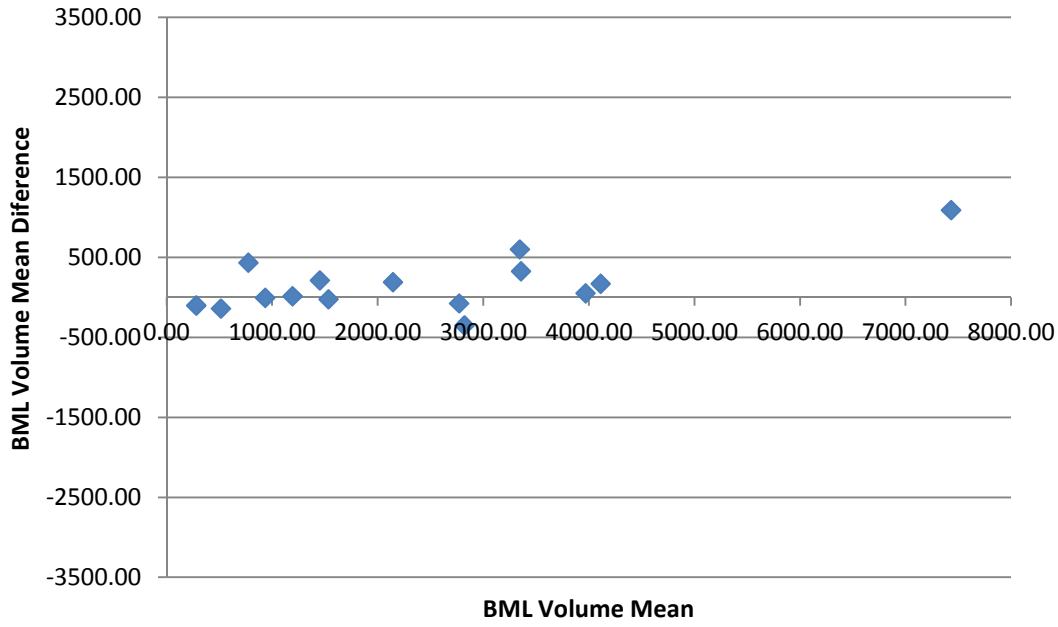
The results of the manual tracing are shown in Table 3.9. The BML mean volume in session one was 2522.12mm^3 (SD 1986.4mm^3) and in session two was 2360.89mm^3 (SD 1757.4 mm^3). A mean volume difference of 161.23mm^3 (SD 352.3mm^3) was found between each session. The RMSE was 252.82mm^3 or 10.4% of the mean BML volume. This difference may be attributed to differences of number of slices, which was increased in five images between sessions.

Table 3.9: The BML volume results in sessions one and two using the manual tracing technique

Study No.	Volume 1 (mm^3)	Volume 2 (mm^3)	Volume Difference (mm^3)	Mean Volume (mm^3)	RMSE (mm^3)	Slice Comparison
p1	7976.60	6883.43	1093.17	7430.02	1093.17	Same
p2	3520.82	3191.75	329.07	3356.29	329.07	Same
1	445.34	583.77	-138.43	514.56	138.43	Same
2	230.97	330.94	-99.97	280.96	99.97	Same
3	4197.01	4025.61	171.40	4111.31	171.40	Extra Slice
4	931.82	934.99	-3.17	933.41	3.17	Extra Slice
5	991.15	556.09	435.06	773.62	435.06	Same
6	2733.75	2807.31	-73.56	2770.53	73.56	Extra Slice
7	2239.37	2047.85	191.52	2143.61	191.52	Same
8	3994.62	3941.63	52.99	3968.13	52.99	Extra Slice
9	1521.13	1543.28	-22.15	1532.21	22.15	Same
10	1557.50	1343.15	214.35	1450.33	214.35	Same
11	1199.97	1184.15	15.82	1192.06	15.82	Same
12	2645.94	2995.57	-349.63	2820.76	349.63	Extra Slice
13	3645.79	3043.82	601.97	3344.81	601.97	Same
Mean	**2522.12**	**2360.89**	**161.23**	**2441.50**	**252.82**	
SD	**1986.40**	**1757.40**	**352.28**	**1867.11**	**288.91**	

The mean-difference plot in Figure 3.3 again shows stability of the measure over a range of volumes.

Figure 3.3: Mean-difference plot for BML manual tracing measurement



Auto Tracing

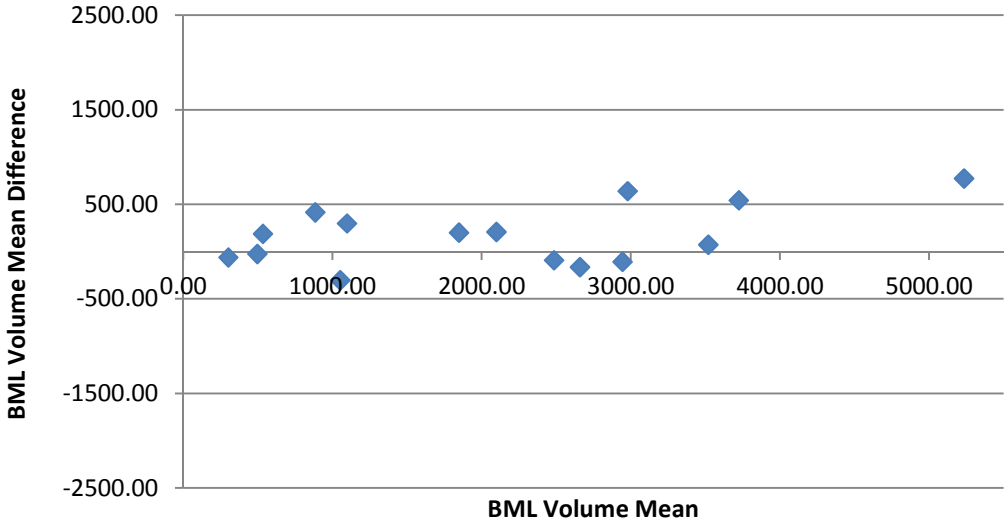
The results of the semi-automated tracing per participant can be been in Table 3.10. The mean BML volume in session one was 2209.52mm^3 (SD 1504.1 mm^3), and in session two was 2035.76mm^3 (SD 1353.7 mm^3). A mean volume difference of 173.76mm^3 (SD 226.7mm^3) between each session was found. The RMSE was 272.85mm^3 or 12.9% of the mean BML volume. This difference may be attributed to differences of slice number between sessions, which were not equal in six of the participant's images.

Table 3.10: The BML volume results in session one and two using the auto tracing technique

Study No.	Volume 1 (mm^3)	Volume 2 (mm^3)	Volume Difference (mm^3)	Mean Volume (mm^3)	RMSE (mm^3)	Slice Comparison
p1	5620.17	4845.76	774.41	5232.97	774.41	extra slice
p2	2890.37	2996.37	-106.00	2943.37	106.00	same
1	483.32	506.25	-22.93	494.79	22.93	same
2	270.53	330.64	-60.11	300.59	60.11	same
3	3994.63	3450.80	543.83	3722.72	543.83	extra slice
4	1091.61	674.74	416.87	883.18	416.87	extra slice
5	627.28	437.44	189.84	532.36	189.84	same
6	2577.13	2739.28	-162.15	2658.21	162.15	extra slice
7	1947.48	1745.77	201.71	1846.63	201.71	same
8	3555.61	3481.26	74.35	3518.44	74.35	extra slice
9	2202.19	1993.36	208.83	2097.78	208.83	same
10	1245.86	946.85	299.01	1096.36	299.01	same
11	899.38	1201.54	-302.16	1050.46	302.16	same
12	2439.49	2529.37	-89.88	2484.43	89.88	extra slice
13	3297.73	2657.02	640.71	2977.38	640.71	same
Mean	**2209.52**	**2035.76**	**173.76**	**2122.64**	**272.85**	
SD	**1504.12**	**1353.74**	**314.33**	**1422.25**	**226.67**	

The mean-difference plot in Figure 3.4 shows stability in the measure over range of volumes.

Figure 3.4: Mean-difference plot for BML volume auto tracing measurements



3.7.3 Discussion

Both manual and automated tracing techniques yielded similar intra-measurement reliability error (RMSE = 252.82mm^3 and 272.85mm^3 respectively), although the manual tracing technique had slightly lower error (-2.5%). Both techniques were susceptible to subjective errors, as the ROI was not identified in the same number of slices in both techniques over two time points. This error occurred at the bottom and top of the bone, associated with difficulties identifying signal intensities at the margins of the bones against increased signal of muscle, tendon, ligaments, sub-dermis fat and joint fluid. Using the auto tracing technique, signal spread beyond the bone was manually edited, possibly adding another technical judgement and decreasing within-user reliability.

Both techniques showed systematic error in the identification of the largest BML volume in the medial cuneiform in the 'pilot one' images. The pattern of BML in the medial cuneiform was associated with osteophytosis and bone

remodelling typical of established OA. For this reason, while the participant was recruited as a pilot case, this image was not included in the main analysis reported later. The irregular bone formation may have affected the margins of the signal and may be explain the systematic error in both techniques.

The intra-measurement reliability evaluated in this sub-study did not include a comparison with a gold standard, and as such the absolute accuracy of each technique could not be tested. Both techniques yielded comparable mean volumes of BMLs, although the manual tracing mean volume 2441.5mm^3 (SD 1867.1 mm^3) was slightly greater than the auto tracing mean volume 2122.64mm^3 (SD 1422.3 mm^3). The larger volume in the manual tracing method was attributed to case 'pilot one', where both manual tracing and auto tracing technique produced most different BML volumes (7430.02mm^3 and 5232.97mm^3 respectively). The mean BML volumes using the manual tracing (1820.25mm^3 SD 1182.9) and auto tracing (1987.40mm^3 SD 1303.92) methods were more comparable after the removal of pilot one and pilot two, which both had advanced joint degeneration. This reduced the error in the manual tracing -70.51mm^3 (182.31mm^3 or 9.2%) however the auto tracing error increased slightly to +25.71mm^3 (247.11mm^3 or 13.6%).

The percentage error observed using both techniques (between 9% and 13%) was felt to be adequate, however there were questions about the measurement of larger BML volumes. The semi-automated tracing technique was felt to be adequate for use in single bone per person, although its use in multiple bones may be called into question if the signal intensity is irregular, affecting the boundaries of the BMLs. In addition, manual tracing can be time consuming, particularly if this technique was adopted for every midfoot bone with a ROI. On the basis of this preliminary work it was felt that further techniques using a newer version of Analyze software with spatial connectivity should be explored.

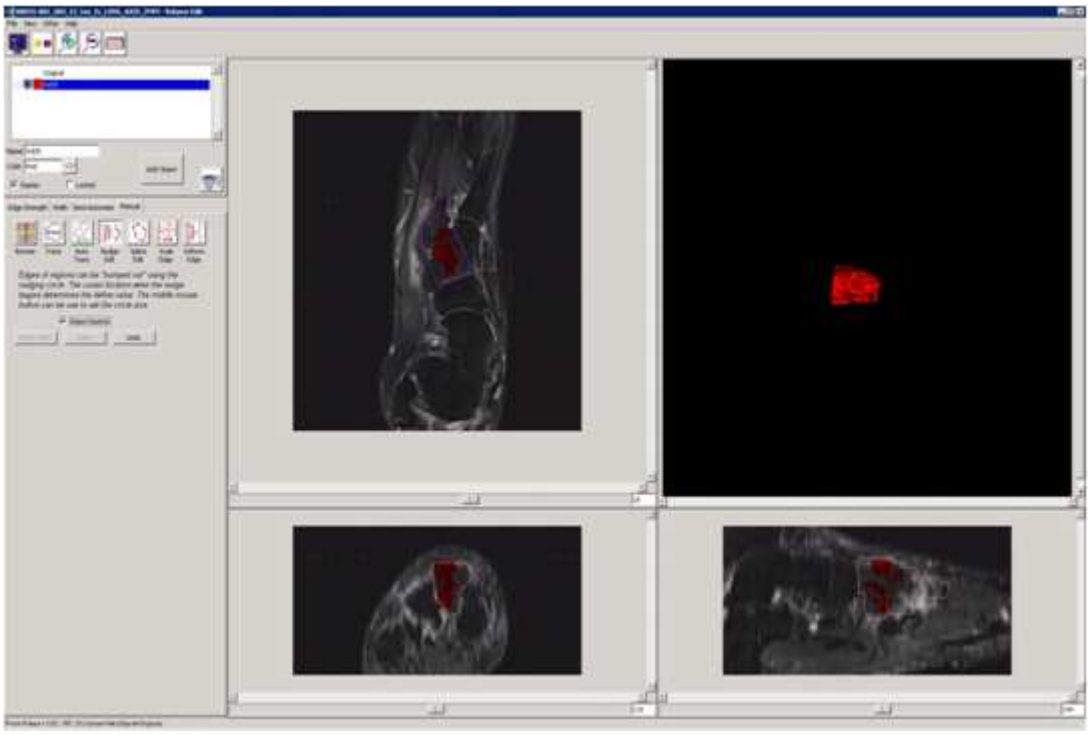
3.8 *In-vivo* study: Intra-Measurement Reliability of Semi-Automated Signal Growth

The aim of this third study was to examine the reliability and face validity of signal thresholding using spatial connectivity methods to quantify BML volumes.

In this next study, a new method of semi-automated signal growth was explored to quantify multiple BML volumes in multiple bones of the midfoot. At this time, enhanced imaging software Analyze version 10 (BIR Mayo clinic Inc. 2010 USA) had become available to test this new method for quantifying area of signal intensity in the midfoot region. This method was investigated further, as multiple bones (rather than one) may provide greater information about the effect of orthoses on patterns of BML in the midfoot known to increase, decrease and migrate.

The MR images of the 20 participants who entered the interventional study were further examined in this sub-study. The new version of Analyze 10 allowed image visualization within a primary plane of interest, in this case the long axis (axial) of the foot as before [331]. Although the MR sequence was again not 3D, 2mm high resolution slices acquired for the main study allowed software analysis in the other two planes (see Figure 3.5) at lower resolution.

Figure 3.5: Analyze 10 software window demonstrating hyper-intense signal render in all three planes



3.8.1 Procedure

As before, the presence of BML (on T2 weighted fat saturated image sequences with 2mm slices) in the midfoot bones was verified by a rheumatologist who has experience with semi-quantitative scoring of BML (DMG). A pragmatic sub-group from the main study was identified by selecting 20 images at random for the reliability study. Twenty T2 weighted fat saturated images were measured in a random order (using a computer generated random numbers table) twice: at baseline and after a one week interval. As can be seen in Table 3.11 the region of BML varied between individual cases in the number and location of bones involved.

Table 3.11: The number of bones with BMLs per participant

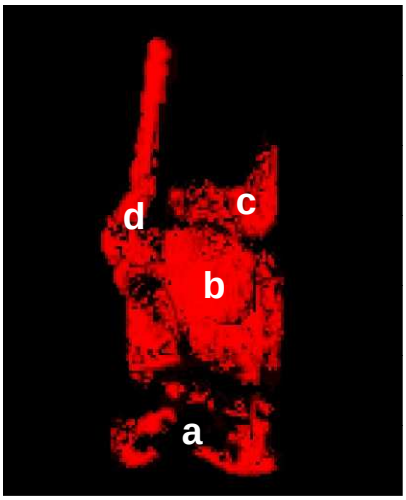
No.	No. of bones with BMLs	BML Locations
1	4	Navicular, Lateral Cuneiform, 3rd Metatarsal, 4th Metatarsal
2	6	Navicular, Medial Cuneiform, Intermediate Cuneiform, Lateral Cuneiform, 3rd Metatarsal, 2nd Metatarsal
3	3	Intermediate Cuneiform, Lateral Cuneiform, 2nd Metatarsal
4	2	Intermediate Cuneiform, 2nd Metatarsal
5	5	Navicular, Medial Cuneiform, Intermediate Cuneiform, 2nd Metatarsal, 1st Metatarsal
6	1	Navicular
7	7	Navicular, Medial Cuneiform, Intermediate Cuneiform, Lateral Cuneiform, 2nd Metatarsal, 3rd Metatarsal, 4th Metatarsal
8	2	Intermediate Cuneiform, 2nd Metatarsal
9	5	Navicular, Medial Cuneiform, Intermediate Cuneiform, 2nd Metatarsal, 1st Metatarsal
10	5	Navicular, Medial Cuneiform, Intermediate Cuneiform, Lateral Cuneiform, 2nd Metatarsal
11	3	Medial Cuneiform, Intermediate Cuneiform, 1st Metatarsal
12	1	Navicular
13	4	Navicular, Medial Cuneiform, Intermediate Cuneiform, Lateral Cuneiform
14	1	3rd Metatarsal
15	2	Intermediate Cuneiform, 2nd Metatarsal
16	2	Intermediate Cuneiform, 2nd Metatarsal
17	4	Navicular, Medial Cuneiform, Intermediate Cuneiform, 2nd Metatarsal
18	2	Navicular, Medial Cuneiform
19	2	Intermediate Cuneiform, 2nd Metatarsal
20	3	Medial Cuneiform, Intermediate Cuneiform, 2nd Metatarsal

Semi-Automated Signal Growth Technique

The ROI was identified empirically by the researcher (JHR) as areas of heterogeneous hyper-intense signal with ill-defined borders, which were distinct within single and multiple bones in the midfoot. Once the ROI was identified, two seed-points were placed (using the Analyze software), in regions of hyper-intense signal in the bone/bones to identify the range of grey-scale that represented the BML. The tissue corresponding to this grey-scale threshold was then rendered in all three planes using a "special connectivity" algorithm (see Figure 3.5 and Figure 3.6).

The software allows the measurement of a specified signal in a pre-identified region, with the capability to view the volumetric render in all three planes simultaneously, allowing for greater visualization of multi-planar signal abnormality (see Figure 3.6).

Figure 3.6: Example of signal threshold render of the midfoot



3D volume render of signal intensity in the following four bones:

a) Navicular,

b) Intermediate cuneiform,

c) Base of the second metatarsal

d) Third metatarsal to mid shaft.

Analysis

The ROI volume was again calculated as a sum of each slice of the signal intensity, per person using the same method as before:

The volume of hyper-intense signal in the bone marrow identified as the ROI was calculated as:

$$\text{BML Volume} = \sum \text{Area BML} \times (\text{Slice Thickness} + \text{Inter-slice Gap})$$

The total volume for the BML ROI was then calculated and tabulated for the mean, difference and RMSE. Rendered 2D images were further compared using the visual volumetric comparison module of Analyze10, which permits face validity assessments of each volume at two time points and provides an overlay of a 2D image for comparison. Each of the 20 participant's two volumes was visually inspected. As previously, the mean-difference was plotted between the two measurements and the distribution pattern examined for bias.

3.8.2 Results

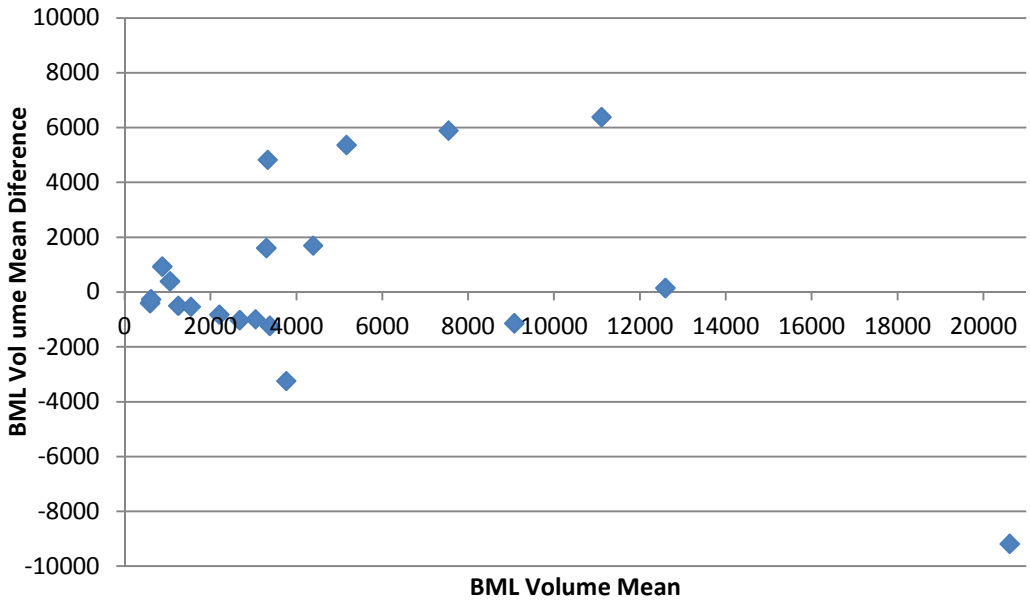
The results of the semi-automated signal threshold technique are shown in Table 3.12. The mean total BML volume for all bones in all participants in session one was 5099.7mm^3 (SD 4893.7mm^3) and 4704.9mm^3 (SD 5774.6mm^3) in session two. A mean volume difference of 394.83mm^3 (SD 3494.86mm^3) was found between the measurement sessions. The RMSE was 2328.74mm^3 or 47.5% of the mean BML volume. This difference may be attributed to measurements in a different number of slices, which occurred in 14/20 images between sessions.

Table 3.12: The results of the total BML volumes in session one and two using the semi-automated signal threshold technique

Study No.	Volume 1 (mm^3)	Volume 2 (mm^3)	Volume Difference (mm^3)	Mean Volume (mm^3)	RMSE (mm^3)	Slice Comparison
1	14296.33	7910.73	6385.60	11103.53	6385.60	Extra Slice
2	5739.20	914.64	4824.56	3326.92	4824.56	Extra Slice
3	1249.19	855.32	393.87	1052.26	393.87	Same
4	7844.40	2481.04	5363.36	5162.72	5363.36	Extra Slice
5	2757.84	3992.13	-1234.29	3374.99	1234.29	Same
6	1334.49	405.01	929.48	869.75	929.48	Extra Slice
7	993.73	1493.00	-499.27	1243.37	499.27	Same
8	2138.11	5382.76	-3244.65	3760.44	3244.65	Extra Slice
9	1270.47	1805.18	-534.71	1537.83	534.71	Extra Slice
10	388.11	787.76	-399.65	587.94	399.65	Extra Slice
11	12666.61	12518.31	148.30	12592.46	148.30	Extra Slice
12	10484.41	4595.55	5888.86	7539.98	5888.86	Extra Slice
13	1789.49	2612.55	-823.06	2201.02	823.06	Extra Slice
14	16018.31	25203.66	-9185.35	20610.99	9185.35	Extra Slice
15	2549.33	3539.13	-989.80	3044.23	989.80	Same
16	5233.28	3539.13	1694.15	4386.21	1694.15	Extra Slice
17	4099.91	2492.40	1607.51	3296.16	1607.51	Extra Slice
18	2162.08	3186.30	-1024.22	2674.19	1024.22	Same
19	8501.58	9641.93	-1140.35	9071.76	1140.35	Same
20	477.07	740.74	-263.67	608.91	263.67	Extra Slice
Mean	**5099.7**	**4704.9**	**394.83**	**4902.28**	**2328.7**	
SD	**4893.7**	**5774.6**	**3494.86**	**5059.04**	**2582.6**	

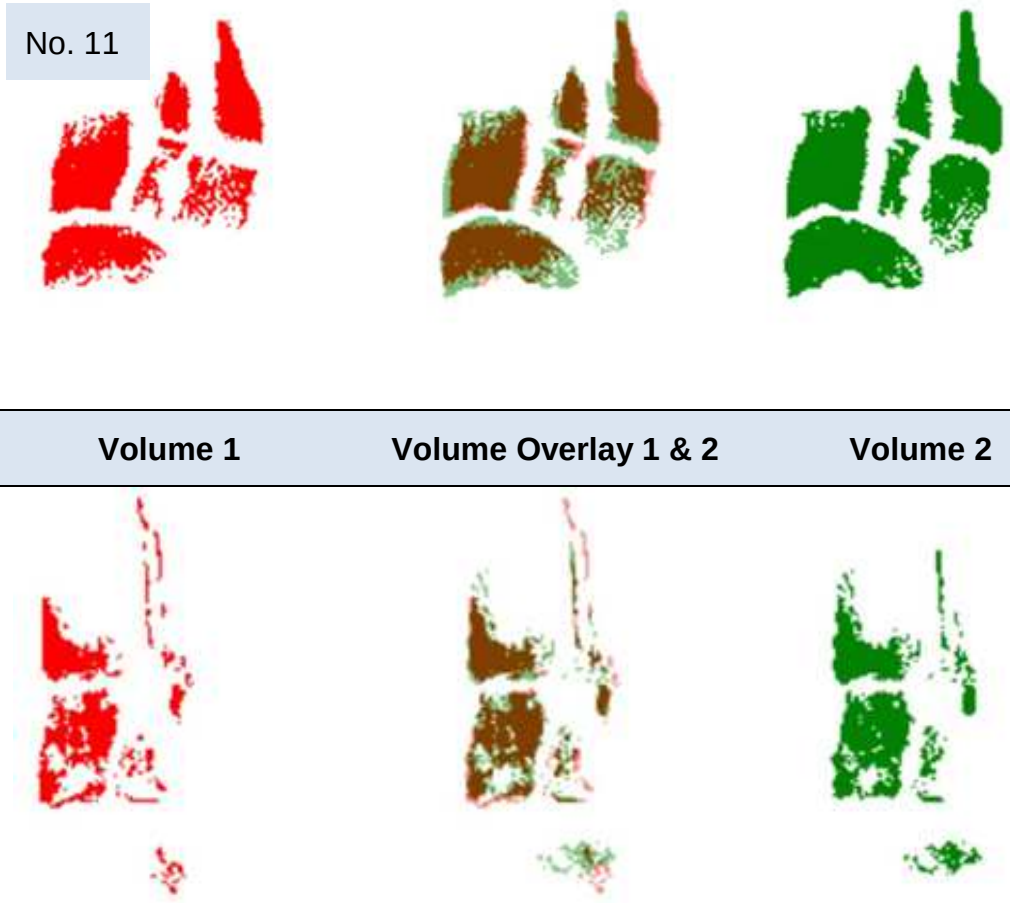
The mean-difference plot in Figure 3.7 indicated a larger intra-measurement reliability error values in mean BML volumes greater than 4000mm^3. This was shown in the distribution pattern that has a general positive linear trend (with the exception on the large negative outlier of case number 14).

Figure 3.7: Mean-difference plot for BML semi-automated measurements



A face validity exercise (example in Figure 3.8) of each of the two measurements reflected the poor agreement shown in Figure 3.7. In the face validity exercise, the distribution of BML showed the same bones were measured at two time points suggesting that some of the hyper-intensity scale was consistent in all BMLs in multiple bones. Those measurements with poor agreement over two time points were associated with different margins of the BML (particularly at the fade-out) at each time point. For instance the outlier (case Number 14) in Figure 3.7 was also the least comparable of the face validity exercise (see Figure 3.8). Those cases with the similar volumes at each visit, showed similar BML patterns in the midfoot in the face validity exercise (case Number 11 in Figure 3.8).

Figure 3.8: Face validity of semi-automated BML quantification: in best case (No. 11) and worse case (No. 14) comparisons



3.8.3 Discussion

This small study investigated the intra-measurement reliability and face validity of semi-automatic spatial connectivity methods to quantify foot BML volumes, using 2D images of the foot. The results show that a semi-automated threshold technique to assess clusters of specified greyscale was not a reliable method for quantifying volumes of BMLs in the foot. This was reflected in the distribution plot, which suggested this measurement technique showed a trend towards higher errors with larger volumes in multiple bones. In smaller volumes with well defined BMLs (see Figure 3.1) the methods were comparable with the techniques described in previous

sections. Where there was a greater volume with larger signal fade-out at the margins, the method performs poorly. This error may have been associated with the grey-scale chosen in the ROI and the inter-connectivity of the pixels with this technique. Compared to the previous tracing techniques, signal thresholding produced poor reliability.

3.9 *In-vivo* study: Intra-Measurement Reliability of Semi-Automated Signal Subtraction

In this final reliability study, a new technique was explored that had the potential benefit of retaining the reliability of manual tracing but which could also be applied to multiple bones, allowing the calculation of BMLs as a percentage of total bone volume. This new approach of normal marrow "signal subtraction" was investigated using imaging software Analyze version 10 (BIR Mayo clinic Inc. 2010 USA).

The aim of this final study was to examine the intra-measurement (between-session) reliability and face validity of bone segmentation using manual tracing and signal subtraction.

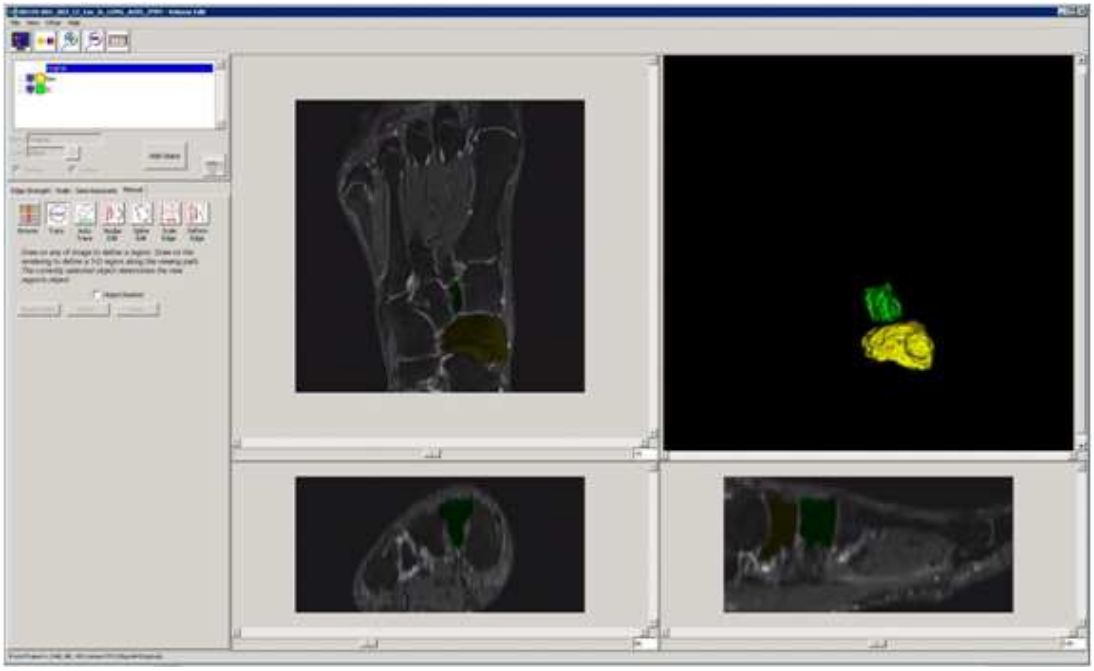
3.9.1 Procedure

Using the same criteria as before, the presence of BML (on T2 Weighted fat saturated image sequences with 2mm slices) in the midfoot bones was verified by the same rheumatologist (DMG). The same twenty T2 weighted fat saturated images (see Table 3.4) were measured in a random order (using another random numbers table) twice after a one week interval. As before, the primary plane of interest remained the long axis (axial) of the foot, with simultaneous visualization in the two other planes at lower resolution (using Analyze software version 10).

Semi-Automated Signal Subtraction Technique

Bones were segmented using the manual tracing function, as used in study one. All bones with BMLs evident, plus an additional non-BML bone were segmented per participant. For each measurement, the long axis image of the tarsal bones was maximized to the largest size, to view the edges of the bone. Using the mouse, inter-connecting points were placed at the edge of the bone to produce a 2D area. This method was repeated by a single researcher (JHR), per slice for each bone to produce a 3D bone volume, for every participant. This method can be seen in Figure 3.9.

Figure 3.9: Analyze 10 manual tracing of foot bones in all three planes

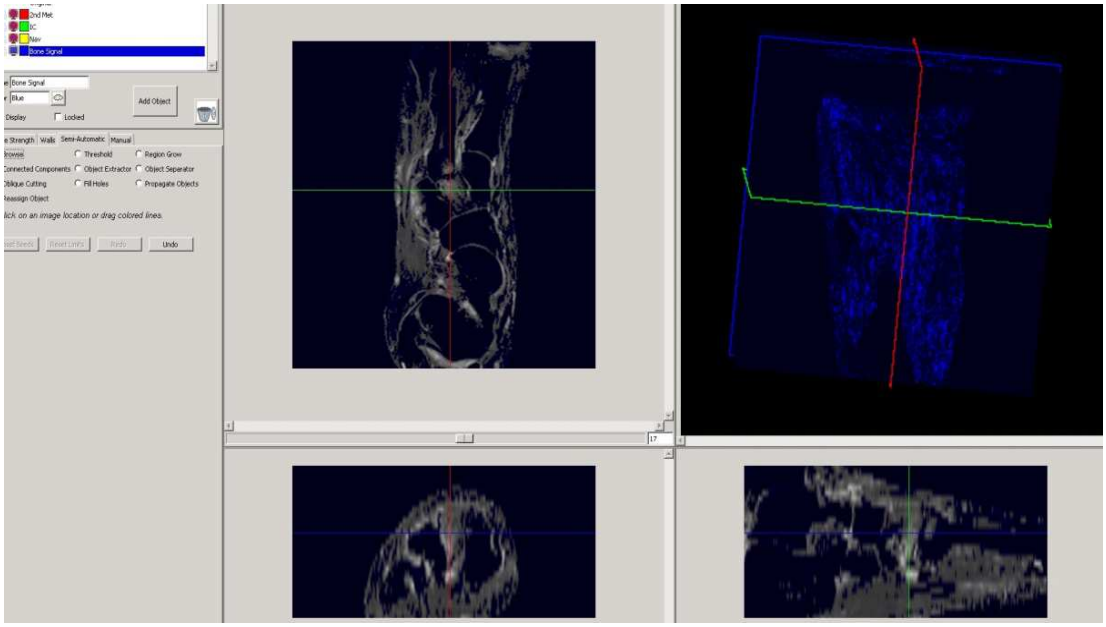


Caption: Outlines of navicular and intermediate cuneiform bones in all three planes that produced the 3D render in the fourth window

The BML volume was determined by identifying the maximum signal of normal fat marrow in the foot bones and using multiple seed-points in normal bone, to measure normal marrow signal intensity (see Figure 3.10). This new threshold range of fat marrow was automatically subtracted from the previously segmented bone to produce a 2D map of the ROI (hyper-intense signal) for each bone, and viewed as a 3D render (see Figure 3.11). The 3D hyper-intense signal was calculated in mm^3 with reference to slice thickness and inter-slice gap to produce the BML volume.

The face validity of the subtraction method was further examined by tracing around an additional non-BML bone for all 20 participants. The face validity of the remaining BML signal was undertaken by comparing the rendered 2D images in the volumetric comparison module of software Analyze 10. This permits a face validity assessment of each volume at two time points and provides an overlay of a 2D image for comparison. Each of the 20 participants' two volumes was inspected visually.

Figure 3.10: Analyze 10 subtraction of hypo-intensity grey-scale of bone signal and surrounding noise in all three planes



Caption: Hyper-intense signal in the intermediate cuneiform and second metatarsal is not subtracted. The bright signal in the bone is equivalent to some of the muscle and soft tissue signal.

Analysis

The analysis was limited, as before, by the 2D sequence. The bone segmentation volume and ROI of the BML volume was calculated as a sum of each slice of the signal intensity per bone using the same method as before [329, 333].

The volume of bone was calculated as:

$$\alpha \text{ Bone Volume} = \sum \text{Area Bone} \times (\text{Slice Thickness} + \text{Inter-slice Gap})$$

The volume of hyper-intense signal in the bone marrow identified as the ROI was calculated as:

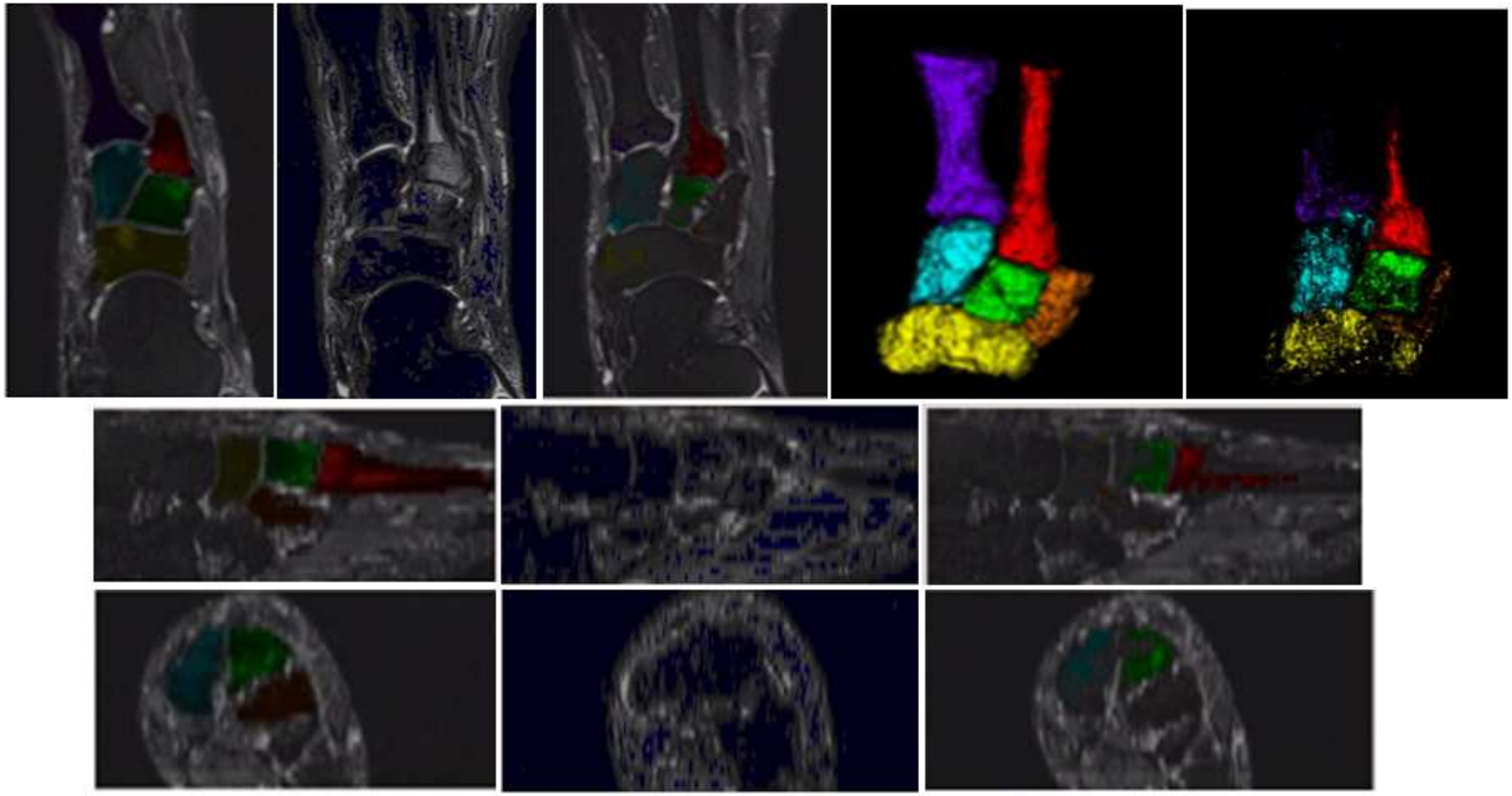
$$\beta \text{ Bone BML Volume} = \sum \text{Area BML} \times (\text{Slice Thickness} + \text{Inter-slice Gap})$$

Where α is the bone volume and the sum of the bone areas are combined with the slice thickness and inter-slice gap.

Where β is the BML volume and the sum of the BML areas are combined with the slice thickness and inter-slice gap.

The total volume for each of the bones and the BML was then calculated per bone and aggregated per person and tabulated for the mean, difference and RMSE. The mean-difference was plotted between the two measurements and the distribution pattern was examined for bias.

Figure 3.11: Bone segmentation and signal subtraction technique used to acquire bones volume and BML volume



3.9.2 Results

Bone Volume Between-Session, Intra-Measurement Reliability

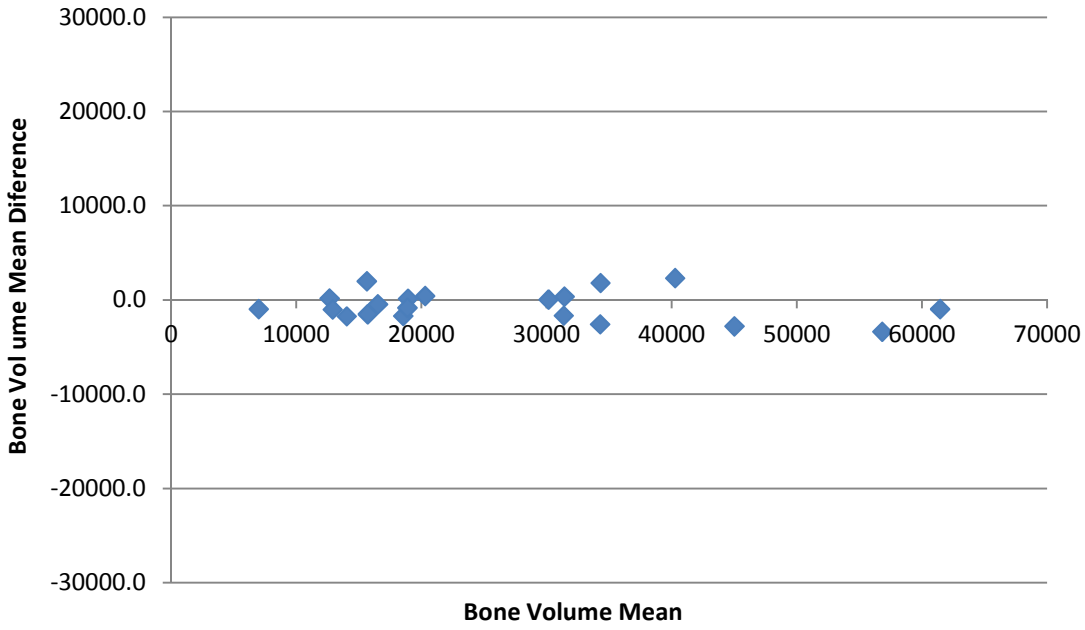
The number of bones with BML identified ranged from one to six per participant, a total of 78 bones. At the participant level, the mean bone volume per participant (shown in Table 3.13) in session one was 26494.2mm^3 (SD 14922.6mm^3) and in session two was 27102.4mm^3 (SD 15259.6mm^3) a difference of -608.4mm^3 (SD 1552.3mm^3). After calculating the absolute difference, the RMSE was 1338.2mm^3 or 5% of the mean volume of the total bones per participant.

Table 3.13: The results of the total bone volume measurements in session one and two using the manual tracing technique

Study No.	Volume 1 (mm^3)	Volume 2 (mm^3)	Volume Difference (mm^3)	Mean Volume (mm^3)	RMSE (mm^3)
1	18986.8	18846.6	140.11	18916.70	140.11
2	16623.6	14631.2	1992.32	15627.40	1992.32
3	20501.1	20072.7	428.42	20286.88	428.42
4	35204.3	33391.6	1812.70	34297.96	1812.70
5	16283.1	16732.1	-449.01	16507.60	449.01
6	31600.3	31233.5	366.71	31416.90	366.71
7	30533.1	32187.7	-1654.59	31360.37	1654.59
8	60948.8	61912.1	-963.32	61430.41	963.32
9	12738.2	12556.9	181.28	12647.56	181.28
10	41422.5	39093.2	2329.29	40257.83	2329.29
11	14950.7	16448.7	-1497.97	15699.68	1497.97
12	13157.0	14881.6	-1724.57	14019.31	1724.57
13	55124.5	58480.4	-3355.87	56802.43	3355.87
14	30167.1	30117.7	49.43	30142.41	49.43
15	43606.7	46386.0	-2779.29	44996.36	2779.29
16	17688.6	19379.3	-1690.68	18533.93	1690.68
17	6508.6	7466.1	-957.46	6987.36	957.46
18	12393.2	13395.4	-1002.26	12894.31	1002.26
19	18463.3	19282.4	-819.10	18872.86	819.10
20	32983.5	35553.4	-2569.84	34268.45	2569.84
Mean	**26494.2**	**27102.4**	**-608.2**	**26798.3**	**1338.2**
SD	**14922.6**	**15259.6**	**1552.3**	**15072.1**	**956.0**

The mean-difference plot in Figure 3.12 shows no pattern of bias. The pattern of distribution showed mixed pattern of error at all sizes of bone volume.

Figure 3.12: Mean-difference plot for total bone segmentation volumes per participant using manual tracing technique



This was also shown at an individual bone level, for all 78 bones (see Table 3.14). The mean bone volume in session one was 6793.4mm^3 (SD 3525.62mm^3) and in session two was 6949.3mm^3 (SD 3613.32mm^3), a difference of -155.9mm^3 (SD 524.7mm^3). After calculating the absolute difference, the RMSE was 427.8mm^3 or 6.2% of the mean volume of each bone.

Table 3.14: The results of the bone volume measurement in session one and two using the manual tracing technique to segment the bones

Study No.	Bone	Volume 1 (mm^3)	Volume 2 (mm^3)	Volume Difference (mm^3)	Mean Volume (mm^3)	RMSE (mm^3)
1	2M	5253.04	5781.22	-528.18	5517.13	528.18
2	IC	3153.48	3153.47	0.01	3153.475	0.01
3	NAV	10580.23	9911.95	668.28	10246.09	668.28
4	2M	5247.03	4542.54	704.49	4894.785	704.49
5	IC	3540.59	3313.20	227.39	3426.895	227.39
6	NAV	7835.94	6775.50	1060.44	7305.72	1060.44
7	2M	6837.82	6303.09	534.73	6570.455	534.73
8	IC	3848.59	3499.25	349.34	3673.92	349.34
9	NAV	9814.68	10270.33	-455.65	10042.505	455.65
10	2M	3630.34	3842.92	-212.58	3736.63	212.58
11	3M	3419.41	3612.21	-192.8	3515.81	192.8
12	IC	2471.88	2104.37	367.51	2288.125	367.51
13	MC	6430.13	6017.36	412.77	6223.745	412.77
14	LC	3151.63	2688.56	463.07	2920.095	463.07
15	NAV	7596.86	7092.61	504.25	7344.735	504.25
16	CUB	8504.06	8033.58	470.48	8268.82	470.48
17	3M	4516.13	4455.96	60.17	4486.045	60.17
18	MC	7852.32	8033.60	-181.28	7942.96	181.28
19	LC	3914.64	4242.54	-327.9	4078.59	327.9
20	1M	13133.18	13318.60	-185.42	13225.89	185.42
21	MC	8538.48	8572.25	-33.77	8555.365	33.77
22	NAV	9928.59	9342.69	585.9	9635.64	585.9
23	2M	5755.60	6473.29	-717.69	6114.445	717.69
24	IC	2977.08	3370.94	-393.86	3174.01	393.86
25	MC	7683.73	8052.07	-368.34	7867.9	368.34
26	LC	4529.49	4672.87	-143.38	4601.18	143.38
27	NAV	9587.17	9618.49	-31.32	9602.83	31.32
28	1M	15248.32	15248.32	0	15248.32	0
29	2M	7969.00	7861.07	107.93	7915.035	107.93
30	IC	5144.30	5283.56	-139.26	5213.93	139.26
31	MC	11358.99	11538.63	-179.64	11448.81	179.64
32	LC	6380.31	6380.31	0	6380.31	0

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Table 3.14 – Continued

Study No.	Bone	Volume 1 (mm^3)	Volume 2 (mm^3)	Volume Difference (mm^3)	Mean Volume (mm^3)	RMSE (mm^3)
33	NAV	14847.83	15600.18	-752.35	15224.005	752.35
34	2M	3462.82	3822.86	-360.04	3642.84	360.04
35	IC	1648.61	2218.73	-570.12	1933.67	570.12
36	NAV	7626.77	6515.33	1111.44	7071.05	1111.44
37	IC	3204.27	3026.30	177.97	3115.285	177.97
38	MC	11451.85	11380.99	70.86	11416.42	70.86
39	LC	4802.73	4521.75	280.98	4662.24	280.98
40	NAV	10122.03	9062.45	1059.58	9592.24	1059.58
41	CUB	11841.59	11101.69	739.9	11471.64	739.9
42	NAV	7816.89	8622.72	-805.83	8219.805	805.83
43	MC	7133.8	7825.94	-692.14	7479.87	692.14
44	2M	4390.9	5641.67	-1250.77	5016.285	1250.77
45	IC	2442.22	2560.89	-118.67	2501.555	118.67
46	MC	6323.9	6679.03	-355.13	6501.465	355.13
47	CUB	14312	14343.24	-31.24	14327.62	31.24
48	LC	5314.44	5509.71	-195.27	5412.075	195.27
49	3M	3969.77	4711.33	-741.56	4340.55	741.56
50	MC	12081.5	12583.29	-501.79	12332.395	501.79
51	NAV	11037.6	11648.94	-611.34	11343.27	611.34
52	IC	3744.82	4228.49	-483.67	3986.655	483.67
53	2M	4664.36	5455.36	-791	5059.86	791
54	LC	5140.46	4819.13	321.33	4979.795	321.33
55	MC	8731.09	8666.02	65.07	8698.555	65.07
56	NAV	8117.3	8439.45	-322.15	8278.375	322.15
57	IC	3268.51	3216.6	51.91	3242.555	51.91
58	2M	4909.76	4976.49	-66.73	4943.125	66.73
59	LC	3468	3641.86	-173.86	3554.93	173.86
60	MC	9194.49	9656.73	-462.24	9425.61	462.24
61	1M	15349.4	16641.35	-1291.95	15995.375	1291.95
62	NAV	7993.16	8579.8	-586.64	8286.48	586.64
63	IC	2946.33	2883.01	63.32	2914.67	63.32
64	2M	4655.33	4983.25	-327.92	4819.29	327.92
65	IC	4290.11	4590.84	-300.73	4440.475	300.73

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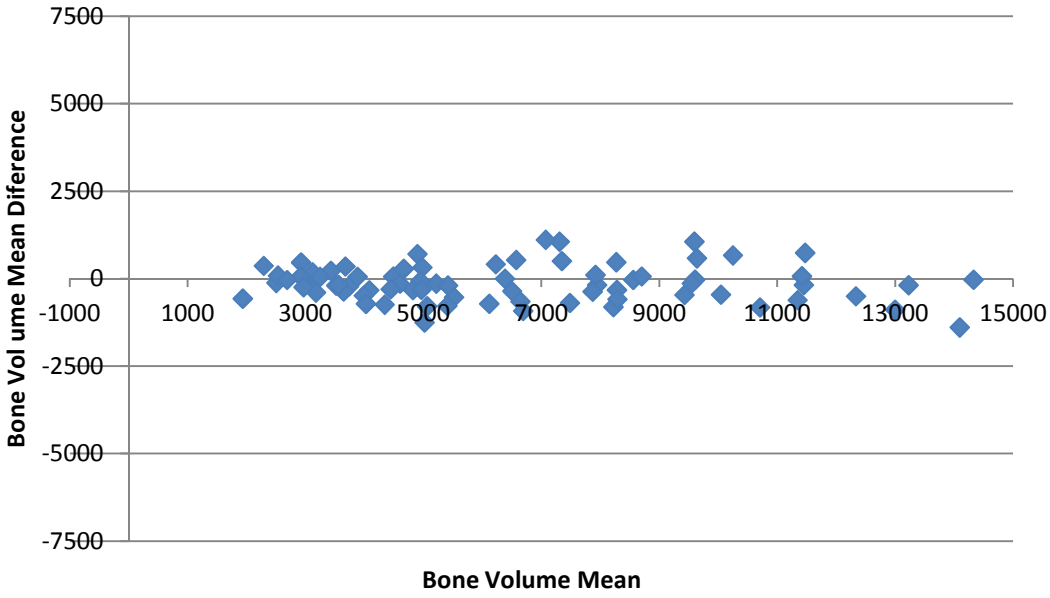
Table 3.14 – Continued						
Study No.	**Bone**	**Volume 1 (mm^3)**	**Volume 2 (mm^3)**	**Volume Difference (mm^3)**	**Mean Volume (mm^3)**	**RMSE (mm^3)**
66	NAV	13398.5	14788.43	-1389.93	14093.465	1389.93
67	IC	2844.38	3085.8	-241.42	2965.09	241.42
68	3M	3664.25	4380.29	-716.04	4022.27	716.04
69	NAV	5013.59	5788.03	-774.44	5400.81	774.44
70	IC	2574.04	2487.82	86.22	2530.93	86.22
71	2M	4805.55	5119.59	-314.04	4962.57	314.04
72	IC	2666.46	2701.91	-35.45	2684.185	35.45
73	NAV	9480.09	9612.76	-132.67	9546.425	132.67
74	MC	6316.76	6967.74	-650.98	6642.25	650.98
75	MC	10293.6	11115.07	-821.47	10704.335	821.47
76	NAV	12553.7	13440.23	-886.53	12996.965	886.53
77	IC	3908.82	3851.15	57.67	3879.985	57.67
78	2M	6227.41	7146.92	-919.51	6687.165	919.51
	Mean	**6793.40**	**6949.34**	**-155.94**	**6871.37**	**427.82**
	SD	**3525.62**	**3613.32**	**524.66**	**3560.09**	**338.38**

No trend towards a systematic error with total volume was seen for any of the volumes (Figure 3.13).

Figure 3.13: Mean-difference plot for each bone segmentation volume using manual tracing technique



Bone Marrow Lesion Volume between-Session Intra-Measurement Reliability Measurement

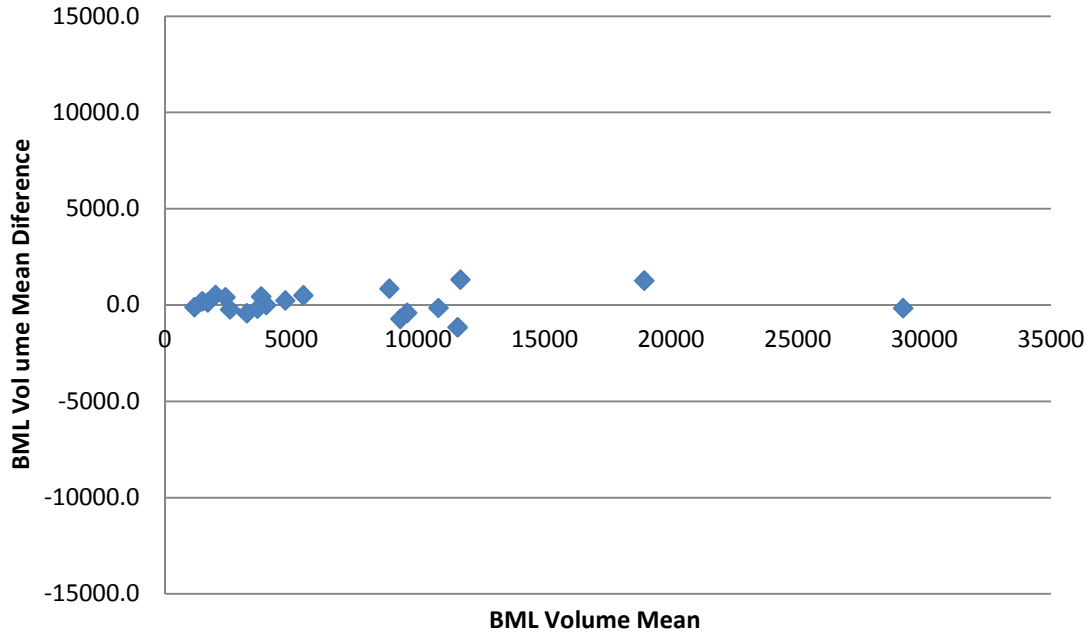
At a participant level, the total BML mean volume in session one was 7358.8mm^3 (SD 6965mm^3) and in session two was 7242.7mm^3 (SD 6927.4mm^3). A mean difference of 116.1mm^3 (SD 613.2mm^3) was found between measurement sessions. The RMSE was 470.96 mm^3 or 6.5% of the mean BML volume (see Table 3.15).

Table 3.15: The results of the total BML volume measurement in session one and two using the semi-automated signal subtraction technique

Study No.	Volume 1 (mm^3)	Volume 2 (mm^3)	Volume Difference (mm^3)	Mean Volume (mm^3)	RMSE (mm^3)
1	3998.07	3998.07	0.00	3998.07	0.00
2	4017.70	3577.68	440.02	3797.69	440.02
3	3018.89	3445.69	-426.80	3232.29	426.80
4	10986.62	12140.14	-1153.52	11563.38	1153.52
5	1563.88	1375.17	188.71	1469.53	188.71
6	5719.49	5216.86	502.63	5468.18	502.63
7	8933.82	9651.51	-717.69	9292.67	717.69
8	9287.21	8436.04	851.17	8861.63	851.17
9	10723.71	10875.29	-151.58	10799.50	151.58
10	3554.26	3750.36	-196.10	3652.31	196.10
11	4870.40	4634.77	235.63	4752.59	235.63
12	2452.93	2681.18	-228.25	2567.06	228.25
13	29079.49	29241.84	-162.35	29160.67	162.35
14	9359.77	9765.98	-406.21	9562.88	406.21
15	19567.22	18300.84	1266.38	18934.03	1266.38
16	2259.16	1729.40	529.76	1994.28	529.76
17	2591.43	2186.02	405.41	2388.73	405.41
18	1109.82	1215.82	-106.00	1162.82	106.00
19	1753.47	1622.45	131.02	1687.96	131.02
20	12328.74	11008.79	1319.95	11668.77	1319.95
Mean	**7358.80**	**7242.70**	**116.11**	**7300.75**	**470.96**
SD	**6965.02**	**6927.42**	**613.20**	**6939.48**	**395.90**

Figure 3.14 shows the distribution of the mean difference. The plot showed no bias, or greater error with either larger or smaller volumes.

Figure 3.14: Mean-difference plot for each participants total BML using semi-automated signal subtraction method



After subtraction, hyper-intense signal as a ROI was identified in 59 bones, as seen in Table 3.16. At a bone level, the total mean volume in session one was 2535.4mm^3 (SD 1893.98mm^3) and session two was 2455.15mm^3 (SD 1793.76mm^3). A mean difference of 80.25mm^3 (SD 300.4mm^3) was found between measurement sessions. The RMSE was 230.37mm^3 or 9.2% of the mean BML volume.

Table 3.16: The results of the BML measurement in session one and two using the semi-automated signal subtraction per bone

Study No.	Bones	Volume 1 (mm^3)	Volume 2 (mm^3)	Volume Difference (mm^3)	Mean Volume (mm^3)	RMSE (mm^3)
1	2M	2210.81	2277.56	-66.8	2244.185	66.75
2	IC	1787.26	1720.51	66.8	1753.885	66.75
3	2M	1211.25	940.16	271.1	1075.705	271.09
4	IC	2806.45	2637.52	168.9	2721.985	168.93
5	2M	1446.01	1580.3	-134.3	1513.155	134.29
6	IC	1572.88	1865.39	-292.5	1719.135	292.51
7	2M	2337.56	2410.89	-73.3	2374.225	73.33
8	3M	2631.7	2571.56	60.1	2601.63	60.14
9	IC	1801.17	2139.81	-338.6	1970.49	338.64
10	MC	771.23	1115.63	-344.4	943.43	344.4
11	LC	2375.46	2828.63	-453.2	2602.045	453.17
12	NAV	1069.5	1073.62	-4.1	1071.56	4.12
13	3M	1043.96	1032.41	11.6	1038.185	11.55
14	MC	519.92	342.76	177.2	431.34	177.16
15	1M	4912.78	4403.55	509.2	4658.165	509.23
16	MC	806.71	813.31	-6.6	810.01	6.6
17	2M	3389.91	3034.77	355.1	3212.34	355.14
18	IC	2326.95	1942.15	384.8	2134.55	384.8
19	MC	1830.91	1789.71	41.2	1810.31	41.2
20	NAV	1739.44	1669.41	70.0	1704.425	70.03
21	1M	136.79	196.94	-60.2	166.865	60.15
22	2M	4827.07	4677.08	150.0	4752.075	149.99
23	IC	2940.9	3112.28	-171.4	3026.59	171.38
24	MC	1733.72	1782.34	-48.6	1758.03	48.62
25	NAV	1085.23	1106.65	-21.4	1095.94	21.42
26	2M	2267.35	2535.12	-267.8	2401.235	267.77
27	IC	1286.91	1215.24	71.7	1251.075	71.67
28	IC	1835.05	2044.34	-209.3	1939.695	209.29
29	MC	1329.95	1245.89	84.1	1287.92	84.06
30	LC	1861.43	1708.98	152.5	1785.205	152.45
31	NAV	5150.82	4652.3	498.5	4901.56	498.52

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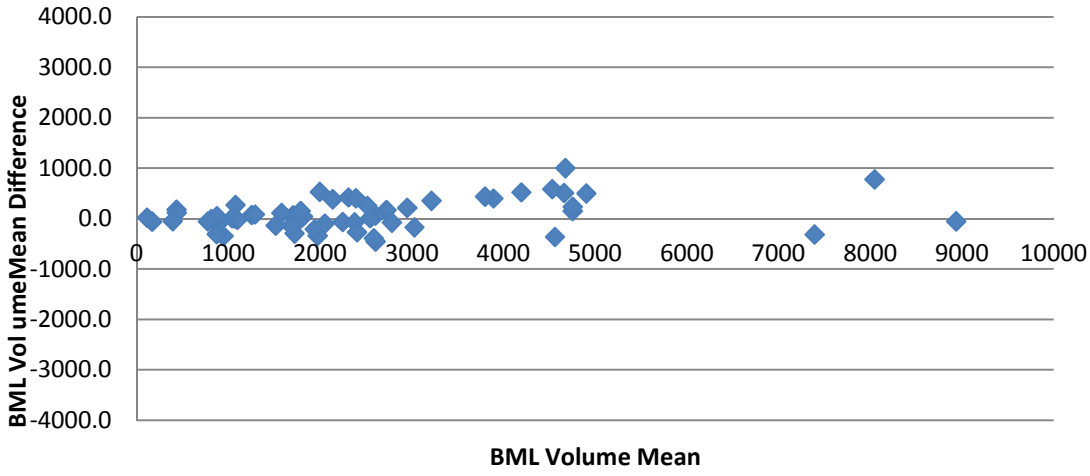
Table 3.16 – Continued

Study No.	Bones	Volume 1 (mm^3)	Volume 2 (mm^3)	Volume Difference (mm^3)	Mean Volume (mm^3)	RMSE (mm^3)
32	NAV	4870.4	4634.77	235.6	4752.585	235.63
33	2M	842.09	933.55	-91.5	887.82	91.46
34	IC	1610.84	1747.63	-136.8	1679.235	136.79
35	LC	2546.81	2538.57	8.2	2542.69	8.24
36	3M	4088.42	3687.99	400.4	3888.205	400.43
37	MC	8907.65	8962.06	-54.4	8934.855	54.41
38	NAV	8434.72	7656.1	778.6	8045.41	778.62
39	IC	2742.93	2819.55	-76.6	2781.24	76.62
40	2M	4015.09	3577.57	437.5	3796.33	437.52
41	LC	4378.32	4740.03	-361.7	4559.175	361.71
42	MC	492.71	376.54	116.2	434.625	116.17
43	NAV	896.43	847.81	48.6	872.12	48.62
44	IC	716.82	1024.15	-307.3	870.485	307.33
45	2M	2388.55	2777.45	-388.9	2583	388.9
46	MC	7233.49	7548.23	-314.7	7390.86	314.74
47	1M	5174.42	4171.67	1002.8	4673.045	1002.75
48	NAV	2517.18	2096.15	421.0	2306.665	421.03
49	IC	2000.55	2098.62	-98.1	2049.585	98.07
50	2M	2641.58	2386.17	255.4	2513.875	255.41
51	NAV	2259.16	1729.4	529.8	1994.28	529.76
52	3M	2591.43	2186.02	405.4	2388.725	405.41
53	IC	365.46	416.09	-50.6	390.775	50.63
54	2M	744.36	799.73	-55.4	772.045	55.37
55	NAV	120.31	100.52	19.8	110.415	19.79
56	MC	1633.16	1521.93	111.2	1577.545	111.23
57	MC	4821.76	4235.93	585.8	4528.845	585.83
58	IC	3053.54	2840.98	212.6	2947.26	212.56
59	2M	4453.44	3931.88	521.6	4192.66	521.56
	Mean	**2535.40**	**2455.15**	**80.25**	**2495.28**	**230.37**
	SD	**1893.98**	**1793.76**	**300.40**	**1838.42**	**206.90**

The mean difference plot showed a slight trend for greater error with larger bone volumes (see Figure 3.15).

Figure 3.15: Mean-difference plot for each BML volume per bone using semi-automated signal subtraction method



The face validity exercise for each of the two measurements (as illustrated in Figure 3.8 for the previous semi-automated BML technique) showed good visual agreement between measures in all of the 20 participants. The segmentation of 20 additional bones with no ROI (BML signal), was undertaken to examine whether subtraction of normal marrow led to better signal removal in both measurement sessions. The same 19 of the 20 segmented bones per participant were totally subtracted in both sessions, showing the subtraction technique was consistent across both sessions. Some error was located in the navicular bone of case number 55, which showed small amounts of hyper-intense signal in the same two slices: 146 voxels in session one and 122 voxels in session two, at the plantar margin in a previously identified non-pathological bone.

3.9.3 Discussion

This small study investigated the intra-measurement reliability and face validity of a novel technique combining bone segmentation and subtraction of normal bone marrow signal. This approach combined the manual (spline) tracing method to segment the bones with a sophisticated new, grey-scale marrow subtraction technique to better differentiate the transition of BML signal into normal bone. Intra-measurement reliability of bone segmentation showed low levels of error that were comparable at a participant level (5% error) and bone level (6.2% error). Signal subtraction of the bone segment also showed good intra-measurement reliability on a participant (6.5% error) level, although this was not as comparable at an individual bone level (9.2% error). The mean-difference plots showed no pattern of bias in the bone segmentation on a person or individual bone level.

The mean-difference BML subtraction plots again showed no pattern of bias the face validity appeared strong. One normal bone was not fully subtracted due to a small amount of signal in two slices of a comparator navicular bone, which suggests that small amounts of hyper-intense signal (in this case 1.3% of the total bone volume) may not relate to BML, and may represent measurement error associated with anomalies such as joint fluid, cortex, ligament or vessels erroneously visualised at the margins of the bone.

The subtraction method offers a novel approach to the volumetric quantification of BML with good intra-measurement reliability and no systemic bias over a range of volumes. The degree of error was considered acceptable therefore the manual (spline) tracing to segment the bone and signal subtraction measurement technique was chosen for application in the main study.

3.10 Chapter Three Discussion

Image segmentation is a difficult problem in the field of MR image processing, particularly for image features that do not have clearly defined borders, such as BMLs. Semi-quantitative measurements of BMLs are the most commonly used method for quantifying lesion size in OA of the knee. Volumetric quantification of BML is a challenge due to the heterogeneous geometry combined with ill-defined lesion borders. The effect of border 'fade-out', where the margins of the lesion are indistinct at the transition with the normal medullary bone, can further hinder the reliability of quantification using segmentation methods. The main aim of this chapter was to investigate signal segmentation methods and BML volume measurements.

In the phantom study, the accuracy and measurement error of semi-automated tracing segmentation techniques to measure water signal in a phantom study was investigated. The results suggested human measurement error was around 10%. The next largest source of error was technical variance in within-day and between-day scans of up to 7.5%. In contrast, the field strength did not have a large effect when the sequences where matched. The parity of measurement results, from the phantom MR scans obtained at 0.2T and 3T provides construct validity and supports the use of the extremity 0.2T MR scanner as a screening tool for BML signal. The advantages of the 3T large bore MR imaging scanner (as the main scanner to detect change of BML) were the range of sequences available, and magnet strength, which allowed a better contrast-to-noise ratio compared to 0.2T extremity MR scanner.

Further studies in this chapter investigated the intra-measurement reliability and face validity of BML measurements. These studies were undertaken to understand the measurement limitations and how this affect the results of the longitudinal change in BML. The reliability of manual and semi-automated tracing in the first study showed promise particularly in well-defined lesions in the centre of the bone. This technique performed poorly

however, in BMLs that articulate with ill-defined joint margins associated with advanced joint degeneration. The drawback of manual and automated tracing was the time burden required to quantify each BML per bone per person.

In the next study, semi-automated quantification of BMLs used a signal range to define the hyper-intense signal in a ROI, across single and multiple midfoot bones. This method showed poor intra-measurement reliability and a bias towards greater error in multiple and/or single large bones with larger proportions of BML 'fade-out'. This error was likely to be the result of the somewhat subjective choice of signal intensity range to define the margin of the BML. Choosing a signal threshold has been found to be highly subjective leading to measurement inconsistency [334]. In addition, the inter-connectivity of the pixels between the joint margins may potentially include marginal signal of joint fluid and soft tissues. This technique, where nearly half of the intra-measurement reliability was subject to error, was abandoned and a return to a technique that can combine manual tracing and signal automation was investigated further.

In the final study, a new approach was undertaken by subtracting normal bone signal from segmented bones of the midfoot with BML signal. For this method, both the intra-measurement reliability of the bone segmentation volume and the volume of abnormal signal in the marrow was investigated. The intra-measurement reliability of bone volume and BML quantification using manual tracing and signal thresholding were combined with spatial connectivity methods. The results indicated that segmentation of the individual bones (using a manual tracing method) showed less error than when used to segment BMLs (using a manual tracing method) in the first study. This result illustrated that tracing the edges of an anatomical region with defined boundaries required less subjective judgement than a BML measurement when the boundaries are not clear. The absolute between-session measurement error in this method showed acceptable results and no pattern of bias.

Image segmentation algorithms, which include either image boundary or regional information, can lack accuracy [335]. Regional techniques, that use signal range, require inter-connectivity of signal, while boundaries require clear changes in the gradient of the greyscale. Using both the boundary of the bone and a specified range of regional signal within the bone may improve this, as the bone edge has a clear boundary that can eliminate the non-bone hyper-intense signal. In addition, identifying the range of hypo-intense grey-scale that represents normal bone may remove some of the subjectivity arising with definition of the edge of the hyper-intense signal. Hypo-intense of marrow was subtracted this to leave the residual hyper-intensity of the BMLs. The results in this study, suggest a subtraction method seemed to improve upon previous attempts, reflected in the lower error reported in the third study compared to the second study.

A similar measurement approach of BML volume by manual segmentation on each slice of BML in osteoarthritic knees has been reported [322]. The study showed good intra-measurement reliability, intra-correlation coefficient for axial views was 0.81 and 0.60 for sagittal views [321]. In the knee, using manual tracing to segment the BML and then calculate the volume showed greater reliability than reported in this study. This may be a more consistent approach due to the homogeneity of signal in the knee. In the foot, multiple bones with BML signal required an alternative approach, and the combined bone segmentation and subtraction method in the third study shows potential for use in volumetric examination of BML patterns of the midfoot bones.

3.11 Limitations

The main aim of this chapter was to find a reliable measurement technique to use to quantify BML volume in the main study. It was not possible to test the absolute accuracy of BML measurement as the mixed pathology of BMLs would be difficult to replicate artificially. To approximate measurement accuracy, a phantom study was undertaken. The phantom study used known water volumes in a cylinder of oil to identify absolute measurement accuracy using a consistent technique. An absolute percentage measurement error of 10% was found, and an additional within-day and between day error of 7.5%. A more accurate assessment of accuracy would have been a cadaveric or animal models using surgically excised bone or artificially induced BMLs in dog models. These investigations were not feasible as this thesis was a clinical investigation and resources were not allocated to develop a new BML outcome measure.

The later three studies of BML measurement reliability in this chapter had some consistent limitations. Firstly, 2D T2 water-sensitive MR image sequences were used for analysis in this study. Fat saturated 3D MR image sequences could not be optimised in the foot as they were prone to failure due to the shape and magnetic heterogeneity of the foot. A 3D sequence may have enabled true isotropic evaluation and possibly improved reliability, as other software techniques would have been available and in plane resolution would have improved, reducing the potential error from partial volume of signal.

Finally, between-researcher inter-measurement reliability of the final technique was not undertaken, as it was not the main focus of the thesis to produce a new BML outcome measure. Within-researcher reliability was however adequate to demonstrate the applicability of the novel technique to the specific longitudinal aim of this study. The application of this BML volume measurement technique beyond the remit of this thesis would therefore require further studies to test the accuracy, between-researcher and between-session reliability.

3.12 Conclusion

In this chapter a phantom study and three *in-vivo* methods of BML volume measurement were investigated to identify a method that has good intra-measurement reliability and face validity. The method of manual tracing to segment foot bones, followed by the subtraction of normal bone signal, produced a BML volume that improved on the first two methods. The segmentation of bone at a participant level showed 5% error and at a bone level 6.2% error. The addition of signal subtraction of the bone segment also yielded good intra-measurement reliability on a participant level with 6.5% error, and 9.2% error on an individual bone level. Ultimately, the wider use of this method as an outcome measure requires further investigations into the between-person and between-session reliability and ideally against a gold standard. It was deemed however that the manual tracing and normal subtraction method was sufficient for use in the main study described in Chapter Four of this thesis.

Chapter Four:

The effect of foot orthoses on patterns of bone marrow response and patient reported outcomes

4.1 Overview of Chapter Four

As noted previously functional foot orthoses can provide clinical benefits, although the underlying mechanism through which they may improve foot pain remains poorly understood. It may be that foot orthoses can modify internal distribution of foot forces, or alter foot movements. In this chapter, the action of orthoses will be explored through MR imaging investigation of BMLs and patient reported outcomes.

Measurement of bone stress was discussed and presented in Chapters Two and Three. This chapter attempts to quantify (using MR imaging) the effects of wearing orthoses on bone stress, specifically the measurement of BML volume. In study three, of Chapter Three, it was shown that using image segmentation and signal subtraction methods, it was possible to measure BML volume with acceptable reliability.

This chapter is an exploratory mechanistic study, which examined whether functional foot orthoses can modify patterns of BML volumes using imaging segmentation and patient reported outcomes.

4.2 Research Aims

As described in Chapter Two, orthoses are frequently prescribed for mechanical foot pain. Theories of mechanical foot pain suggest that abnormal foot movement may lead to repetitive stress, which may have an impact on the bone structure, for which BML may be a surrogate marker of bone stress. Therefore the specific aims of this chapter are:

I. To identify patterns of bone marrow lesions, which are observed with magnetic resonance imaging, in patients with mechanical medial midfoot pain.
II. To explore the association between patient reported outcomes and distribution of bone marrow lesions.
III. To explore the effect of in-shoe foot orthoses on patterns of bone marrow lesions in the medial midfoot region.
IV. To explore the effect of in-shoe foot orthoses on foot pain and impairment.

4.3 Introduction

Mechanical foot pain is common and typically associated with movement impairment, suggesting there is a functional influence [1] as discussed in Chapter Two.

Theories of mechanical foot pain suggest that abnormal movements of foot may lead to repetitive stress and as a consequence, pain and pathology. This may be the case, however the evidence for this is based on small to moderate sized cross-sectional studies. In these studies, participants with mechanical foot pain exhibited different foot motion compared to control groups. Without prospective gait studies, it is unclear however whether abnormal movements are causal or consequential of foot pain.

Another theory is that altered or pathological distributions of forces within the foot may lead to foot pain and injury. This is supported by prospective studies of acute pain in military personnel and sports performers that suggest that both foot morphology and foot pressures may be a risk factor for foot and lower limb injury (as discussed in Sections 2.4.2 and 2.5.1). In these studies, randomised trials of foot orthoses appeared to reduce the risk of acute bone injuries [282]. These clinical benefits are supported by *in-vitro* experiments that show foot orthoses can reduce skeletal strain in the foot and ankle bones [296].

Techniques for the direct measurement of the internal bone and joint forces are highly invasive and are not suitable for clinical studies. Bone implants are the most direct method, however they may also alter walking function and potentially confound the results. Imaging can provide an indirect measure of bone stress in the form of BMLs in patterns typical of a stress response (shown on MR images). Patterns of BMLs associated with bone stress in the foot have been identified more frequently in the metatarsals and medial midfoot bones (see Table 2.1) and these sites correspond with greater levels of skeletal stress and injury [294, 295]. These studies suggest that the foot is susceptible to specific patterns of internal foot stress.

Patterns of BMLs in the foot associated with either injury or mechanical syndrome can be responsive to altered mechanical stress as resolution rates are improved with immobilisation treatments [288, 289]. Anti-pronatory foot orthoses that can theoretically modify mechanical stress have been shown to reduce the incidence of bone injury and when placed under the lateral foot to provoke pronation can induce new BML patterns [282, 283]. These studies suggest that BMLs associated with mechanical pain and bone stress may be modified.

Foot orthoses and pharmacological treatments for BMLs in the foot have been evaluated using a range of imaging methods. There is however, no validated MR imaging outcome measure that has been developed to detect

the change in foot BMLs. Previous imaging studies have utilised semi-quantitative scoring or quantitative image measurements. For instance, patterns of BMLs have been described with simple scoring of the MR images, noting the presence, absence and location of BMLs pre and post orthoses and immobilisation interventions [123, 283, 288]. Other studies have shown regression and resolution of BML by examining BML signal intensity pre and post immobilisation treatments in neuropathic joint disease [291, 292]. These foot studies have shown changes in BML patterns treated with a range of orthotic interventions, however the effect of anti-pronation functional foot orthoses on the pattern of foot pain and BMLs has not been investigated.

To examine a cohort of people with foot pain and BMLs associated with mechanical stress poses challenges. The relationship between stress response BMLs and foot pain has been described in a range of imaging cohorts (Table 2.1), however the incidence of BMLs in healthy and foot pain people is unclear. For instance in the knee around 15% have asymptomatic BMLs, and around 50% are symptomatic [93, 315, 336]. In the foot access and costs have limited the feasibility of conventional (1.5T) and high strength (3T) MR imaging in epidemiology studies. To address this, low-field (extremity) MR imaging (0.2T) has been recommended as a low cost solution for screening [337]. Low field MR imaging has been validated extensively in the hands of rheumatoid arthritis patients, where it has shown reasonable detection of BMLs [338]. In comparison to conventional MR imaging (typically 1.5 T) extremity MR has been credited for its specificity however, sensitivity was only moderate in the hands and knees [83, 339]. In the foot and ankle, extremity MR imaging missed 4% of lesions compared to conventional MR images [340] showing better sensitivity than the hand study. In this chapter, low field (0.2T) MR imaging was used as a screening tool for people with foot pain to test for the presence of BMLs. All cases were later confirmed subsequently using higher field strength (3T) MR imaging.

In this mechanistic exploratory study, a group of people with medial midfoot pain and stress induced BMLs and a normal group with no foot pain were identified. The quantification of BML volume plus patient reported outcomes measurements were undertaken prior to and following 12 weeks of wearing functional foot orthoses or a flat cushioning insole.

4.4 Methodology

This chapter centres on two studies: (i) a cross-sectional observational study, and (ii) an exploratory intervention study to investigate the effect of orthoses on MR imaging detected BMLs.

4.4.1 Ethical Approvals

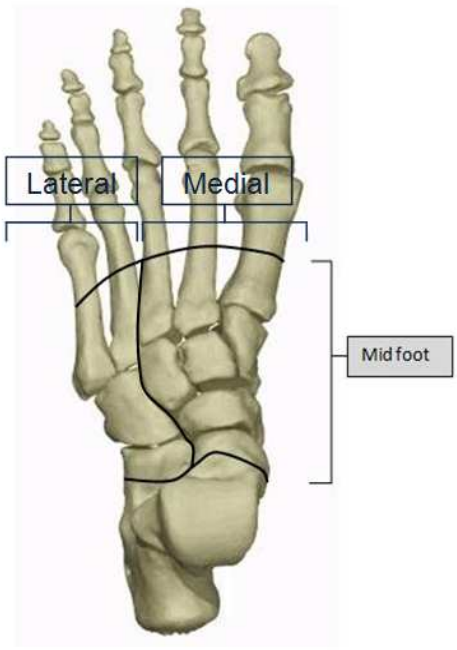
In accordance with the Declaration of Helsinki (6th revision 2008)[341], ethical approvals (reference number: 09/H1305/10) and NHS governance permissions (reference number RR08/8897) were obtained prior to the start of the study.

4.4.2 Recruitment

A specific group of participants were identified for this study who presented with midfoot mechanical pain to podiatry departments across Leeds. For this thesis, a case definition of midfoot mechanical foot pain was applied as follows:

Mechanical midfoot pain is a non-inflammatory, local musculoskeletal pain in the region of the midfoot that is aggravated by standing and walking. The midfoot region starts from the neck of the talus medially and the peroneal sulcus of the cuboid laterally, extending distally to the mid shafts of the metatarsals (see Figure 4.1).

Figure 4.1: Illustration of bones and joints of the midfoot



Clearly depicting the distinction between medial and lateral regions:

The midfoot includes seven joints: calcaneus-cuboid, talus-navicular, navicular-cuneiforms, medial cuneiform-first metatarsal, intermediate cuneiform- second metatarsal, lateral cuneiform-third metatarsal, cuboid-fourth and fifth metatarsals.

Variants in anatomy may also include the anterior calcaneus-talus and cuboid-navicular joints and cuboid-navicular joints.

Using this case definition, potential participants were identified. In addition, a second group of controls was recruited with no evidence of foot pain. The inclusion and exclusion criteria for both groups have been outlined in the Table 4.1.

Table 4.1: Inclusion and exclusion criteria for participant cohorts

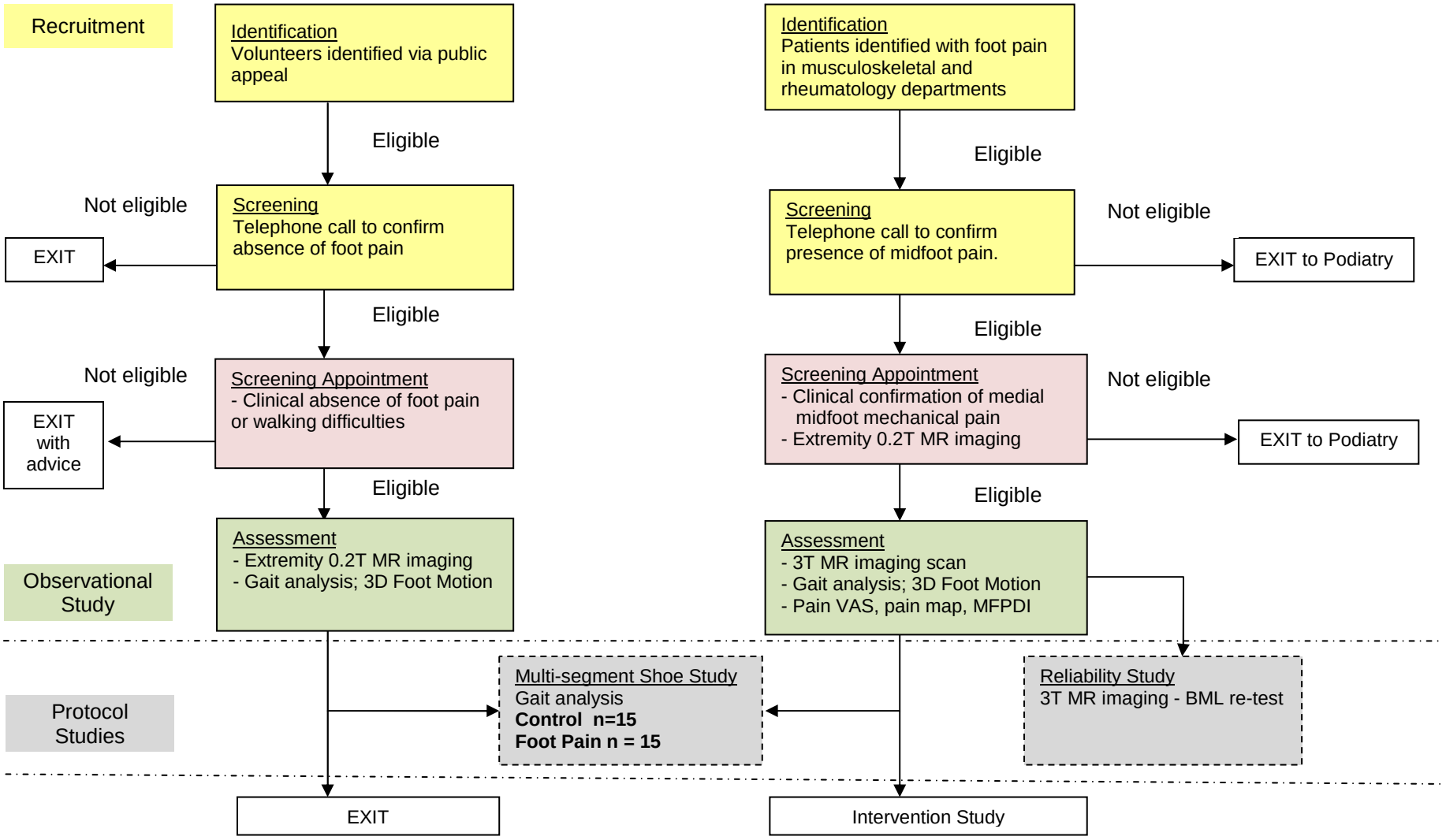
	Mechanical foot pain group	Controls
Inclusion Criteria	▪ An episode of foot pain when weight bearing of between 3 and 24 months duration. ▪ Pain located in the medial midfoot region. ▪ Type of pain considered consistent with pain of mechanical origin by an experienced musculoskeletal specialist podiatrist. ▪ Aged 18 or over. ▪ Able to understand and provide informed consent.	▪ No history of foot pain in the last 24 months. ▪ Able to walk for 30 minutes without pain or discomfort in any other lower limb joints. ▪ Aged 18 or over. ▪ Able to understand and provide informed consent.
Exclusion Criteria	▪ Established OA of the midfoot region confirmed by radiography report of definite joint space loss or osteophytosis. ▪ Foot surgery in the last 12 months. ▪ Localised plantar heel pain typical of plantar fasciitis. ▪ Foot pain typical of undiagnosed inflammatory arthritis: o Foot pain with diurnal variation or at rest or asleep. o Early morning stiffness of 30 minutes or more. o Inflamed joints, bursitis, tenosynovitis enthesitis. ▪ Foot pain typical of neurological pain: o Pain at rest, referred pain, diffuse pain. o Burning pain, tingling pain, allodynia o Foot pain red flags: ▪ Constant unremitting pain, nocturnal pain. ▪ A medical history of unstable diabetes mellitus or diabetic complications. ▪ A medical history of peripheral arterial disease. ▪ A medical history of systemic inflammatory disease. ▪ Known pregnancy. ▪ A medical history of kidney disease. ▪ A medical history of organ transplantation. ▪ A patient fitted with a pacemaker or any other implant contra-indicated for MR imaging scanning. ▪ Recent heart bypass surgery in the last 6 months. ▪ Currently wearing in-shoe orthoses device. ▪ A medical history of neurological disorders or positive clinical findings of pedal sensory neuropathy.	▪ A medical history of unstable diabetes mellitus or diabetic complications. ▪ A medical history of peripheral arterial disease. ▪ A medical history of systemic inflammatory disease. ▪ Known pregnancy. ▪ A medical history of kidney disease. ▪ A medical history of organ transplantation. ▪ A patient fitted with a pacemaker or any other implant contra-indicated for MR imaging scanning.

4.4.3 Participants

Potential participants were identified with midfoot pain from two routes (waiting lists and direct clinician referral) and from two departments: Leeds primary care musculoskeletal podiatry department and the Leeds Teaching Hospital Trust secondary care podiatry departments from June 2009 to March 2011. Potential participants were identified from referrals to the podiatry departments as they were triaged and invitation letters were sent to potential participants. All potential participants were then screened by phone once they replied to the letter. The study was explained by phone and if they met the above criteria (see Table 4.1) and would like to be involved in the study, potential participants were sent a screening appointment along with a copy of the study information sheet. The participation flow chart can be seen in Figure 4.2.

As a comparator control group, an opportunistic sample of participants with healthy, pain-free feet were identified via public appeal; the appeal was distributed in June 2009 by staff at the hospital and placed in public areas till recruitment ended in January 2011.

Figure 4.2: Participation flowchart



4.4.4 Screening

All participants were asked to attend a screening appointment to i) provide consent, ii) complete verbal questions regarding medical illnesses and medication, and iii) undergo a physical assessment of foot joints. At the screening, the study was explained, questions answered, any imaging contraindications identified and informed consent was obtained.

For the foot pain group, the appointment included identification of the pain in the medial midfoot region using foot pain maps, and if eligible, an extremity MR imaging midfoot was used to identify participants BML in the medial midfoot region.

For the control (pain-free) group, each participant underwent a gait assessment and an extremity 0.2T MR imaging scan.

A single foot was identified for each participant on the basis of the most painful foot in the foot pain group. If the foot pain was equal then the most dominant foot was chosen. In the control group the most dominant leg was also chosen. Leg dominance was determined by asking to turn in the opposite direction to the researcher and a step forward, limb initiation was taken to determine the leg dominance and study foot.

4.4.5 Imaging Protocol

The imaging in this thesis was undertaken using both extremity low field 0.2T MR imaging and whole body high field 3T MR imaging scanners.

Participants with mechanical medial midfoot pain were scanned using the extremity low field (0.2T) scanner, an Esaote C-scan small bore extremity MR scanner (Esaote S.p.A Genova Italy) with a standard four channel knee coil and specific sequences for the foot study. Participants with BMLs then went onto have repeated scan at baseline in the Siemens Magnetom Verio

(3T) large bore MR scanner (Siemens Medical Solutions, USA) using an eight channel foot and ankle coil and specific optimised sequences.

Low field MR imaging was used to screen in a group with foot pain and also a control group. To understand the role of BMLs in pain a control group was screened with low field MR imaging. Additionally in the foot pain group, specific areas of foot pain were noted, to understand whether regions related to underlying sites of BMLs.

4.4.6 Bone Marrow Lesions

Bone marrow lesions are heterogeneous with ill-defined borders, where the margins of the lesion are indistinct at the transition with the normal medullary bone [79]. In this thesis, a standard definition of BML terminology was applied that has a consensus in the radiology literature for the knee and applied for sites of BML in the foot [342].

In this thesis the definition of bone marrow lesions was:

Region of hyper-intense signal within medullary bone on two slices of water-sensitive sequences observed in two planes.

Pattern of BMLs have been categorised in the knee according to clinical finding and anatomical location and pattern of signal [342]. There is no such document for the foot, however these categories were adopted for identification of participants for this study where previous research identified these pattern in the foot [342]:

I. Bone marrow oedema syndrome - multiple diffuse foot bones [343].
II. Traumatic BML - diffuse BMLs in single or multiple bones typical of overuse [73], which may also be local to sub-tendinous sites with soft tissue pathology [120], all of which may represent a continuum of bone stress.

III. OA associated BML - Diffuse BML directly adjacent to cartilage lesion in a kissing pattern described in the foot [344], although established radiographic OA was excluded in this group, as it was not the particular aim of this thesis to explore the effect of foot orthoses on prodromal OA.

All foot images were acquired using the following scanners and protocols:

Extremity 0.2T MR Image Scanner (Esaote C-scan - Esaote S.p.A, Genova, Italy)

A short tau inversion ratio or STIR sequence *(TR 2760ms, TE 24, NEX 2, TI 85, flip angle 90°, 3mm and 0.6 inter-slice gap, Matrix 192*144)* in all three planes.

Three Telsa MR Image Scanner (Siemens Magnetrom Verio - Siemens Medical Solutions, USA). A water-sensitive high resolution sequence was chosen as the primary image to quantify BML:

A T2 weighted fat saturated sequence (*TR = 3000-3600 ms, TE69, flip angle = 155-160º, 2mm slices and 0.4mm inter-slice gap, Matrix 256*256*).

A secondary sequence was chosen image as the foot is susceptible to fat saturation failure at the margins of the foot due to the heterogeneous shape of the foot in the magnetic field. Inversion of the signal (using a STIR) does not have this susceptibility.

A short tau inversion ratio sequence or STIR *(TR =4500 ms, TE33, NEX 2, TI 200, flip angle 90°, 3mm slices and 0.6mm inter-slice gap, Matrix 192*144)* in all three planes.

For screening in the foot pain and control group, the presence of BML on images was identified using a STIR sequence images on the extremity 0.2T

and whole body 3T MR images. For both groups BMLs were scored dichotomously as present or absent in the bones of the midfoot by a single rheumatologist with experience of MR scoring in the foot (DMG). In the foot pain group, these participants went onto further scanning (3T MR imaging) and foot bones identified were then measured using a quantitative image analysis.

4.4.7 Procedure

Potential participants were invited and consented to enter the study, once they met the inclusion and screening criteria for both the foot pain group and the control groups. Foot pain group participants then underwent further assessments, these included:

I. Medical and Clinical History.
II. Gait Assessment.
III. Patient Reported Outcomes.
IV. Magnetic Resonance Imaging 3T Foot Scan.

Control group participants underwent the following assessments, these included:

I. Medical and Clinical History.
II. Gait Assessment.
III. Magnetic Resonance Imaging 0.2T Foot Scan.

These assessments contributed to the following study outcomes and recorded in the case report form.

i) Medical and Clinical History

In the foot pain group this included demographic details, medical history, and the clinical history of the foot complaint. In the control group demographic

details and medical history were included to check against the inclusion criteria.

ii) Gait Assessments

Gait assessments that included foot kinematics were undertaken in the normal control and the foot pain groups. These results are described in detail separately in Chapter Five.

iii) Patient Reported Outcomes

The severity of pain was estimated by the participant placing a mark on a 100mm visual analogue scale (VAS), an ordinal scale commonly used in the measurement of musculoskeletal pain and one that is sensitive to changes in pain intensity over time [345-347]. The VAS was used by the participant to quantify foot pain on the day of measurement.

The modified Manchester foot pain and disability index (MFPDI) measures the impact of foot pain over the previous [348, 349]. This questionnaire can provide an index of foot impairment in two scales: pain and function to measure the impact of foot pain at baseline and the change over three months.

Participants were also asked to provide a verbal self-reported scale of their foot pain using a categorical scale of improved, no change or worse.

iv) Magnetic Resonance Imaging Outcomes

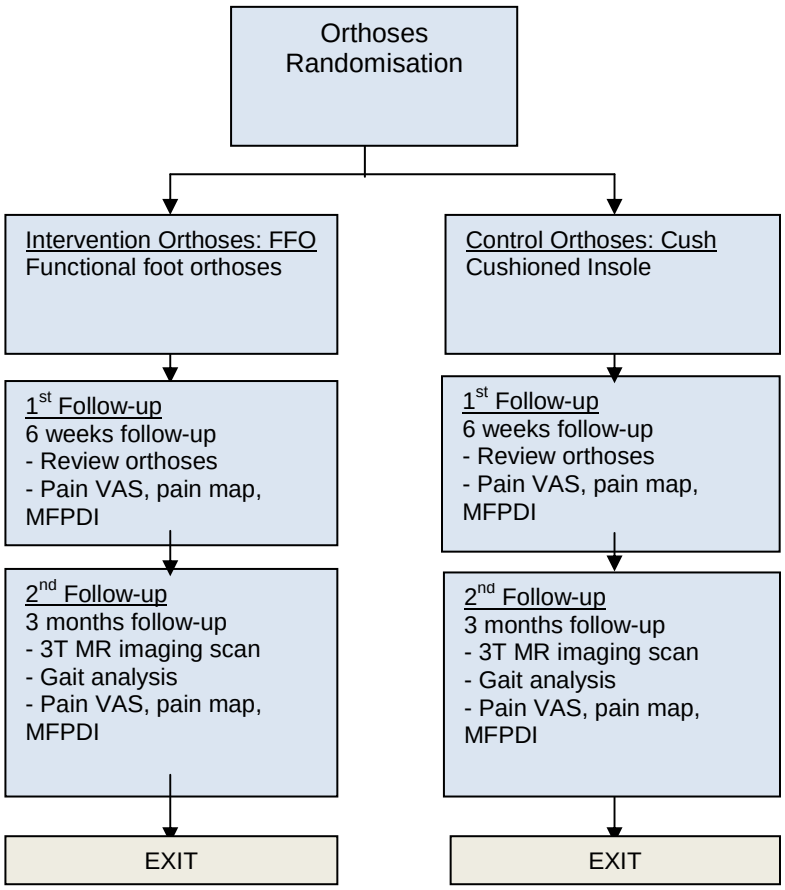
Extremity MR imaging was undertaken in both the foot pain and control groups as part of the screening process previously described. For the foot pain intervention group, BMLs were further quantified using 3T MR images, using T2 weighted fat-saturated sequences, by the following approach.

Bone marrow lesions were assessed with specialised software at baseline and follow-up images (using the methods developed in Chapter Three, Section 3.9).

The BML measurement was undertaken using Analyze software version 10 (Analyze-Direct, Lenexa, Kansas USA) to measure the volume of hyper-intense signal verified as BMLs by previous subjective image assessment to define the presence or absence of BML in the bones of the foot by a single rheumatologist with experience of MR imaging in the foot (DMG). The reader of the images (DMG) and researcher who undertook the image analysis (JHR) was blinded to the treatment allocation as all the images were anonymised and allocated a new imaging number by the radiology research team who undertook the MR imaging scans (Leeds Musculoskeletal Biomedical Research Unit).

Each bone with BMLs was segmented: the borders of bone were identified using a manual (spline) tracing function (using polynomial lines that semi-automates the tracing process) for each cross-sectional area per slice. Signal of normal bone was then identified and marrow greyscale signal was subtracted from the bone. This software provided a cross-sectional slice area of the bone and BML signal and with the additional information of slice thickness and the slice gap, the volume was calculated (see Section 3.9). The individual bone volumes and BML volumes were calculated and totalled per person.

Figure 4.3: Intervention study flowchart



4.4.8 Intervention Study

The intervention study is a randomised exploratory study. Two types of foot orthoses were randomised in the foot pain group. Primary outcomes of foot pain and BML measurements and secondary outcomes of foot impairment were obtained at baseline assessment, prior to the randomisation and then repeated at 12 weeks follow-up. An interim evaluation of the patient reported outcomes (foot pain and impairment) were also obtained at a review appointment, conducted at six weeks (see interventions study flowchart Figure 4.3).

Participants were provided with a pair of either functional foot orthoses (FFO) as an intervention or cushioned (Cush) insole as a control. Although

this preliminary study was not being run as a formal randomised controlled trial, to follow best practice the intervention was randomly allocated. Randomisation was on a 2:1 basis, favouring the active intervention (FFO) to minimise the exposure of patients with pathology to the cushioning control intervention (Cush). An external member of the team applied a random number protocol and blind envelope allocation. An opaque envelope was used to conceal the allocation and revealed to the researcher sequentially at each participant's baseline appointment.

The intervention for this study was a pre-formed orthotic device called VectOrthotics (Healthy Step [Sensograph] Ltd Oldham UK) (see Figure 4.4). VectOrthotics are modifiable orthoses, consisting of a composite polypropylene plastic shell with a contoured arch and a heel cup. These are equipped with adjustable hindfoot posts allowing inversion of the hindfoot by two, four or six degrees. The orthoses were finished by adding a compressed closed cell polyethylene foam cover with a brushed Nylon top sheet. In this study an optional cover with midfoot support was used to optimise the potential functional affect of the device on the medial midfoot region.

Each participant who was randomised to the intervention arm received an orthotic device that was modified for each participant so as to produce a foot posture index score of zero. The foot posture index is a 25 point continuum quantifying foot posture from cavoid to planus, scored with the patient standing in relaxed standing position [350]. The participants were given verbal and written information regarding functional orthoses use. This functional foot orthoses device will be abbreviated to an FFO throughout the thesis.

To provide a control comparative intervention arm, a proportion of the participants were given a cushioned insole (Cush) that comprises of 4mm of flat compressed (closed cell polyethylene) foam with a brushed Nylon top sheet adhered to it (Healthy Step [Sensograph] Ltd Oldham UK). This thin

insole did not have any functional features associated with prescription devices (a rigid, contoured shell, a stabilising heel cup or applied wedges to position the foot joints) and was proposed as a control (sham) intervention. This will be referred to as a cushioning insole throughout the study to reflect the properties of the device and will be abbreviated to Cush throughout the thesis.

Figure 4.4: Photo of the VectOrthotic pack

Caption: The pack includes the shell (1), the posts (2) and the cover (3)

Evaluation of Orthoses

A concordance diary was provided to log the number of hours the orthoses intervention was worn. Participants were monitored over two appointments. After six weeks, the participants attended an appointment to review the foot pain using the specified patient reported outcomes and discussed compliance of the orthoses using the diary. After 12 weeks a final appointment was undertaken, at which all the baseline tests, patient reported outcomes, gait analyses and 3T MR imaging, were repeated.

4.5 Analyses

The primary outcome of this study was foot pain (VAS) and 3T MR BML volume and secondary outcome included foot impairment (MFPDI). The main aim of this study was to examine the changes of outcomes between baseline and 12 weeks in the intervention groups: functional orthoses and cushioning insole. The secondary aim was to explore the association of mechanical medial midfoot pain, foot impairment and distribution of BMLs.

As this was an exploratory investigation, full inferential analysis was not proposed for this study. Demographic and clinical data was input from the case report form in addition to compiling results from the BML outcomes. Exploratory statistical analyses were performed to identify any potential associations between baseline BML results and patient-reported pain and impairment measurements. Differences in outcomes between the foot pain group and the control group at baseline were explored, and differences in change scores between the intervention groups at the end of the study were reported to highlight potential mechanisms of foot orthoses.

Baseline interrelationships between 3T MR imaging and pain measures were explored, comparing the participants in the foot pain and control groups. Given that this exploratory study was powered only by rules of thumb for pilot studies, statistical advice was sought and any association where Spearman's rho was greater than r=0.3 was pre-specified *a priori* to be potentially worthwhile [351].

The effects of the in-shoe orthoses interventions were assessed pre-and-post treatment in the foot pain group. Differences in BML volumes, pain and impairment scores were be tested using the mean and CI. In addition, mean differences and CI in 3T MR imaging outcomes, pain and disability scores between the orthoses groups (functional and cushioning), were explored for treatment effect. The mean and CI were calculated using IBM SPSS Statistics (Version 19, IBM Software USA).

4.6 Results

This results section is split into three sections:

I. Participant characteristics.
II. Baseline cross-sectional findings.
III. The effect of foot orthoses intervention.

4.6.1 Participant Characteristics

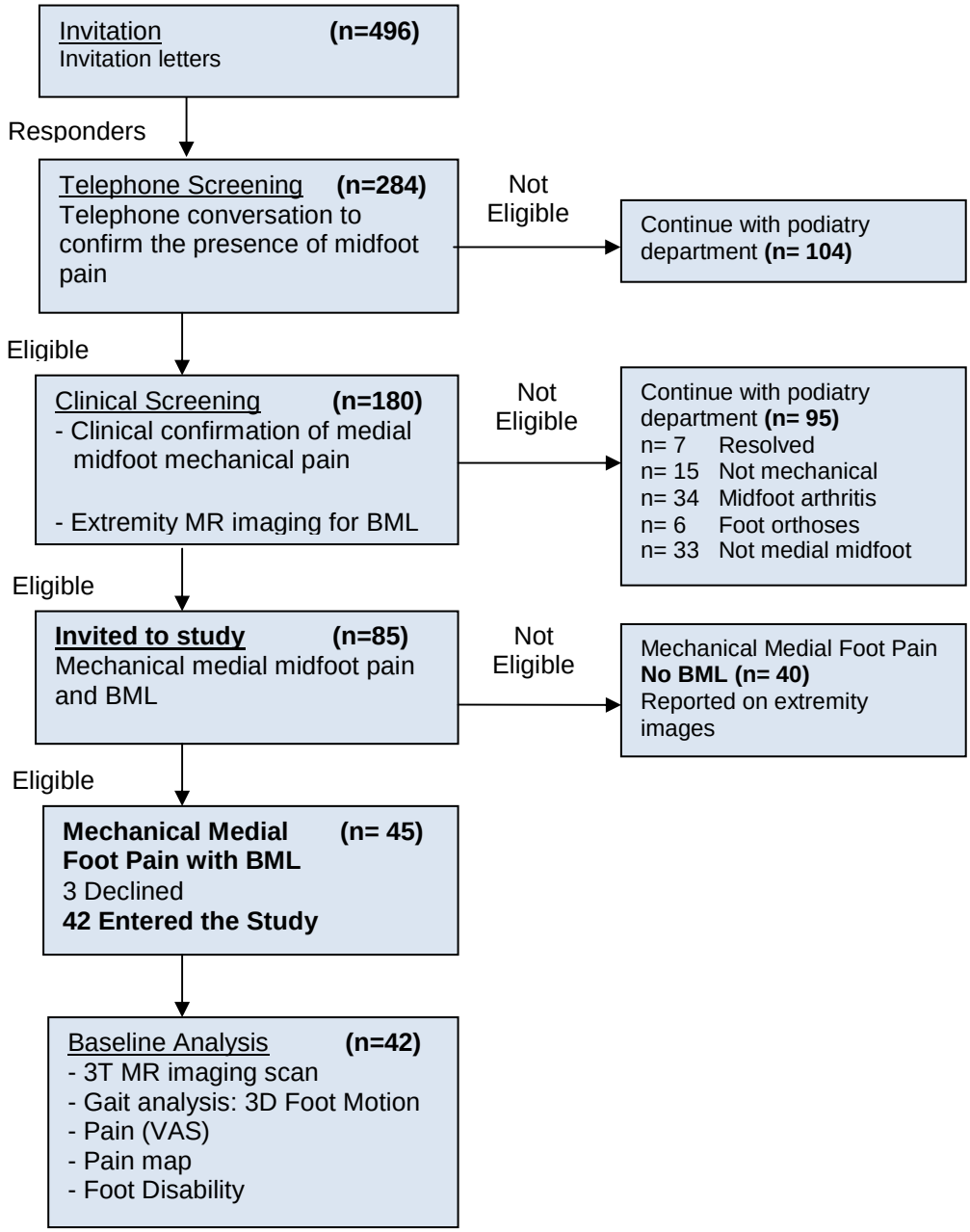
Recruitment

Participant recruitment took place between July 2009 and March 2011. Invitation letters were sent to 496 patients on the musculoskeletal and rheumatology podiatry department waiting lists. From the initial invitation, 57% responded (284 people) by contacting the researcher (JHR) by telephone. A telephone interview regarding the foot pain was conducted on 284 people by the researcher (JHR). In this phase 104 were not deemed eligible. The remaining 180 were invited to attend a screening appointment. The screening appointment included basic data about the foot pain, location using a foot pain map and an extremity MR imaging. In this clinical screening phase, a total of 56 people were excluded as foot pain was either associated with arthritis (n=34), not aggravated by movement (n=15) or had resolved (n=7). Mechanical foot pain was identified in 124 people, a further six were excluded as they wore foot orthoses and another 33 people were excluded as they were not eligible as the foot pain was not local to the midfoot.

The screening appointment identified 85 people with mechanical medial midfoot pain. A total of 85 people were invited to the study with mechanical medial midfoot pain and had an extremity MR imaging scan. The extremity MR images were read by a single rheumatologist (DMG) and the presence and location of BML in the foot bones were identified 45 people of the 85 people, which met the recruitment target. Three people declined and 42

people entered into the foot pain group with BMLs in the midfoot (see Figure 4.5).

Figure 4.5: Enrolment and recruitment flow diagram



Demographics

The foot pain group included 42 participants (30 females and 12 males) with a mean age of 53 and a wide range of ages (22 to 76). In the control group 41 participants (21 females and 20 males) were recruited with a mean age of 45 and similar range of ages (22 to 71). There were more women than men in the foot pain group (78%) compared to the control group, which constituted equal gender (see Table 4.2).

Table 4.2: Demographic profile of the control group and foot pain group (the latter subdivided according to treatment allocation (FFO and Cush)

Demographics		**Foot Pain (n=42)**		*(FFO) (n= 26)*		*(Cush) (n=16)*		**Control (n=41)**	
Age	Mean (SD)	**53**	**(12.3)**	*55*	*(10.8)*	*49*	*(13.6)*	**45**	**(14.1)**
Gender	Females (%)	**30**	**(71)**	*20*	*(77)*	*10*	*(63)*	**21**	**(51)**
Height	Mean (SD)	**1.66**	**(0.1)**	*1.66*	*(0.1)*	*1.67*	*(0.1)*	**1.70**	**(0.1)**
Weight	Mean (SD)	**82.13**	**(13.2)**	*80.9*	*(12.8)*	*84.0*	*(13.5)*	**77.93**	**(14.4)**
BMI	Mean (SD)	**29.96**	**(5.1)**	*29.5*	*(4.1)*	*30.6*	*(6.5)*	**26.71**	**(3.8)**
Total No. of co-morbidities	Mean (SD)	**2.21**	**(1.6)**	*2..08*	*(1.5)*	*2.44*	*(1.8)*	**0.95**	**(1.2)**
Total No. of medications	Mean (SD)	**1.98**	**(1.8)**	*1.88*	*(1.8)*	*12.13*	*(1.9)*	**0.78**	**(1.5)**
Total No. of painful joints	Mean (SD)	**1.36**	**(1.2)**	*1.73*	*(1.2)*	*0.75*	*(0.9)*	**0.63**	**(0.9)**
Limb		**26 Right**		*15 Right*		*11 Right*		**30 Right**	

The BMI in the foot pain group was higher (mean 29.96, SD 5.1) than the control group (mean 26.71, SD 3.8). Also those with foot pain had twice as many co-morbidities (2.21 in the foot pain group, versus 0.95 control) and concomitant medications (1.98 foot pain group, versus 0.78 control) compared to the control group. The most frequent co-morbidities were OA, hypertension, obesity, asthma (see Table 4.3).

Table 4.3: Frequency of co-morbidities in ascending order per group and subgroup

Disease	Foot Pain Group			Control Group
	Total (n=42)	*FFO (n=26)*	*Cush (n=16)*	**Total (n=41)**
Osteoarthritis	**17**	*12*	*5*	**8**
Obesity	**13**	*6*	*7*	**3**
Hypertension	**12**	*6*	*6*	**4**
Asthma	**7**	*5*	*2*	**1**
Hypercholesterolaemia	**6**	*3*	*3*	**2**
Hypothyroid	**6**	*4*	*2*	**1**
Benign Joint Hypermobility	**4**	*2*	*2*	**0**
Joint replacement	**2**	*1*	*1*	**0**
Diabetes	**1**	*0*	*1*	**2**
Osteopenia/Osteoperosis	**1**	*1*	*0*	**2**
Heart disease	**1**	*0*	*1*	**1**
Hay fever	**2**	*0*	*2*	**2**
Depression	**1**	*1*	*0*	**2**

Foot pain was the only site of pain in 33% of the foot pain group. The majority (38%) of the groups reported pain one other proximal joint and 21% reported pain in two additional joints, and three joints was the least common joint pain pattern (7%). The knee was most reported site of additional proximal joint pain (40%). There was a greater number of proximal painful joints in the foot pain group (mean total 1.36 foot pain versus 0.63 control) compared to the control group. This would likely to be accounted for in greater frequency of OA and obesity in the foot pain group.

In summary, using the extremity MR images, the presence of BMLs was confirmed in around 50% of screened participants with mechanical midfoot pain. Participants in this group were typically females in the fifth decade and above. The group tended to present with multiple co-morbidities such as OA, obesity and hypertension. The foot pain group also reported pain in proximal joints and the knee was the most frequently reported site.

Foot Pain Presentation

Baseline patient reported outcomes for participants in this study are shown in Table 4.4. The mean duration of foot pain was just over a year (mean 14.4 months, SD 12.5). The minimum duration of foot pain was three months (for study inclusion) through to approximately five years (60 months).

Table 4.4: Baseline patient reported outcomes

Patient Reported Outcomes	Mean	(SD)
Foot pain duration (months)	14.4	12.5
Pain intensity (0 to 100mm)	34.67	17.3
Foot pain impairment (range 7-21)	13.62	2.96
Functional impairment (range 9-27)	16.88	4.63

The onset of medial mechanical foot pain was characterised and categorised. Most participants had a slow onset (43%), followed by acute onset (36%), while 10% recalled a specific traumatic event, and 12% categorised their pain was subtle at onset. The type of foot pain was characterised, most described it as both sharp (26%) and an ache (29%), and only some described the pain as burning (5%) pain. The last category of dull pain was rarely reported in isolation (2%), and was often reported with an ache type of pain (14%). A moderate proportion of participants (38%) used more than one descriptor and categorised a general ache pain that was also sharp with movement (24%).

Medial midfoot pain was reported with moderate pain and functional impairments as captured on the MFPDI (see Table 4.4). The type of weight-bearing activity was classified into six options. A quarter of participants reported pain only with walking, though most of the group reported pain with multiple activities. Participants reported walking pain with standing (19%), walking on uneven ground (17%), intense activity (17%), stair climbing

(10%), and the remaining 30% of participants reporting foot pain with a multiple activities. Out of the group, only six participants (14%) reported pain with footwear.

Medial midfoot pain was mostly reported in the dorsum of the midfoot (91%), followed by the medial arch (29%), plantar midfoot (18%) and medial ankle (10%). Foot pain was frequently reported with joint movement in the medial midfoot (88%). In these cases, joint movement pain was local to the tarso-metatarsal joints (52%) and navicular-cuneiform joints (12%) in isolation. A smaller number reported multiple joint pains in the foot (12%), while 10% had pain with movement in all foot joints of the medial midfoot (see Figure 4.5).

Figure 4.5: Distribution of painful foot joints

Legend:

1-5%	6-10%	11-15%	16-20%	21-25%	26-52%

Caption: The proportion of people with joint movement pain in colour legend

In summary, the foot pain group reported midfoot pain (on average) for just over a year and with a slow or sudden onset without trauma. The midfoot pain was mostly described as a sharp and or an ache and was associated with moderate pain and functional impairments. Midfoot pain was most frequently reported in dorsum of the foot and local to the tarso-metatarsal joints and was aggravated with joint movement.

4.6.2 Bone Marrow Lesions and Patient-Reported Outcomes

In this section patterns of BMLs are identified in patients with mechanical medial midfoot pain. The baseline associations between patient reported outcomes and patterns of BMLs are explored.

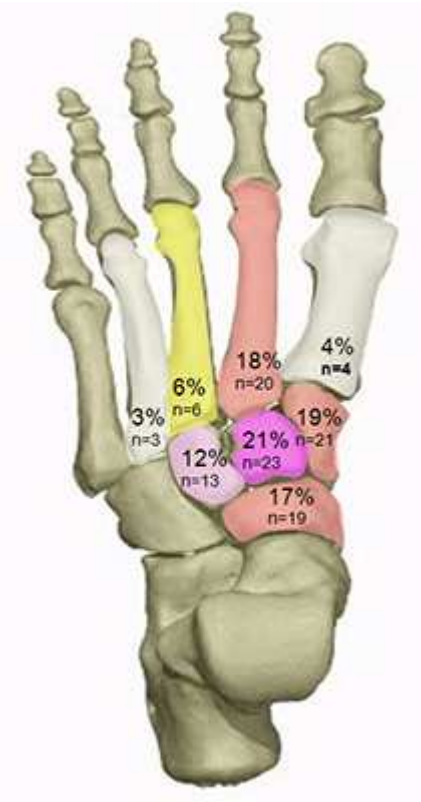
Frequency and Pattern of Bone Marrow Lesions on MR Imaging

In the foot pain group of 42 participants, on high field imaging (identified by low field imaging) BMLs were reported in 108 bones (see Table 4.5). An average of 2.57 involved bones per person (SD 1.6). By comparison in the control group seven participants (reported on the low field MR images) were reported as demonstrating abnormal bone signal. Three were isolated cysts in the first metatarsal, navicular and cuboid bone, one with subchondral sclerosis in the second metatarsal and three with BMLs (second metatarsal, intermediate cuneiform and medial cuneiform). The BMLs found in this study showed the foot pain group had a different pattern to that seen in the comparative control group (see Table 4.5).

Table 4.5: Frequency of BMLs in the foot pain and control groups			
Bone Frequency	**Foot Pain Group (n=42)**		**Control Group (n=41)**
	Presence of BML per bone	**(%)**	**Presence of BML per bone**
1st Metatarsal	4	(4)	0
2nd Metatarsal	20	(19)	1
3rd Metatarsal	6	(6)	0
4th Metatarsal	3	(3)	0
Medial Cuneiform	20	(19)	1
Intermediate Cuneiform	23	(21)	1
Lateral Cuneiform	13	(12)	0
Navicular	19	(18)	0
Total (%)	**108**	**(100)**	**3**
Mean (SD)	**2.57**	**(1.6)**	

The distribution of involved bones as a proportion of the total bones can be seen Figure 4.6 in the foot pain group, which illustrates that the cuneiforms and second metatarsal were the most commonly affected sites.

Figure 4.6: Distribution of BMLs in the foot pain group



Legend:

1-5%	6-10%	11-15%	16-20%	21-25%	26-30%

Caption: The proportion of bones affected are shown in the colour legend

A third of the foot pain group (14 participants) had a single bone involved, and the most frequent was the navicular (14%) followed by the medial cuneiform (10%), lateral cuneiform (7%) and the third metatarsal (2%). The intermediate cuneiform and second metatarsal bones were not seen in isolation but in combination (19%), as around a third (29%) of the group had a pattern of two bones involved. The combinations of two bones varied among the participants; the medial cuneiform was combined with the navicular (2%) or the intermediate cuneiform (2%), the navicular combined with the intermediate cuneiform (2%) and finally second metatarsal with the third metatarsal (2%).

A pattern of three bone involvement was observed in the three participants with BMLs involving the intermediate cuneiform and second metatarsal plus the medial cuneiform or lateral cuneiform, or the first metatarsal and medial cuneiform with the intermediate cuneiform. In these patterns of two and three bones with BMLs, the signal was mirrored in the articulating joint suggesting the cuneiform joints and tarso-metatarsal joints are susceptible to pathological patterns.

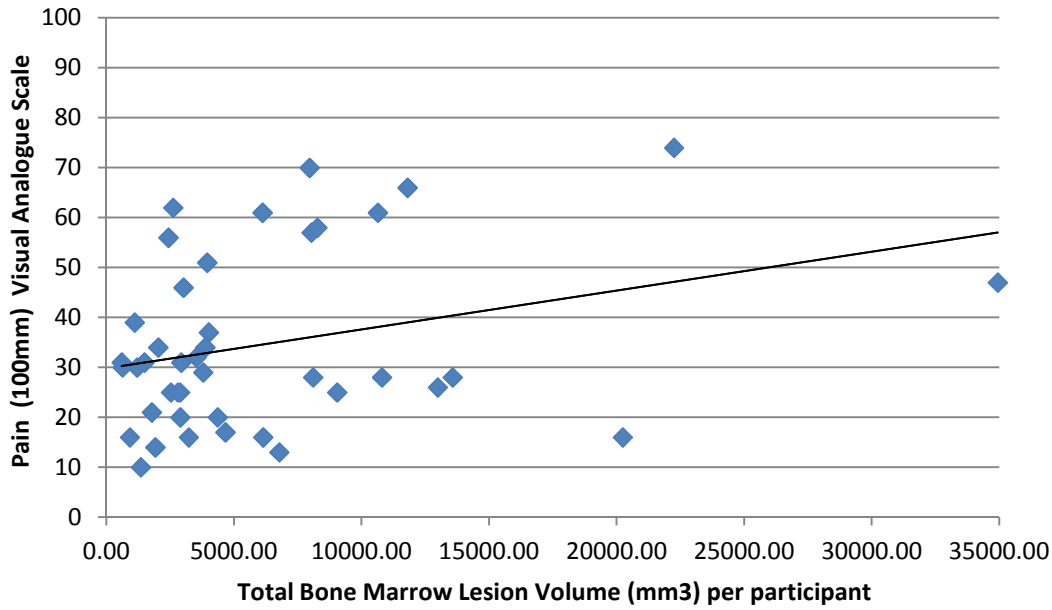
Around a fifth of the foot pain cases had a pattern of four bones involved (seven participants), in two cases all the cuneiforms with the navicular were involved. In one case all the cuneiforms were combined with the second metatarsal. The navicular was combined with the two cuneiforms and either the first or second metatarsal in two cases. In one case the navicular was combined with the lateral cuneiform with the third and fourth metatarsal. In the last case the second to fourth metatarsal with the lateral cuneiform was involved.

Only in two cases was there BML signal in most of the medial midfoot bones, six bones (cuneiforms, navicular and second metatarsal) and seven bones (all the cuneiforms, second to fourth metatarsals and navicular).

Associations between Bone Marrow Lesions and Patient Reported Outcomes

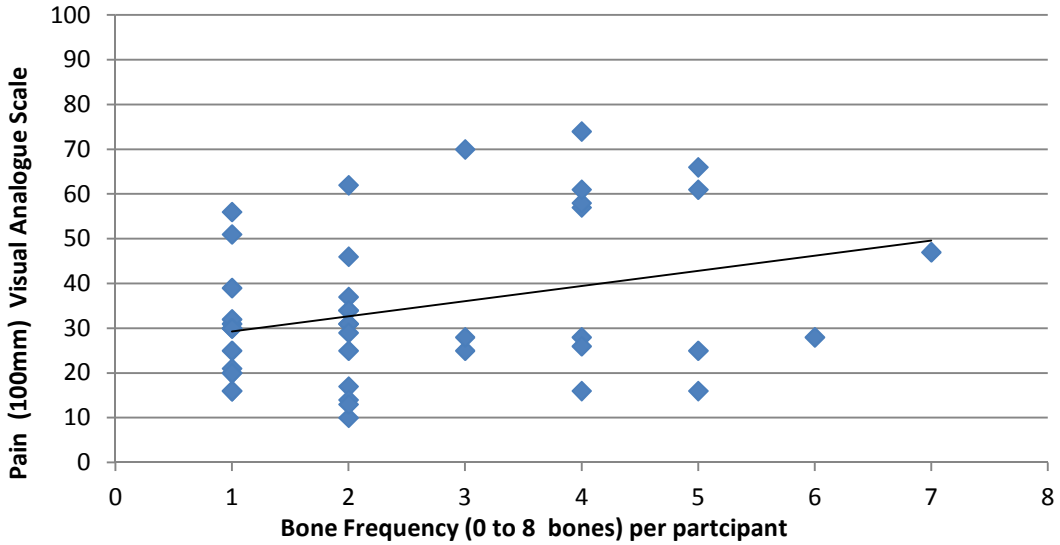
The relationship of between BMLs volume, midfoot pain and impairment was explored. In common with previous imaging studies of knee pain, Spearman's rho correlation coefficient demonstrated a low relationship ($r=0.22$, $p=0.160$) between foot pain (as measured on the 100mm VAS) and the total volume of BMLs (illustrated in Figure 4.7).

Figure 4.7: Relationship between foot pain and BML volume



When the relationship between foot pain and the total number of bones involved was explored, the Spearman's rho showed a low relationship (r=0.23, p=0.139) between foot pain and the number of bones affected (see Figure 4.8).

Figure 4.8: Relationship between pain and number of bones with BMLs



In summary, this group of participants with mechanical medial midfoot pain presented (on average) with BMLs in two or more bones. The pattern of the BMLs in this study showed that larger bones, such as the navicular or medial cuneiform, can present in isolation. The typical pattern in this study showed BMLs in two bones, commonly in the intermediate cuneiform and the second metatarsal. This pattern was different to that seen in the control group, suggesting a systematic pathological pattern that presented with mechanical medial midfoot pain. The severity of foot pain was poorly correlated with the total volume of the BML or number of affected bones per person.

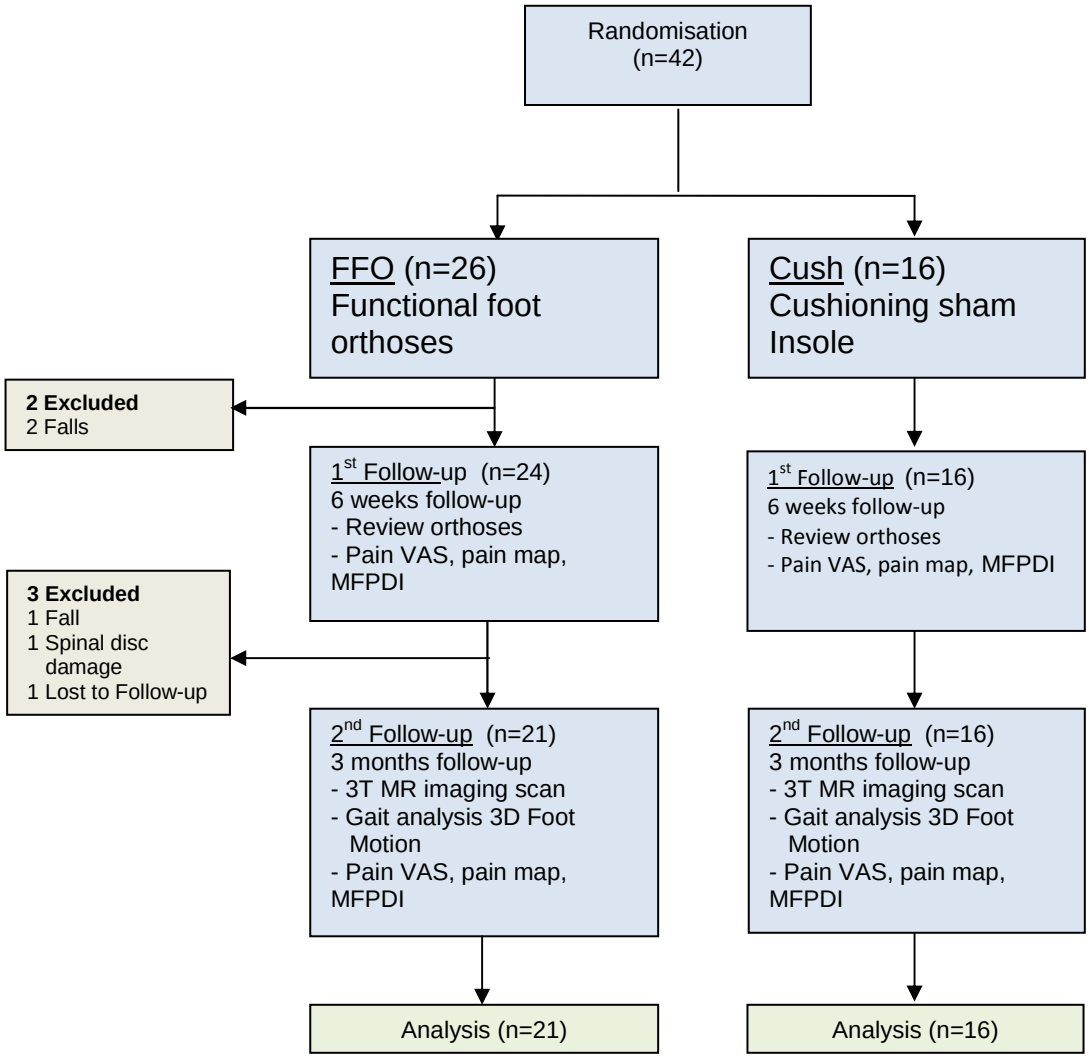
4.6.3 Results of the Intervention of Foot Orthoses on Bone Marrow Lesion Volume and Patient Reported Outcomes

The aim of this section was to primarily explore the effect of wearing in-shoe functional foot orthoses for three months on patterns of BMLs and secondarily on foot pain and impairment in the medial midfoot region.

Forty two participants with mechanical midfoot pain entered the study, and were randomised on a 2:1 ratio for treatment with functional orthoses (FFO group) or control cushioned insoles (Cush group). Three declined to take part and an additional five did not complete the three month follow-up (see Figure 4.9). One left the study due to health reasons, three experienced ankle sprains during an accidental fall in icy conditions and one was lost to follow-up. Those five who did not complete the study were randomised to the FFO group.

Adherence to wearing the foot orthoses was evaluated in both groups using a daily log to estimate the number of hours the orthoses were worn per day. At the initial review the average hours per week of orthoses adherence was slightly higher in the Cush group (mean 34.5; SD 16.6 hours) compared to the FFO group (mean 32.2; SD 13.7 hours). At the final review, the mean number of hours of orthoses per week remained higher in the Cush group (mean 42.3; SD 17.0 hours) compared to the FFO group (mean 39.5; SD 22.4 hours). The results suggest that orthoses adherence improved over the course of the three month study, with the Cush group reporting longer average use per week than the FFO group throughout the three month period.

Figure 4.9: Intervention flow chart



The Effect of Foot Orthoses on Patterns of Bone Marrow Lesion

Bone marrow lesions were directly measured from the MR images to quantify volume of bone and the BML and to compare the changes between baseline and follow-up in the two groups allocated FFO or cushioned insole. This exploratory analysis was made on a participant level and an individual bone level. Changes in the total BML volume and patterns of BML migration (resolution and formation) to different bones were noted (see Tables 4.6, 4.7 and 4.8).

Table 4.6 The baseline BML outcomes per group		
Baseline	**Foot Pain Treatment Groups**	
	FFO (n=21)	**Cush (n=16)**
Mean Bone Volume (mm^3) (SD)	18380.48 (9828.38)	19750.48 (15763.29)
Mean BML Volume (mm^3) (SD)	5977.28 (5023.00)	7183.83 (9125.35)
Mean Percentage BML per Bone (SD)	33.14 (20.81)	35.12 (19.73)

The bone volume, BML volume and the percentage of BML per bone, per person are summarised in Table 4.6. Discrepancies between the groups can be accounted for by the different size of the groups at baseline.

Table 4.7 Follow-up BML outcomes per group		
Follow-up	**Foot Pain Treatment Groups**	
	FFO (n=21)	**Cush (n=16)**
Mean Bone Volume (mm^3) (SD)	18300.52 (9453.37)	20234.69 (16269.20)
Mean BML Volume (mm^3) (SD)	4432.89 (3239.49)	6868.05 (8533.31)
Mean Percentage BML per Bone (SD)	26.66 (19.58)	34.56 (24.41)

Baseline (Table 4.6) and follow-up results (Table 4.7) were compared in the FFO group and Cush group (see Table 4.8). In the FFO group there was a trend of a mean BML volume reduction by 1544.39mm3 (CI -3660.4 to 571.6) per person, a relative decrease of 25.8%. In the Cush group there was a small reduction in BML volume (315.78mm3, -1528.2 to 896.7) per person, a relative decrease of 4.4%.

Table 4.8 The difference between baseline and follow-up BML outcomes per group		
Difference Between Baseline to Follow-up	**Foot Pain Treatment Groups**	
	FFO (n=21)	**Cush (n=16)**
Mean Bone Volume (mm^3) (CI)	-79.96 (556.8 to -396.8)	484.21 (-51.9 to 1050.3)
Mean BML Volume (mm^3) (CI)	-1544.39 (-3660.4 to 571.6)	-315.78 (-1528.2 to 896.7)
Mean Percentage BML per Bone (CI)	-6.48 (-13.9 to 0.9)	-0.56 (-6.7 to 5.6)

On a bone level, the relative change in the number of bones and the mean percentage of the BML per bone was explored in terms of BML volume among the different intervention groups. In the FFO group a total of seven bones showed complete resolution and in the Cush group two bones resolved (see Table 4.9).

Table 4.9: The distribution of bones with BML and the change in number of bones affected at follow-up and mean volume change as a percentage of the bone

Foot Bone	**FFO**			**Cush**		
	BML Bones (n=60)	BML Bones +/-	BML Volume % Change	BML Bones (n=46)	BML Bones +/-	BML Volume % Change
1st Metatarsal	2	-1	-90	1	+1	+100
2nd Metatarsal	10	-1	-15	8	0	+5
3rd Metatarsal	3	0	-28	3	0	-2
4th Metatarsal	1	0	-77	2	0	+1
Medial Cuneiform	12	+1/-1	-46	7	+1/-1	-7
Intermediate Cuneiform	15	+4/-4	-4	10	+1/-1	0
Lateral Cuneiform	7	+1	+24	7	0	-36
Navicular	10	0	-25	8	+1	-1

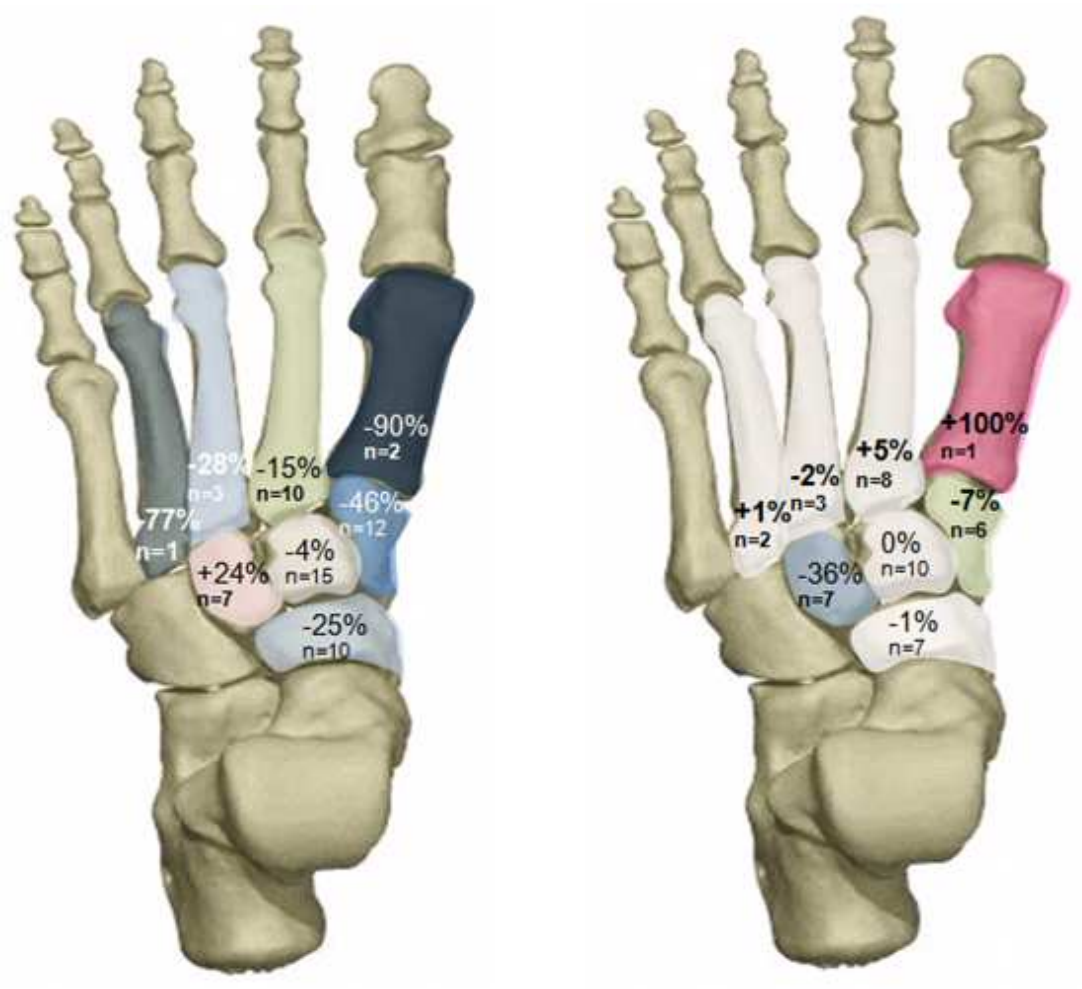
Figure 4.10 presents the mean reduction of BML volume per bone schematically, with blue (cool) colours representing a decrease of BML volume, pale colours representing little or no change and pink (warm) colours representing an increase of BML volume. In the group allocated to active FFO intervention, the total mean percentage reduction of 26% was mostly attributable to reductions in the medial cuneiform, navicular and the metatarsal bones. In contrast these same bones showed very little mean change in BML volume in the Cush group, suggesting the FFO may have a systematic effect on the distribution of the mechanical stress within the medial midfoot.

This was further supported by the contrasting pattern of lesion distribution in two groups. There was a trend towards increases in BML volume in the lateral bones and a decrease of volume in the medial bones in the FFO group. There was an opposite trend in the control Cush insole group. The lateral cuneiform was involved by equal amounts in both groups however, there was a moderate reduction of BML volume in the Cush group and a similar increases in volume in the FFO group. The first metatarsal bones also showed a similar contrasting redistribution pattern in both groups and an increase in the Cush group and a decrease in the FFO group although there were only a small number of first metatarsals involved that requires cautious interpretation.

Bone marrow lesion migration (the resolution and formation of BML sites) was examined. The intermediate cuneiform (in both groups) was particularly susceptible to new formation of BMLs. This occurred more in the FFO group (four bones) than the Cush group (one bone).

Figure 4.10: Schematic of BML volume changes per orthoses group

A - FFO Group **B - Cush Group**



Legend:

-81-100	-61-80	-41-60	-21-40	-6-20	-5-5	6-20	21-40	41-60	61-80	81-100

Caption: Images A and B illustrate the change of BML volume in patients with midfoot pain after wearing - A functional orthoses (n=21) and - B cushioning orthoses (n=16) for three months.

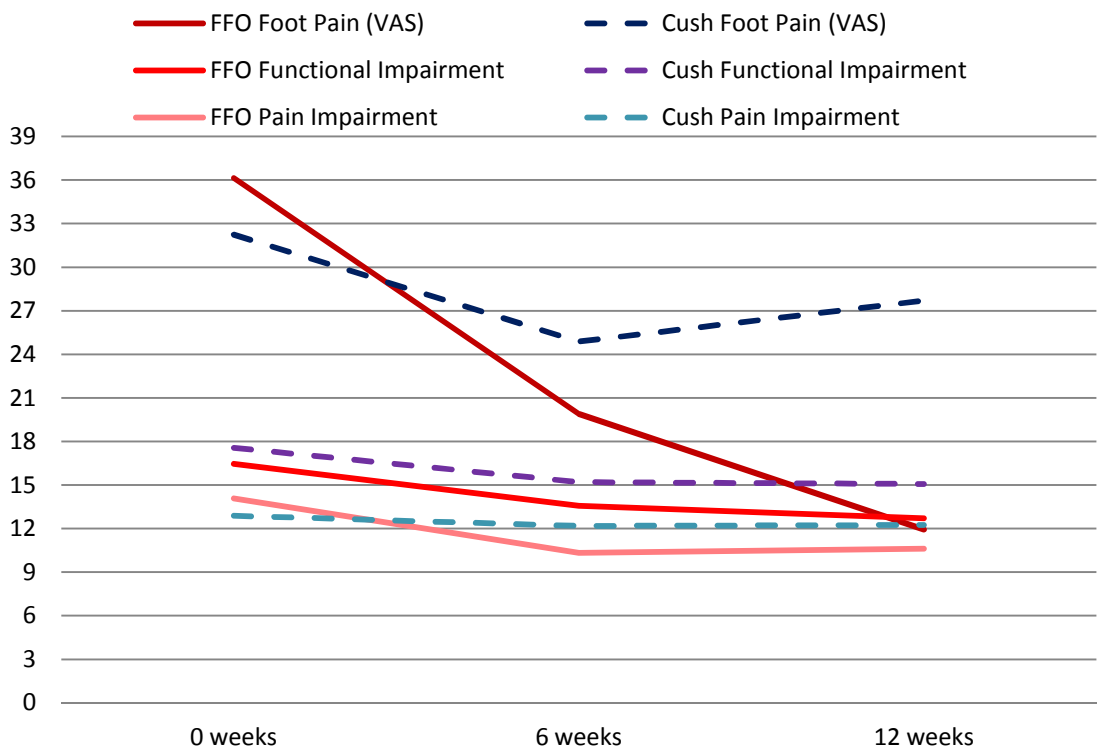
In the Cush group four bones showed new lesion formation in four separate participants in varying degrees (5%, 6%, 11%, and 100%). In the FFO group, new bone patterns changes can be attributed to one participant that had new bone formation in three bones: lateral (58%), medial (17%) and intermediate (41%) cuneiforms. The other three BMLs were newly formed in separate three intermediate cuneiforms (64%, 6%, and 6%). None of the bone resolutions occurred in the same participants with new BML formation. All the new occurrences of new BMLs were in addition to baseline BMLs.

The Effect of Foot Orthoses on Patient Reported Outcomes

The patient reported outcomes per orthoses treatment arm (FFO and Cush) are presented and discussed at the two follow-up periods (6 and 12 weeks). As previously described these included a self reported foot pain (100mm VAS), and the pain (range 7-21) and functional impairment (range 9-27) subscales of the MFPDI.

The change in participant reported outcomes at the two follow-up periods can be seen in Table 4.10 and Figure 4.11. Self-reported foot pain (100mm VAS) in the FFO group systematically reduced in the first six weeks, an average of -14.81mm (CI -22.3 to -7.3 mm) and there was a trend towards foot pain reductions from six to 12 weeks (mean -7.07, CI -15.0 to 0.9mm). In contrast the Cush group showed a small trend of foot pain reduction in the first six weeks, although the 95% CI crossed zero (mean -7.37mm, CI -19.9 to 5.2mm) and there was variable increase of foot pain between six and 12 weeks follow-up with wide CIs (mean +2.81mm, CI -9.1 to 14.7mm).

Figure 4.11: Mean change in patient reported outcomes from baseline to follow-up per FFO and Cush orthoses group



Both groups showed small systematic reductions of functional impairment (MFPDI) in the first six weeks of orthoses therapy (FFO mean -3.50, CI -5.1 to -1.8; Cush mean -2.13, CI -4.3 to 0.0). There was a greater mean reduction noted in the FFO group, however the CI was similar in both groups. At the second follow-up, both groups showed no change of functional impairments (FFO mean 0.42, CI -1.7 to 0.9; Cush mean -0.37, CI -2.4 to 1.7).

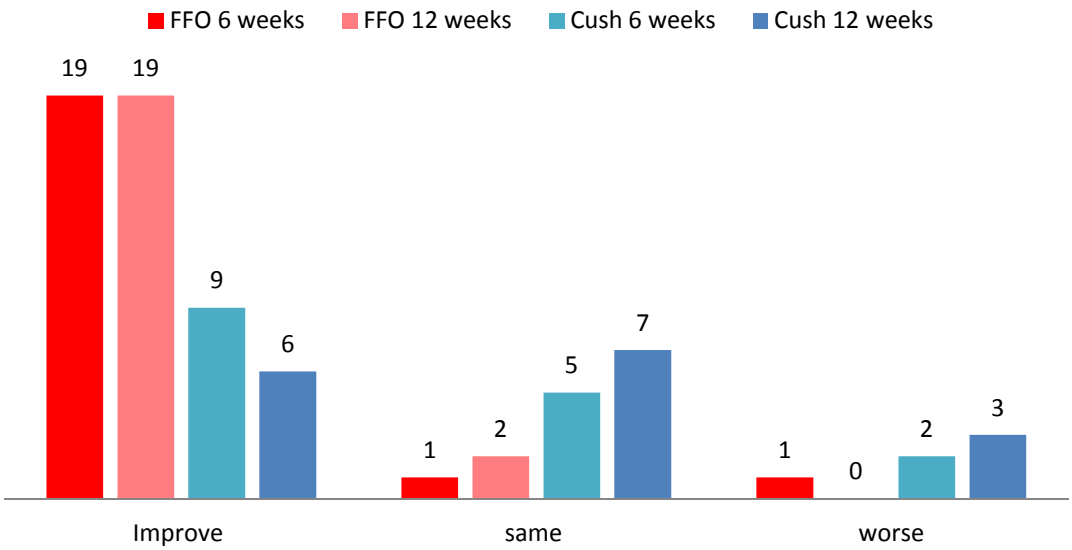
Table 4.10: Change in foot pain and impairment outcomes at 6 and 12 weeks follow-up

	FFO Difference		Cush Difference	
Mean	0 to 6 weeks	6 to 12 weeks	0 to 6 weeks	6 to 12 weeks
Foot Pain	-14.81	-7.07	-7.37	2.81
(CI)	(-22.3 to -7.3)	(-15.0 to 0.9)	(-19.9 to 5.2)	(-9.1 to 14.7)
Foot Pain Impairment	-3.50	0.81	-0.69	0.06
(CI)	(-5.1 to -1.9)	(-0.3 to 1.9)	(-1.1 to 2.5)	(-1.3 to 1.5)
Foot Function Impairment	-3.50	0.42	-2.13	-0.37
(CI)	(-5.1 to -1.8)	(-1.7 to 0.9)	(-4.3 to 0.0)	(-2.4 to 1.7)

Foot pain impairment (MFPDI) was reduced systematically in the FFO group in the first six weeks (mean -3.50, CI -5.1 to -1.9), although at 12 weeks there no change (mean +0.8, CI -0.3 to 1.9). In contrast there were no systematic reductions of foot pain impairment in the Cush group after six weeks (mean -0.69, CI -1.1 to 2.5) or 12 weeks follow-up (mean +0.06, CI -1.3 to 1.5). These results suggest foot pain and foot pain impairment systematically reduced in the first six weeks in the FFO intervention group and not in the control group. Functional impairment reduced systematically in both groups in the first six weeks of intervention, and plateaued to 12 weeks of orthoses intervention.

In the self-reported evaluation of the orthoses intervention (see Figure 4.12), most of the FFO group reported improvement by the end of study period and two stayed the same in the FFO group. In the Cush group, over half of the Cush group reported either no improvement or worse foot pain by the end of the study.

Figure 4.12: Self reported treatment response (at 6 and 12 weeks) per FFO and Cush orthoses group



In summary, BML volume decreased more in the active FFO group than the cushioning insole group. Bone marrow lesion patterns were altered in the FFO treatment group with a reduction of BML volume in the medial bones, while lesion patterns were largely unchanged in the cushioning group. Most of the participants in the FFO group reported clinical improvement compared to less than half of the cushioning group in the Cush group. The FFO group reported greater reductions in pain compared to the Cush group, while both groups showed similar reductions of functional impairments over the three months, which warrants further discussion.

4.7 Chapter Four Discussion

In this Chapter we aimed to explore the ability of functional foot orthoses to modify patient reported outcomes and patterns of BML volume using MR imaging segmentation. The clinical profile of mechanical foot pain cohort was described and the cross-sectional association between foot pain and the patterns of BMLs were explored. Following intervention with functional orthoses, change in the patterns of BML volume and patient reported outcomes were explored.

4.7.1 Foot Pain and Bone Marrow Lesions

Participants in this study who presented for screening with a mechanical medial midfoot pain, around half showed patterns of corresponding BMLs using extremity MR imaging scanning techniques. In contrast only three participants in the normal group had BMLs in the foot bones. All participants with BMLs reported on extremity MR images (0.2T) were confirmed at higher field strength MR imagining (3T), demonstrating that the extremity image scanning showed good specificity for BMLs in the foot. These results are supported by a comparison of 0.2T and 1.5T imaging of spondyloarthropathy in the heel, which reported high agreement between high and low field imaging for BML detection [352]. This is the first study to have recruited a prospective clinical midfoot pain cohort with BMLs, therefore the concurrent presence of BML and foot pain was unknown. The greater frequency of BMLs and corresponding foot pain and was similar to that reported in knee studies where there is a higher likelihood of BMLs (41%) with painful knees than healthy pain-free knees (15%) [315, 353, 354].

Participants with mechanical midfoot pain and BMLs in this study were mostly females in the fifth decade and above, whereas in knee studies gender has a mixed relationship with the incidence of knee BMLs [93, 269, 315, 355]. Further epidemiological studies are needed to confirm these findings and understand the role of gender and foot pain and BMLs, and further explore the role of bone density [110].

The foot pain group also tended to present with multiple co-morbidities such as OA, obesity and hypertension, factors which are commonly reported in foot pain studies [6, 10, 356]. The foot pain group had greater body weight than the control group (BMI 30), this is unsurprising as BMI greater than 28 can increase the likelihood of foot pain [6, 357] and incidence of BML in the knee [269, 353]. Mechanical foot pain participants tended to present with multiple pains in the proximal joints; the knee was the most frequently reported site. These results concur with one large population study that showed knee and foot pain is a common combination of multi-joint pain and is associated with walking and standing impairments [17].

Most people in this study presented with foot pain between six to 18 months duration; an average of 14 months. Foot pain was reported as either a slow or sudden onset without trauma. This is not surprising as the foot is a relatively rare site of traumatic injury compared to the ankle for example [358]. Midfoot pain was characterised by participants as a sharp and/or an ache type of pain with moderate intensity and functional impairments. The location of foot pain was mostly reported in the dorsum of the foot as was painful movement of the tarso-metatarsal joints. The location of foot pain and joint movement pain concurred with the location of the BMLs in the cuneiforms and metatarsals, suggesting a clinical association of pain and bone stress. This presentation is supported by imaging studies primarily in military and sports people (illustrated in Table 2.1 and Figure 2.1) that report frequent involvement of BMLs in the metatarsals and cuneiform bones associated with foot pain.

Foot studies suggest the metatarsal and cuneiform bones are particularly vulnerable to exercise-induced mechanical stress and are a common site of bone injuries [73, 133]. These studies suggest that mechanical loading of the bones can lead to bone stress that can be captured on MR imaging. The results of this study concur with previous imaging studies that the metatarsals and cuneiforms were common sites of abnormal BMLs. Bone

morphology and external bone forces may be one explanation for locations of stress. The narrow shaft of the metatarsal bones, for instance, does not protect against torsional forces (foot pronation), while fatigue and external loading can also increase bone strain [294, 295, 304].

Bone marrow abnormalities in the foot did not tend to present in isolated bones, instead BMLs presented in multiple bones, typically two: the intermediate cuneiform and the second metatarsal, followed by the medial cuneiform and the navicular. The combination of metatarsal and cuneiform bones as a pattern of bone stress has been shown in military training injuries [127]. Whereas, a greater number of bones are typically involved in presentations of bone marrow oedema syndrome (mean 4.7 bones) [123] or marathon induced BMLs (mean 3.4 bones) [126].

The pattern of BMLs in this study, particularly the medial and intermediate cuneiform-metatarsal joints may represent mechanical trauma, occurring at sites associated with painful midfoot OA [309]. An association between BML sites the subsequent development of radiographic OA have been observed at the knee, particularly in patterns of large BMLs focal to the subchondral regions, where new sites of cartilage lesions can form [94, 315, 336]. In the foot this pattern has been shown in post-traumatic Lisfranc ligament tears, where patterns of BML with diastasis precede degenerative changes [359, 360].

In this study the severity of current foot pain (as measured by the 100mm VAS) was not correlated with the total volume of the BML or total number of affected bones per person. There is also a mixed relationship between regional pain and BML size in the knee. Baseline associations between BML size and knee pain are poor, while stronger relationships have been shown between worsening pain and increasing size of BML over time [97, 361-363].

4.7.2 Foot Orthoses Intervention

Patient reported outcomes and BML volume was compared from baseline in the FFO group (21 participants) and the Cush group (16 participants). The BML volume was decreased by 26% per person in the active FFO group, and by 4% in the control Cush group. Changes in the control Cush group were well within the margins of error associated with intra-rater measurement variability shown in Chapter Three. This suggests there was no measurable change on a group level in the cushioning control group was shown. Minor changes of BML reported in the control group over the three month period appears to correspond with previous reports of foot BMLs, which suggest resolution can take a year or longer [121].

Individual BML patterns were altered in the FFO group, with a reduction of volumes in the medial bones, while patterns were largely unchanged in the control cushioning group. Resolution of BMLs in the foot bones was greater in the orthoses intervention group compared to the cushioning insoles. These results agree with studies of immobilisation interventions where a reduction of BML patterns have been shown [289] however the specific action of foot orthoses on foot and concurrent evaluation of BML patterns has not been explored before. In this study functional orthoses reduced BML volume in specific bones, which may change bone stress after three months of use. These results are supported by invasive experimental studies of functional foot orthoses that have shown an immediate reduction of bone stress (using strain-gauges) in the tibial and second metatarsal bones [296, 364].

The intervention of functional orthoses showed not only reduction of BML volume but also some patterns of migration. The formation of new bone was greater in the FFO group than the cushioning group potentially affecting the change of mean BML volume per group. New sites of BMLs and corresponding resolution have been reported in longitudinal imaging studies of the knee; shifting from medial to lateral condyles [365]. Patterns of migration in the foot bones in this study were different, as new formation

occurs in addition to existing BMLs, no concurrent resolution was shown. In the foot this has been shown in a third of persistent cases of painful bone marrow oedema syndrome after 12 months [121-123, 343, 366]. None of these studies, however reported a specific pattern of local migration within the foot bones, whereas in the present study the intermediate cuneiform was identified as a site susceptible to new BML formation. The intermediate cuneiform may be affected due to its location at the highest point of the midfoot in the transverse arch and the increased force exerted by the external orthotic device (in four cases). Although this has not been reported before, when an external device was applied in one study under the lateral column of the foot to cause pronation, new patterns of BMLs were mostly induced in the lateral bones, as well as in the medial, proximal and distal bones [283].

In this study the functional orthotic intervention not only reduced BML volume but also reduced short-term pain and impairment, more than the control insole. The reductions in pain were similar to those reported in plantar fasciitis and posterior tibial tendon dysfunction randomised trials (see Table 2.2). The orthoses intervention did not improve functional impairment (as measured on the MFPDI) more than the control group, however both groups showed similar reductions over the three months. A study of functional orthoses (as part of a package of treatment for falls) also showed similar reductions in both intervention and control groups suggesting that function may respond independently to foot pain in patient reported outcome measures [367]. Further work is needed to understand the responsiveness of the MFPDI subscales as an outcome measure for intervention studies.

4.8 Limitations

To explore the effect of functional orthoses on bone stress, the pattern and volume of mechanically induced BMLs (verified on MR imaging) was proposed as a surrogate measure of force distribution in the foot. A substitute method was proposed, as direct measures of bone stress are

highly invasive and not appropriate for clinical studies (as discussed in Chapter Two, Section 2.7.2). The application of MR imaging as an outcome of clinical studies to investigate bone marrow oedema syndrome has been informally reported but not specifically validated.

In this chapter, quantification of BML volume per foot bone was used to describe changes of bone abnormities pre and post intervention. This method was partially validated in Chapter Three with an intra-rater between day reliability study, further validation with repeated MR images over two time points would have enabled a further understanding of any errors introduced by the repeated scanning. This was not undertaken due to limited resources and it was not an aim of this thesis to develop a new outcome measure of BML volume measurement in the foot.

Participants with foot pain and concurrent BMLs were identified for this study using low field extremity MR imaging. This approach may have identified a group with larger volumes of BML in the foot bones as lower resolution MR systems have lower signal to noise ratio, reducing the contrast and therefore the distinction of normal and abnormal bone signal. In this study the average proportion of BML in the foot bones was 30%, if higher field strength MR scans were employed for screening, participants with smaller volumes of BMLs may have been included. Utilizing conventional higher strength imaging for screening would have improved the sensitivity, however it may have considerably reduced the sample size due to resource implications.

This intervention study would have been strengthened with a larger sample size and equal randomisation into the treatment groups. This study carried significant imaging costs, however as the study required around 100 extremity (0.2T) MR scans and 78 high resolution (3T) MR scans. The limited access to MR imaging affected the numbers available for screening and the investigation of orthoses intervention for BML at baseline and follow-up. A larger sample may have allowed greater and equal numbers in the orthoses groups and permitted inferential statistical analyses. The resource

implications of this study meant there were unequal numbers in each of the intervention groups. This may have affected the comparisons between the BML patterns in the different orthoses groups, particularly on a bone level. A larger sample may have permitted inferential statistics, however this was an exploratory mechanistic study rather than a randomised clinical trial.

The smaller numbers in the cushioning group (n=16) may have affected some of the results of the exploratory analysis undertaken in this study. Although the group did not show a consistent clinical improvement or reduction of BML volume, this may have been affected by the sampling and randomisation methods. In addition, the cushioning group were provided an flat insole to act as a sham device, without any supposed mechanical effects. The addition of an in-shoe cushion into daily footwear was not tested and may have had a clinical effect, potentially improving comfort and reducing in-shoe pressure. An in-shoe pressure analysis would have tested this effect and was not conducted, this was a limitation of this study.

By adding a randomised control group into this study, this research has improved on previous biomechanical and imaging studies, however further research is required to explore the effect of sham device and the differences between cushioning versus functional foot orthoses.

4.9 Conclusion

In-shoe functional foot orthoses improved clinical outcomes of foot pain and impairment more than the control group, corresponding with previous research. The intervention of functional foot orthoses reduced BML volumes compared to the cushioned insole, mainly in the medial midfoot bones. The cushioning insole only had minor effects on the total volume or pattern of individual BMLs. There was some regional migration of BMLs that occurred more in the functional intervention group.

Chapter Five:

The effect of function foot orthoses on gait parameters and foot kinematics

5.1 Overview of Chapter Five

The central principle of this thesis is to explore the clinical mechanism of action of functional foot orthoses, using MR imaging and gait analysis. Chapter Three described an imaging measurement method developed to quantify BMLs, which was then applied in Chapter Four to investigate the effect of two different orthoses on the distribution of BMLs. This chapter now goes on to describe a motion analysis study, which was undertaken to explore the effects of foot orthoses on foot kinematics and general gait parameters.

To further explore the main aim whether functional orthoses have a systematic effect on foot biomechanics, two types of foot orthoses (cushioned insoles and functional orthoses) were provided to participants over a three month period, as described in Chapter Four. In addition to baseline and follow-up MR imaging, detailed motion analysis was also undertaken. Assessments of gait were collected in three walking conditions: i) barefoot, ii) shod (walking in a novel gait shoe) and iii) with orthoses (using the gait shoe in conjunction with the allocated orthoses). The first phase of this Chapter focuses on the development and validation of a novel in-shoe method for collecting multi-segment foot model data from an optoelectronic motion-tracking system. The second phase describes the effect of orthoses on gait kinematic parameters with and without foot orthoses in-situ.

5.2 Research Aims

The specific aims of this chapter are:

I. To investigate whether multi-segment foot kinematics can be measured in-shoe using an optoelectronic motion analysis system and to compare segmental kinematics in healthy and pathological groups.

II. To investigate the effects of foot orthoses use on foot kinematics and gait parameters and compare the difference between the two types of foot of orthoses within shoe and shoe-only.

5.3 Introduction

Motion analysis can provide useful clinical information about joint function and can identify abnormal movement patterns often associated with joint impairment, pain and disease. Models for large joints with relatively straightforward anatomy (such as the knee and hip) are well developed and robust. Modelling complex anatomical structures such as the foot can be more difficult however, due to the number of bony and soft-tissue elements and the subtlety of joint motions. While there is progress towards a full 26 segment foot model, the majority of models in current use simplify the foot in to fewer functional units. Nonetheless, over the last ten years, foot models have increased in number and complexity and most of the kinematic foot models in current use measure segmental foot motion *in-vivo* in two to nine segments [169, 175, 178, 368-371]. When such models have been applied in clinical gait studies, people with foot pain have been shown to walk with different motion patterns to those seen in healthy controls. As discussed in Chapter Two, comparative multi-segment kinematic studies of posterior tibial tendon dysfunction, OA of the midfoot and metatarso-phalangeal joint and plantar fasciitis have all shown altered kinematics in patients compared to pain-free controls [186, 188].

As described above, there are many published foot models, however the most widely used and reported are those representing a compromise between complexity and robustness, typically four-segment models (illustrated in Figure 2.2), as discussed in detail in Chapter Two (Section 2.5.2). For the purpose of the current thesis, the Oxford foot model (OFM) (Vicon Motion, Oxford UK) was chosen as it has shown good internal and external validity and is one of the most commonly used of the four-segment models [372].

Oxford Foot Model

The Oxford multi-segment foot model is a rigid segment model that separates the ankle and foot into four defined regions (see Figure 2.5). The model was originally developed and validated in adults by Carson *et al.* (2001) [169] and later in children by Stebbins *et al.* (2006) [371].

The OFM has been shown to exhibit high within-session and within-day reliability, as discussed in Chapter Two [169, 373]. This attribute endorses the application of the OFM in cross-sectional, comparative studies where subtle differences exist between the different cohorts [373], for instance, in rheumatoid arthritis [374], hallux valgus [192] and pes planus [183]. These three studies established that the OFM is able to detect differences between pathological groups and controls in the hindfoot, forefoot and hallux segments.

In contrast, the between-day, intra-rater reliability of multi-segment foot motions (one week and month apart) has been reported to be poor, with the OFM yielding highly variable motions for defined foot segments [169, 374-376]. This may be attributed to any combination of segmental positioning, marker placement accuracy or the number of markers used. Variability in body segment parameters, such as segment lengths and marker placements are known to affect peak angular outputs, possibly accounting for the longitudinal irregularity [377].

It is clear from OFM reliability studies however, that some segments and planes are more reliable than others over time. The most reliable segment appears to be the hindfoot and the most reliable plane is the sagittal plane [373, 375, 376]. The most between-day variability was shown in the hallux segment (+6.5°) followed by the forefoot segment (+ 4.3°) and the hindfoot segment (+3°) [169]. One of the main limitations of longitudinal repeated measures (using the OFM and Vicon Nexus software) appears to be the artefact of a systematic off-set of angular motions found between measurements undertaken on different days. Differences of four degrees or more were found by Curtis *et al.* (2009) [375] and the problem was also highlighted by Stebbins *et al.* (2006) in the validation of the Oxford model [371]. Position of the participant in the static reference frame is one of the main sources of variability, particularly with regard to hindfoot eversion. Reproducing the same static position over two time points appears to reduce systematic error between sessions, although it is not clear if this can be accurately achieved between days without the use of an external positioning device [373]. Further between-day reliability research is needed to understand the longitudinal application of multi-segmental measurements, to examine the change of gait patterns over time and to test interventions such as foot orthoses over clinically relevant time-periods.

Measurement of Multi-Segment Foot Kinematics In-Shoe to Assess Foot Orthoses

Foot orthoses include a range of in-shoe devices (described in Chapter Two). One of the most common interventions for mechanical foot pain is the provision of functional foot orthoses, which are intended to alter the motions and/or internal distribution of forces within the foot. Foot orthoses have been shown to improve clinical outcomes such as pain, disability and impairment for a number of common foot and lower limb complaints (as seen in Table 2.2). While there is some evidence that foot orthoses can modify foot motions such as hindfoot pronation, the mechanism through which foot orthoses can improve foot pain remains poorly understood.

Previous multi-segment kinematic investigations of foot orthoses have been limited by the difficulty of measuring the effects of the foot orthoses within the shoes that are required to retain them in place. Previous researchers have overcome this limitation to some extent by assessing the effect of foot orthoses on multi-segment foot kinematics within sandals and modified footwear, although concerns remain that the footwear is a significant confounder of the OFM model. Such studies have examined the effect of foot orthoses in pain-free healthy people, people with pes planus [241, 378-380] and people with midfoot OA [193]. A summary of these findings can be seen in Table 5.1, where the differences between foot kinematics in a shoe-only condition and wearing foot orthoses are presented.

The five studies (shown in Table 5.1) used a variety of kinematic variables to represent the action of the foot orthoses in-shoe, ranging from single segmental motions of the midfoot, to ranges of variables from the forefoot to the tibia. Consequently, comparisons between the studies are difficult and the conclusions are, to some degree, conflicting. A comparison between walking kinematics in a shoe-only condition and then while wearing foot orthoses showed a reduction in the peak internal tibial rotation (-5.75 to -5.89) in two studies that analysed this segment (see Table 5.1) [241]. Three studies analysed peak hindfoot eversion (+0.2° to -0.3°), which showed no systematic effect, while the effect on the medial arch was variable (-2.79° to +0.2°) (see Table 5.1). These small studies also failed to detect consistent changes between pre-fabricated versus custom orthoses, however firm flat carbon fibre orthoses (that simply stiffen the shoes) showed an expected systematic reduction in sagittal motions in all the foot segments (hallux, arch angle and forefoot) in two separate studies (see Table 5.1).

Table 5.1: Summary of multi-segmental kinematic studies of foot orthoses in-shoe versus shoe-only

Author	Participants and Models	Orthotic Device	Biomechanical Measures	Kinematic Differences
Lin *et al.* 2012 [379]	Healthy group n=10 Single session shoe vs orthoses 4 segment cast model	Carbon fibre flat orthoses	Maximum MTPJ dorsiflexion	-4.1°
			Minimum arch angle	+0.4°
			Maximum forefoot plantarflexion	-1.6°
Ritchie *et al.* 2011 [380]	Healthy group n= 21 Single session shoe vs orthoses 3 segment custom model	Prefabricated arch support	Midfoot eversion:	
			*Maximum loading	- 0.67°
			*Maximum midstance	- 2.79°
			*Maximum propulsion	- 3.4°
Ferber & Benson 2011 [241]	Healthy group n=20 Single session shoe vs orthoses 3 segment custom model	Semi-custom arch moulded	Maximum hindfoot eversion	- 0.3°
			Medial arch angle	-0.1°
			Maximum internal tibial rotation	-5.75°
		Prefabricated arch support	Maximum hindfoot eversion	+0.2°
			Medial arch angle	+0.2°
			Maximum internal tibial rotation	-5.89°
Cobb *et al.* 2011 [378]	Healthy Group n=16 Single session shoe vs orthoses 4 segment custom model	Customised orthoses Impression cast	Maximum hindfoot eversion	-0.2°
			Maximum first MTPJ abduction	-0.46°
		Customised orthoses Neutral cast	Maximum hindfoot eversion	-0.28°
			Maximum first MTPJ abduction	-0.54°
Rao *et al.* 2009 [193]	Midfoot OA n= 20 Single session shoe vs orthoses 4 segment custom model	Carbon fibre flat orthoses	Maximum MTPJ dorsiflexion	-2.1°
			Sagittal MTPJ range of motion	-3.2°
			Maximum forefoot dorsiflexion	-1.1°
			Forefoot sagittal range of motion	-0.5°
			Forefoot transverse range of motion	+0.7°
			Maximum forefoot abduction	+0.3°
			Maximum hindfoot eversion	-1.1°
			Hindfoot frontal range of motion	-0.1°
			Maximum hindfoot dorsiflexion	+0.3°
			Hindfoot sagittal range of motion	+0.2°
		Customised orthoses Neutral cast	Maximum MTP dorsiflexion	+1.5°
			Maximum hindfoot dorsiflexion	+0.4°
			Maximum hindfoot plantarflexion	-4.5°
			Maximum hindfoot abduction	-2.9°
			Maximum hindfoot eversion	-2.2°
			Maximum hindfoot dorsiflexion	-0.7°

Caption: Carbon fibre flat foot orthoses are not shaded

Grey shading indicates casted and pre-fabricated foot orthoses

The biomechanical studies (seen in Table 5.1) investigated the action of foot orthoses by comparing the multi-segment kinematics within shoe-only and when wearing the foot orthoses after a period of acclimatisation (one day to one month). These studies outlined in Table 5.1 did not show any consistent effect of functional foot orthoses on multi-segment kinematics. This may be as most of these studies were limited to investigations in healthy groups that have not used a control comparison group.

Further foot studies are needed to understand the immediate and long-term affect of foot orthoses on multi-segment foot kinematics in a range of painful foot disorders to understand the clinical mechanism of action. In this chapter the kinematic effects of pre-fabricated functional orthoses, (contoured devices with a firm arch support, a heel cup and metatarsal support) are compared to those of a simple cushioning insole.

One of the reasons there have been few multi-segment kinematic studies of the effects of foot orthoses may be due to the difficulties of measuring multiple passive reflective markers inside the shoe during walking. This can further compound the known difficulties in prospective studies where the accurate (re)placement of marker is problematic even without accommodating a shoe. Measuring multi-segmental foot kinematics in-shoe poses some specific technical difficulties, as shoes may confound the marker sets. In traditional hindfoot-only models, accommodating one or two heel surface markers was achievable by removing material at the heel counter, which had a minimal detrimental effect on shoe function [233]. In contrast, multi-segment protocols require multiple surface markers, dispersed across the dorsum of the foot. Previous attempts to measure multiple segments within a shoe have used sandals or modified shoes to accommodate the numerous foot markers. In these studies, the sandals or modified shoe solution did not resemble a functional shoe as the shoe upper was often largely absent. This particular issue will be explored within this chapter of the thesis.

In this next section of Chapter Five, a preliminary study is described which details the development of a “gait shoe” designed to accommodate passive infra-red markers while maintaining the functional integrity of a shoe. The test-phase compares barefoot and in-shoe foot kinematics in two groups: patients with active midfoot pain and pain-free healthy controls.

5.4 Phase One: The Gait Shoe Study

5.4.1 Introduction

This study aimed to develop and test a novel “gait shoe” developed with the intention of being able to accommodate, without compromising shoe function, the 11 reflective markers that must be mounted on the foot to use the OFM. This phase details the development of the gait shoe, and the preliminary validation through the assessment of foot kinematics in people with mechanical midfoot pain and pain-free controls.

As noted in the Section 5.3.2, previous research employing multi-segment foot models to measure in-shoe kinematics has relied on footwear modifications. In one of the few studies to have focused on maintaining shoe integrity optimized hole size to accommodate less holes (four) by using surface mounted wands that hold a triad or quad cluster of markers [381]. This in-shoe foot kinematics solution is therefore limited to cluster markers that use bespoke multi-segment models. There are no published cluster multi-segment models therefore a solution is needed that can accommodate established skin-mounted makers that are in widespread use. For the traditional skin-mounted approach, recent studies have employed sandals to accommodate reflective markers or have removed material from a standard shoe [382]. This is a problem for the evaluation of in-shoe orthoses, which are difficult to secure in sandals and the set-up may not reflect the orthoses-shoe interaction, which is an essential element in orthotic therapy [383].

A “gait shoe” was developed using a novel webbing upper that maintains the integrity of a shoe upper while allowing access to the skin and visualization of skin-mounted markers. The next section describes an investigation of the gait shoe by comparing barefoot and in-shoe multi-segment foot kinematics in participants with mechanical midfoot pain with those in a pain-free control group.

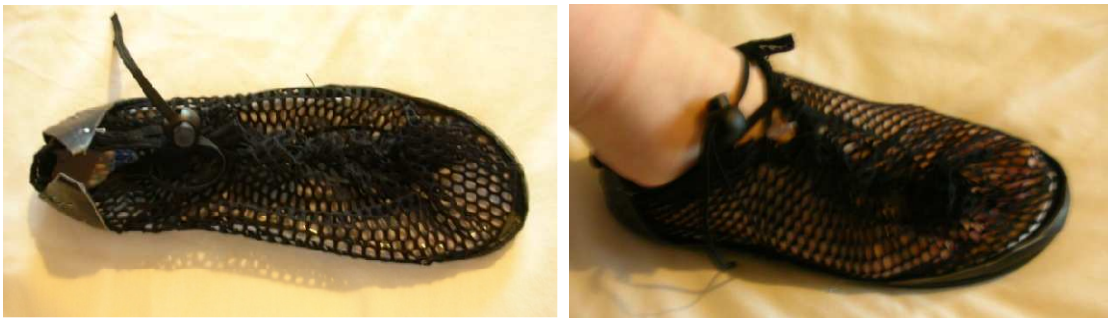
5.4.2 Methods

The methodology of this study is presented in five sections including gait shoe design, participants, procedure, data handling and analysis.

Gait Shoe Design and Refinement

The gait shoe was developed to accommodate the feet, in-shoe foot orthoses and the eleven reflective markers per foot required for defining the hallux, calcaneus and metatarsal segments of the OFM. In the prototyping phase (see Figure 5.2), a first version was developed in which the entire upper was replaced with webbing material. During initial walking tests the first prototype did not to fit to the foot securely was not firm or durable enough to accommodate the foot orthoses securely. The loose fit may also have affected the gait pattern of participants in the study, a confounder this study was aiming to minimise.

Figure 5.2: Photos of the first prototype shoe



In a revised version, a shoe was chosen that had initial strength and structure and that would allow for partial modification of the upper. A basic canvas plimsoll shoe was chosen for modification that had a 2mm canvas upper, a conventional four laced fastening and a flat uniform rubber sole. This shoe style was also chosen because of its minimal likely impact on foot function, the soft plimsoll having no specifically functional features such as a raised heel, rigid heel cup or contoured arch.

Figure 5.3: The canvas shoe prior to and following modification

A	B

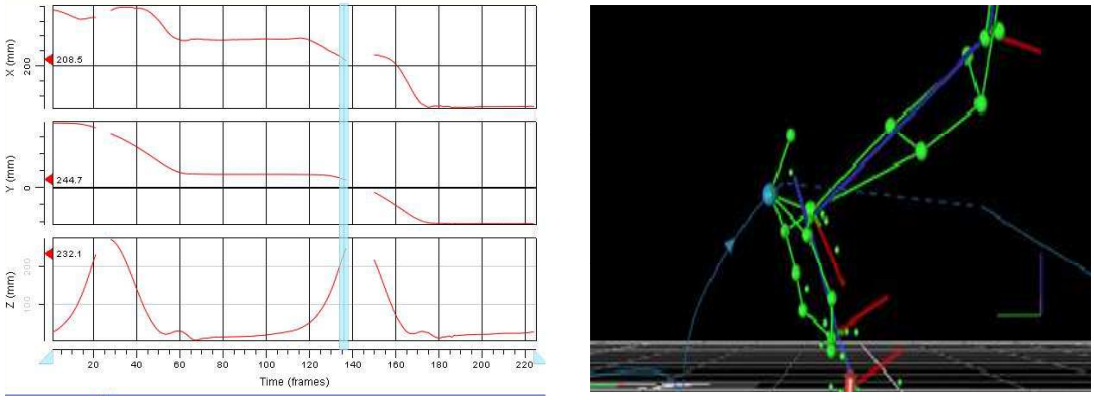
Caption:

A is a photograph of the chosen canvas shoe prior to modification.

B is a photograph of the gait shoe in action with the Oxford multi-segment foot model marker set.

The upper of the chosen shoe was modified by removing the canvas panels at the lateral and medial borders and the medial half of the toe-box upper was also removed. All panels were then and replaced with a rigid webbing material with similar physical properties of resistance to stretch, and with apertures to accommodate skin-mounted markers. A portion of the heel cup and the tongue were removed to accommodate the heel and dorsal metatarsal markers but all shoe seams that support the shape and function of the upper were preserved. The webbing material was chosen to enable the protrusion of markers through the mesh, with customised slits added locally to eliminate fouling of markers (see Figure 5.3).

Figure 5.4: An in-shoe heel marker trajectory graph and corresponding tracking



The feasibility of the new shoe was evaluated in two stages which explored:

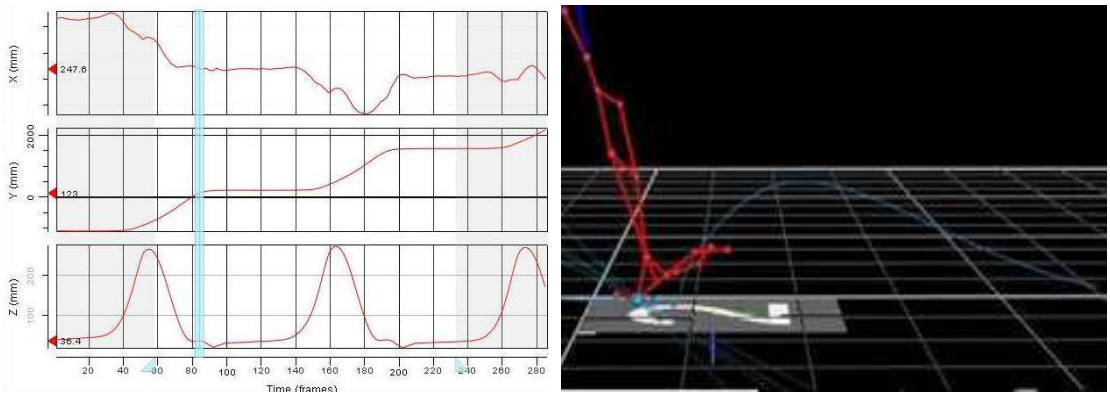
i) Comfort and comparability to a normal shoe.

ii) Adequacy of marker tracking during walking.

In early tests of marker tracking, the heel marker was systematically lost at heel lift, possibly due to the downward movement of the foot in-shoe (see Figure 5.4). To optimise the marker tracking the window at the base of the heel was enlarged while maintaining the heel seam. After alterations were made the pilot analyses were repeated. The larger heel window improved the heel marker tracking see Figure 5.5.

With this modification achieving the desired aims, the design was finalised and replicas were made in UK sizes four to eleven.

Figure 5.5: An in-shoe heel marker trajectory graph and corresponding virtual tracking



Participants

Ethical approval and governance permissions were gained through the same process as described in Section 4.4.1. A group of participants were recruited as part of the larger interventional study (see Section 4.4.3) and a sub-group investigated in this chapter. In this "gait shoe" study, a sub-group consisted of the first 15 consecutive assenting volunteers with midfoot pain from the larger intervention study and a convenience sample of 15 healthy pain-free volunteers.

The groups were had a comparable mean age in the control group (mean 51 years, range 27 to 72) and the foot pain group (mean of 55 years, range 22 to 76 years), and gender (11 females in each group). Both groups were of a similar mean height (controls mean 1.62m and foot pain group 1.66m), while the foot pain group had a greater body weight (mean BMI 31, range 24 to 44) compared with the controls (mean BMI 26, range 20 to 29). Gait parameters and foot kinematics were assessed in both groups in two walking conditions: barefoot and shod (in-shoe) in a random order.

Procedure

Foot kinematics was captured using an eight camera, 3D infra-red passive marker motion-capture system operating at 150Hz (Vicon Motion Systems

Ltd., UK). The Vicon MX system, with T40 cameras, was integrated with a force plate capturing at 1000Hz (Bertec Corporation, USA) to detect foot contact events. Foot model kinematics was processed using Vicon Polygon v 3.1. All 30 participants undertook one session of gait analysis in two conditions: barefoot (referring to barefoot walking) and shod (referring to in-shoe walking), in a random order. A single foot was analysed; either the more painful limb (patient group) or the dominant limb (control group). Foot markers (9.5mm) were placed on a single limb by a single clinician (JHR) according to the OFM and participants were placed in a static reference neutral position with a limbs in a parallel stance and the forefoot to hindfoot parallel as described in the foot posture index, representing a score of zero [350]. All participants completed a five minute acclimatisation period wearing the shoes.

Gait data was captured for five gait cycles at a self selected walking speed, with events, such as heel strike and toe-off identified by the force plate and auto-correlated to marker trajectories for the subsequent heel strike. Consistency graphs were plotted and the most representative single gait cycle: the median was chosen for each participant and condition. Data were processed by manually filling trajectory gaps and filtering the data using a Woltring fifth-order spline-interpolating function. Kinematic outputs for the calcaneus and metatarsal segments were generated using the OFM. Trials for each participant were then normalized to 100% of the gait cycle and collectively averaged at 2% intervals to 51 centiles.

Data Handling and Analyses

Data were analyzed graphically by exporting each selected trial to an Excel workbook. Data were reported by producing motion-time curves for the mean motion of each individual segment in each of three anatomical planes. This was undertaken for the group as a whole and for each sub-group (foot pain and control groups).

More detailed analysis was under taken in four kinematic foot motions, as these planes are of clinical importance and reference data have been published using the OFM:

- hindfoot sagittal plane motion (dorsiflexion/plantarflexion).
- hindfoot frontal plane motion (inversion/eversion).
- forefoot sagittal plane motion (dorsiflexion/plantarflexion).
- forefoot transverse plane motion (adduction/abduction).

Agreement between the barefoot and shod kinematic patterns for the combined foot pain and control groups was quantified using the coefficient of multiple correlation (CMC) as described by Kadaba *et al.* (1989) [384]. Due to the relatively small sample sizes in both groups, it was felt that wide ranging inferential analyses were not appropriate for comparisons. The mean and CIs were calculated therefore, to compare walking conditions within foot pain and normal groups using IBM SPSS Statistics (Version 19, IBM Software USA). Barefoot and shod conditions were compared in both the foot pain and control groups. The mean difference and CI between peak hindfoot and forefoot segment motion for each group were compared at 50% of the stance phase in the gait cycle.

5.4.3 Results

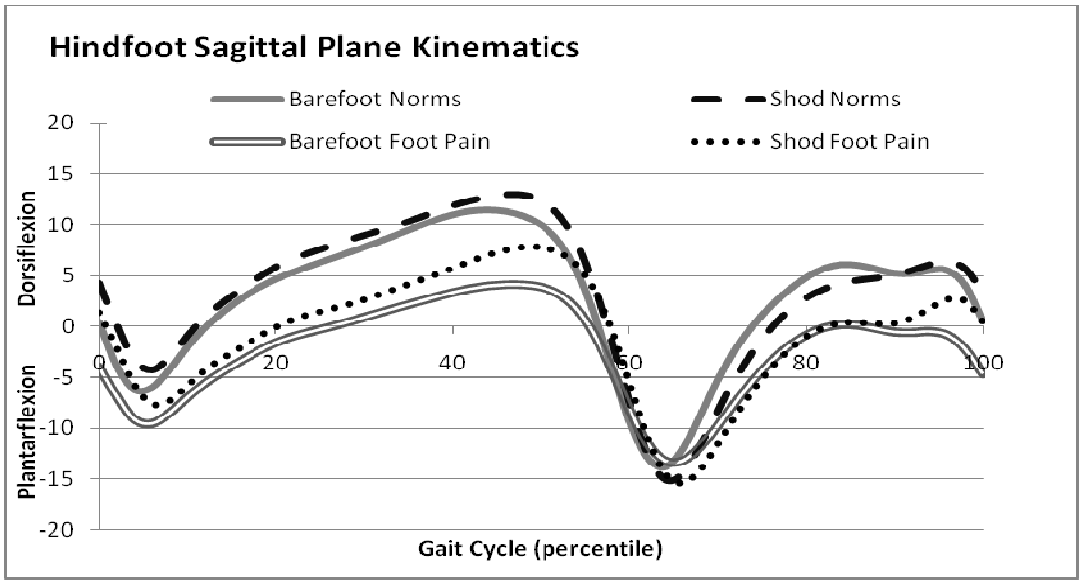
The agreement between barefoot and shod kinematics for the whole sample (total of 30 participants) was excellent in both planes of the hindfoot (sagittal plane CMC of 0.967, and CMC 0.981 frontal plane). In the forefoot, the sagittal plane motions showed good agreement (CMC = 0.743) between the barefoot and shod conditions. The forefoot transverse plane data showed similar kinematic patterns in both conditions, although in the shod conditions there was a systematic four degree off-set at heel strike and throughout stance, which meant that a CMC analysis was not possible as the square root of the ratio was a negative number and no correlation coefficient could be calculated [384].

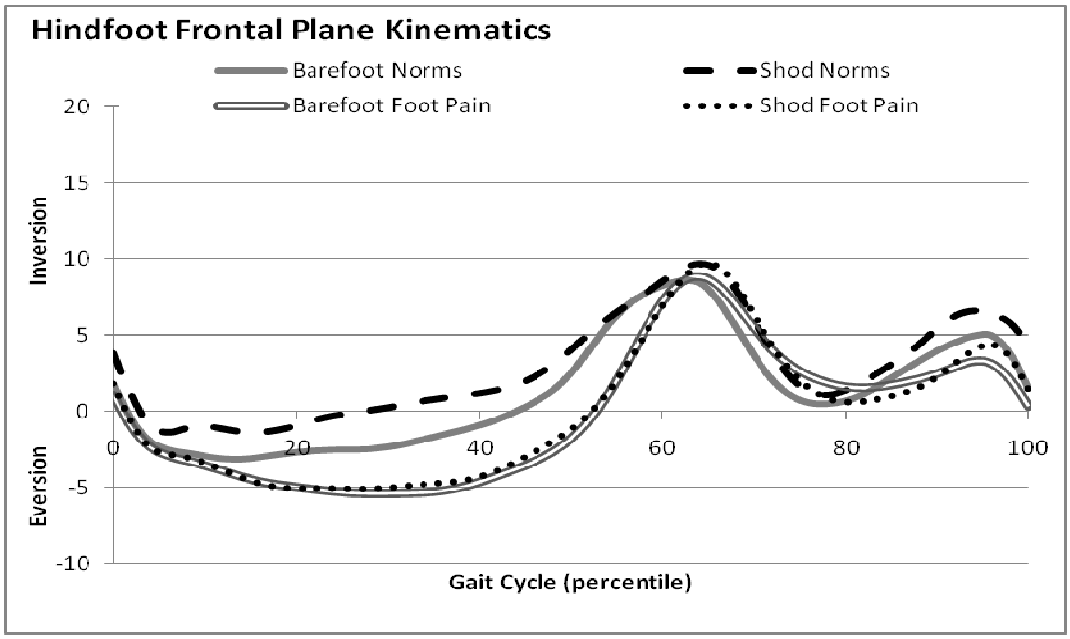
Average walking speed was comparable in the control group for the barefoot (mean 1.25m/s, CI 1.2 to 1.3m/s) and shod conditions (mean 1.25m/s, CI 1.2 to 1.4m/s). The foot pain group walked more slowly than the control group in the barefoot condition (mean 1.05m/s, CI 1.0 to 1.1m/s) and also in the shod condition although the wearing of shoes ameliorated the effect a little (mean 1.11m/s, range 1.0 to 1.2m/s). This suggests that the healthy groups walking speed was maintained barefoot and shod, while some of the foot pain group (four cases) had a therapeutic response to wearing a shoe.

Table 5.2: Mean values and CI at 50% of stance for the hindfoot and forefoot kinematics in the normal control group and the foot pain group

Mean Values 50% Stance	Hindfoot Dorsiflexion	Hindfoot Eversion	Forefoot Dorsiflexion	Forefoot Adduction
Barefoot Control	8.74°	-1.94°	1.48°	1.3°
(CI)	(5.3 to 12.1)	(- 4.6 to 0.8)	(-1.1 to 4.1)	(-1.8 to 4.5)
Barefoot Foot Pain	1.77°	-5.68°	5.45°	0.47°
(CI)	(-0.7 to 4.3)	(-8.7 to -2.7)	(2.5 to 8.4)	(-3.3 to 4.2)
Barefoot Difference	**6.97°**	**3.74°**	**-3.97°**	**0.83°**
Shod Control	11.01°	0.93°	-0.94°	4.49°
(CI)	(7.0 to 15.1)	(-2.0 to 3.9)	(-4.1 to 2.2)	(-2.0 to 7.0)
Shod Foot Pain	4.13°	-4.93°	1.71°	3.67°
(CI)	(0.3 to 7.9)	(-7.2 to -2.6)	(-1.6 to 5.0)	(-0.1 to 7.4)
Shod Difference	**6.88°**	**5.86°**	**-2.65°**	**0.82°**

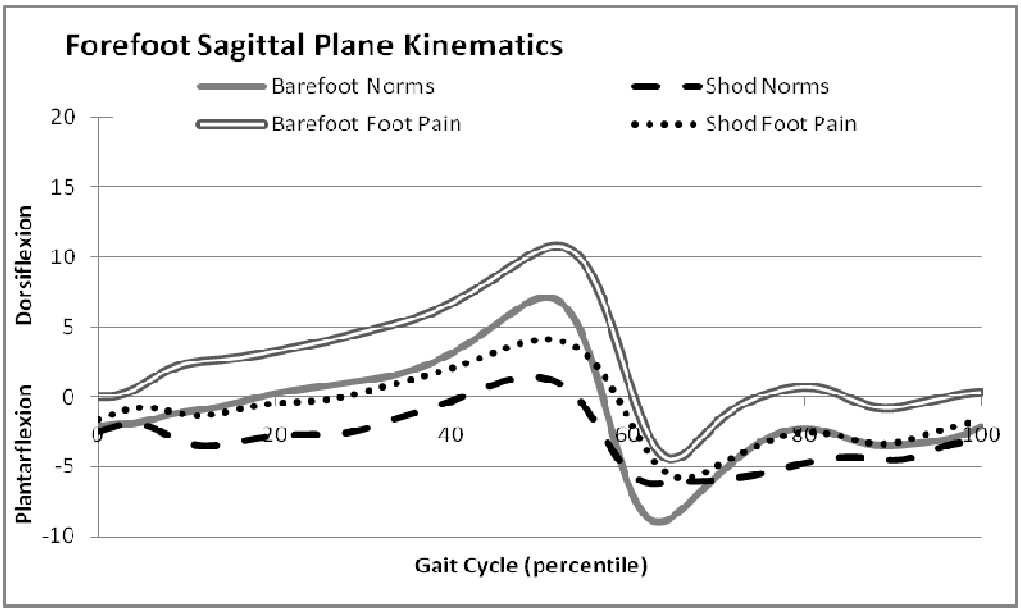
Figure 5.6: Kinematic graphs for hindfoot sagittal and frontal motions in both conditions (barefoot and shod) and both normal control (Norms) and foot pain groups

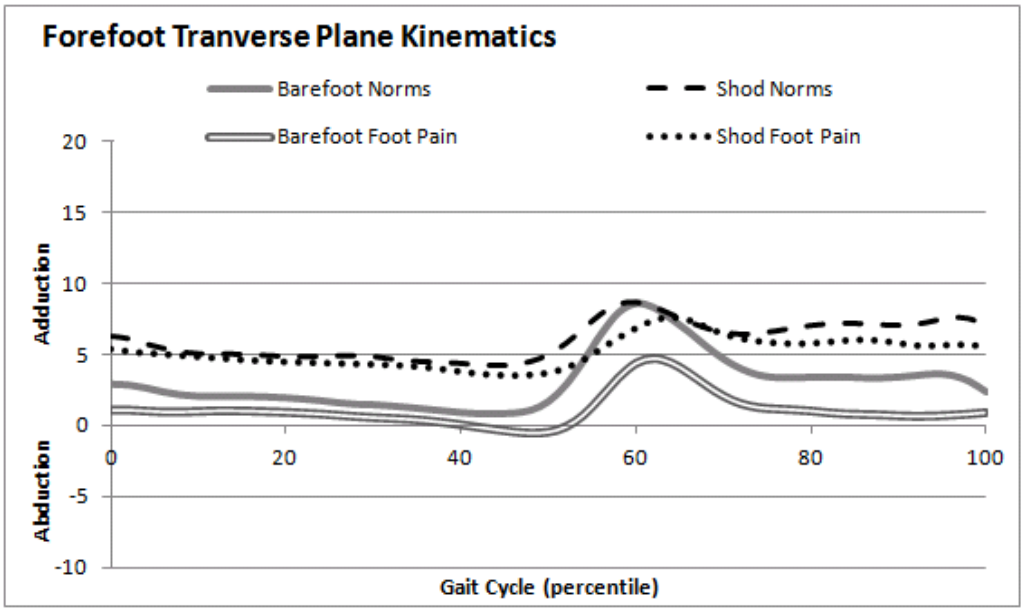




Hindfoot and forefoot kinematics at 50% of stance (Table 5.2) showed that the foot pain group had less hindfoot dorsiflexion compared to the controls and that this effect was observed in the barefoot data and preserved when shod. The foot pain group also showed greater hindfoot eversion than the controls when walking barefoot and again the effect was preserved in the shod condition (Figure 5.6).

Figure 5.7: Kinematic graphs for forefoot sagittal and transverse motions in both conditions (barefoot and shod) and both normal control (Norms) and foot pain groups





Forefoot dorsiflexion was lower in the control group compared to foot pain group and again the effect was seen in both the barefoot and shod condition. Forefoot add/abduction was similar in the foot pain and healthy control group for barefoot walking but some reduction in total excursion was evident while wearing shoes. Figure 5.6 and 5.7 shows clear differentiation between the normal (grey single and black dashed line) and foot pain groups (grey

double and black dotted line) in the hindfoot sagittal and frontal kinematics whether barefoot or shod. At the forefoot, the shod kinematics shows some degree of offset, as the shod and barefoot kinematics was closely aligned.

5.4.4 Discussion

The Oxford multi-segment foot model has been shown to be reliable when used in a barefoot state for comparing normal and pathological gait in adults and children in cross-sectional studies. Using the new gait shoe, the differences between symptomatic foot pain cases and a comparative normal control group were retained in the hindfoot and to some degree in the forefoot. There were issues in the measurement of forefoot kinematics, in comparison to other segments, due to a greater variability in motions associated with skin movement artefact [179]. Forefoot transverse segment motions in this study demonstrated high between-subject variability in both barefoot and shod conditions. This and other studies confirm therefore that forefoot motions, whether obtained barefoot or shod require cautious interpretation [373, 375].

This preliminary study suggests that participants with mechanical foot pain demonstrate systematic differences in kinematic patterns of foot motion compared to controls. Greater hindfoot eversion, less hindfoot dorsiflexion and less forefoot dorsiflexion were found the foot pain group. These results are similar to those previously reported in people with hallux valgus and pes planus deformities [183, 184, 192]. In this preliminary study, these subtle differences at the hindfoot between the groups were also observed when wearing the new gait shoe.

At the forefoot, the gait shoe had some effect in reducing the magnitude of the excursions (see Figure 5.6). The between-subject variation was high for many of these measures however and the differences between the foot pain and control groups, or between shod and barefoot conditions at the forefoot

transverse plane lacked consistency (see Table 5.2). The variation in the mean motion-time curves between participants is a well recognized limitation of the OFM [371, 375]. In this study, 5° of forefoot transverse plane excursion was found with 10° range of angular variations limiting barefoot and shod comparisons. In view of this variability, the forefoot transverse plane kinematics will not be further analyzed as a kinematic variable in the next phase of Chapter Five.

Previous studies of in-shoe multi-segment foot kinematics have relied on using a sandal or cutting windows from standard footwear. To maintain shoe integrity, small apertures in combination with surface mounted wands that hold a triad or quad cluster of markers can minimize loss of shoe material. The cluster-marker models require further investigation and comparisons to current surface-mounted single marker models. One advantage of the gait shoe developed in this thesis is the webbed upper is not targeted to a specific model and may be utilized to accommodate existing models with different surface marker configurations.

5.4.5 Conclusion

The gait shoe had a minimal functional effect on the frontal and sagittal hindfoot kinematics and the small but systematic differences observed between the normal and pathological group were retained. The gait shoe appeared to have a greater effect on the forefoot kinematics. Differences between the groups were retained in the sagittal plane barefoot and shod, however the transverse plane remains difficult to quantify reliably, either barefoot or shod. This study suggests that the gait shoe developed in this thesis offers a practical solution to measuring selected multi-segment foot kinematics within a shoe using passive surface mounted infra-red marker sets, however there may be an effect of the shoe on the forefoot kinematics.

5.5 Phase Two: The Effect of Functional Foot Orthoses on Gait Parameters and Foot Kinematics

5.5.1 Introduction

The main aim of this study was to investigate whether wearing foot orthoses can alter gait parameters and foot kinematics systematically after three months. The treatment of foot pain with functional foot orthoses has shown good efficacy, however the underlying premise is poorly understood due to limited clinical studies.

There is some evidence that foot orthoses can systematically modify hindfoot motions, reduce pain and deformity in participants with rheumatoid arthritis [216]. Otherwise most other biomechanical research of foot orthoses (as discussed in Chapter Two) has been limited to investigations in normal populations, which suggest small, and non-significant mean changes of foot and leg movement may confounded by subject-specific responses [385]. This study improves on current research as it is clinical study of participants with midfoot pain that has investigated the effect of functional foot orthoses on multi-segment foot motions compared to a cushioned insole.

The specific research aims are i) to compare temporal and spatial gait parameters and foot kinematics in-shoe and with the addition of the allocated orthoses treatment and ii) to investigate whether functional foot orthoses systemically modify gait parameters and foot kinematics differently to a cushioned insole.

5.5.2 Methodology

Participants

In this study, a subset of first 20 participants was identified from the main interventional study outlined in Chapter Four (Section 4.4). In addition to MR imaging prior to and following orthotic therapy, all participants also underwent detailed motion analysis. As described previously, two types of foot orthoses were assigned to each participant using sealed envelope randomisation, to minimise bias. Of the 20 participants in the motion analysis sub-study, ten were allocated to functional foot orthoses (FFO) and ten were allocated to receive a pair of 4mm foam contoured cushioning (Cush) insole.

Procedure

All 20 participants undertook gait analysis in two sessions three months apart using 3D, high resolution motion analysis system (described in Section 5.4.2) employing an eight camera motion-capture system with integrated force plates. Joint motions and forces were then fed into software models to produce gait parameters and foot segmental kinematics as described previously.

The proprietary lower limb marker set was used, constituting 16 reflective markers (14mm in diameter) placed on the hip, thigh, leg and foot in addition to joint widths input to define the lower limb segments and joint centres from the hip to the ankle. A further 14 smaller reflective markers (9.5 mm diameter) were placed on the study foot, as described by the OFM, to define the segments of the lower leg and foot [371]. The study limb was either the more painful foot or the dominant limb, as determined by first step preference in walking initiation.

Gait was measured within $5m^3$ capture volume within a 12 meter walkway, gait events were defined using the force plate. The stance phase of gait was determined directly by the loading/unloading events derived from the force

plates at heel strike and toe-off. The full gait cycle was defined by the successive heel strike on the same limb using the auto-correlate function. All 20 participants undertook two gait analysis sessions, in which three conditions: i) barefoot (walking barefoot), ii) shod (walking wearing the gait shoe-only) and iii) orthoses (walking wearing the gait shoe and with the allocated FFO or Cush orthoses in-situ) that were acquired in a random order. Before commencement of gait analyses, participants were placed in a static frame reference position corresponding to a zero score on the FPI-6 (previously described in Section 5.4.2). The static reference frame was processed and the model attached and visually verified. Following a five minute acclimatization period each participant were asked to walk at a self-selected speed. Five gait cycles were recorded and processed.

Marker trajectories were processed by manually filling any trajectory gaps and low-pass filtered with a 4th order Butterworth filter using a cut-off frequency of 6Hz with zero lag in accordance with standard recommendations for kinematic signal noise processing [386]. Temporal and spatial parameters and foot kinematics were obtained using the Vicon Plug-in Gait and OFM (Vicon Motion System Ltd., Oxford UK).

Once the data was processed and modelled to produce segmental kinematic outputs, data was normalized to 100% of the gait cycle and collectively averaged at 2% intervals to 51 centiles. Consistency graphs for each chosen segment and plane were plotted for analysis and the most representative cycle was chosen (median trace) for further analysis in each gait condition and each participant.

5.5.3 Data Handling and Analyses

Choice of Gait Parameters and Foot Kinematics

There are a large number of kinetic and kinematic parameters produced using the plug-in-gait and OFM for the foot and lower limb. For analysis in

this chapter specific gait variables were chosen to assess the orthoses interventions.

Temporal and spatial gait parameters (gait velocity, step length and stride time) for all the conditions (barefoot, shod and orthoses) were included in the analyses. In addition, specific kinematic variables per segment and per plane were chosen for further analysis (see Table 5.3). The choice of variables for this study was based on the best available evidence, with a particular emphasis on variables with the good between-day repeatability.

Data Analysis Plan

Continuous data was explored for homogeneity using visual inspection of histograms (see Appendix A). Due to the small sample size and heterogeneous distribution, descriptive statistics rather than inferential statistics were utilised. To compare the difference between baseline and follow-up kinematics and gait parameters, the mean and CIs were calculated using IBM SPSS Statistics (Version 19, IBM Software USA).

A data analysis plan was formulated, based closely on the remaining research aims to avoid data mining. To investigate the effect of foot orthoses on the chosen gait and kinematic variables (see Table 5.3), a cross-sectional comparison was made on the three month follow-up data. The mean and CI of the follow-up orthoses sub-groups was compared for i) shod only versus cushioning orthoses and ii) shod versus functional orthoses. These groups were compared to evaluate whether functional orthoses altered the gait analyses differently to the cushioned insole.

Table 5.3: List of gait parameters and kinematic variables chosen for analysis

Gait Parameters	Kinematic variables	
Hindfoot Calcaneus to tibia flexion/extension	Mean angle and timing of Maximum Dorsiflexion Total Range of Motion	
Hindfoot Calcaneus to tibia inversion/eversion	Mean angle and timing of Maximum Eversion Total Range of Motion	
Forefoot Metatarsals to Calcaneus flexion/extension	Mean angle and timing of Maximum Dorsiflexion Total Range of Motion	
Forefoot Metatarsals to Calcaneus inversion/eversion	Mean angle and timing of Maximum Inversion Total Range of Motion	
Walking Speed	Mean speed	(meter per second)
Step Length	Mean length	(meters)
Stride Time	Mean time	(seconds)

5.5.4 Results

Demographics

The demographic profile of each orthoses group can be seen in Table 5.4. The mean age of the group assigned the cushioning orthoses was seven years lower than the FFO group, although this was largely due to one outlier who was 20 years younger than the mean age. There was a difference between the groups in terms of body weight; the cushioning group were heavier than the functional orthoses group, although the ranges of weight were similar. This difference between the groups may be attributed to the small sample for this exploratory study, which resulted in an inability to balance out the random allocation of two lighter participants in the FFO group and a one heavier participant in the Cush group.

Table 5.4: Demographic profile of both orthoses groups: FFO and Cush

Group	No	Gender	Limb	Mean Age	Mean Height	Mean Weight	Mean BMI
FFO	10	3 Male	4 Right	58	1.69m	81 Kg	28.4
Range				(41 to 72)	(1.53 to 1.79)	(64 to 116)	(24 to 37)
Cush	10	4 Male	5 Right	51	1.65m	83 Kg	31.1
Range				(22 to 76)	(1.5 to 1.78)	(67 to 110)	(22 to 43)

Results of a cross-sectional comparison of temporal and spatial gait parameters and foot kinematics for subjects in a shoe-only condition and while wearing foot orthoses in-shoe.

This section of the results presents data comparing gait variables measured in a shoe-only condition and while wearing orthoses, allocated at random, after three months of acclimatization. The mean and 95% CI are presented for the two groups with and without the insoles in-situ.

Gait Parameters

Table 5.5 shows that within each orthoses group there was very little change in gait speed and stride length with and without the allocated insoles in-situ.

Table 5.5: The follow-up gait parameters of both orthoses groups: FFO and Cush.			
ORTHOSES: FFO	**Gait Speed (meters/second)**	**Stride Length (meters)**	**Stride Time (seconds)**
Mean Shod	**1.21**	**1.32**	**1.09**
(CI)	(1.15 to 1.28)	(1.24 to 1.40)	(1.04 to 1.14)
Mean FFO	**1.21**	**1.33**	**1.11**
(CI)	(1.16 to 1.26)	(1.26 to 1.41)	(1.05 to 1.16)
Mean Difference Shod & FFO	**0.00**	**0.01**	**0.02**
ORTHOSES: Cush			
Mean Shod	**1.22**	**1.33**	**1.10**
(CI)	(1.12 to 1.31)	(1.13 to 1.43)	(1.06 to 1.13)
Mean Cush	**1.23**	**1.33**	**1.08**
(CI)	(1.13 to 1.34)	(1.23 to 1.43)	(1.05 to 1.12)
Mean Difference Shod & Cush	**0.01**	**0.00**	**-0.02**

Hindfoot Kinematics

After wearing either the FFO or Cush orthoses for three months, a cross-sectional comparison was made of the hindfoot kinematics observed in the shoe-only (shod) condition and while wearing the allocated insoles (see Table 5.6.).

The mean hindfoot angles were similar and the CI suggests equally variability in both groups either, shod or wearing orthoses, and in both the frontal plane and sagittal plane. There were no measures where the mean of one condition lay beyond the bounds of the 95% CI of the comparator. There was a trend towards an effect of later maximum eversion in the FFO group, although this was not definitive. There were no other trends towards any other systematic effect.

Table 5.6: Follow-up shod and orthoses hindfoot kinematics per orthoses groups: FFO and Cush

	Frontal Plane Heel Strike	Time of Max Hindfoot Eversion	Hindfoot Frontal ROM	Sagittal Plane Heel Strike	Max Hindfoot Dorsiflexion	Time of Max Dorsiflexion	Hindfoot Sagittal ROM
ORTHOSES: FFO							
Mean Shod	0.00°	17.50%	11.04°	4.91°	14.70°	45.40%	24.44°
(CI)	(-6.0 to 6.0)	(8.2 to 26.8)	(2.5 to 19.6)	(1.4 to 8.4)	(10.4 to 19.0)	(41.4 to 49.4)	(21.3 to 27.6)
Mean FFO	0.35°	26.50%	13.73°	4.69°	14.52°	47.60%	24.01°
(CI)	(-3.2 to 3.9)	(14.6 to 38.4)	(5.7 to 22.5)	(0.1 to 9.3)	(9.7 to 19.4)	(45.0 to 50.2)	(20.1 to 27.9)
Mean Difference Shod & FFO	**0.35°**	**9.00%**	**2.69°**	**-0.22°**	**-0.19°**	**2.20%**	**-0.43°**
ORTHOSES: Cush							
Mean Shod	0.52°	23.00%	12.59°	1.77°	11.11°	47.50%	21.92°
(CI)	(-3.7 to 4.7)	(10.3 to 35.8)	(9.6 to15.6)	(-1.6 to 5.1)	(6.1 to 16.2)	(45.7 to 49.3)	(17.6 to 22.0)
Mean Cush	0.44°	24.60%	14.25°	1.78°	11.22°	47.60%	21.98°
(CI)	(-3.8 to 4.6)	(13.3 to 35.9)	(11.7 to 16.9)	(-3.5 to 7.1)	(5.7 to 16.8)	(45.0 to 48.4)	(17.6 to 26.3)
Mean Difference Shod & Cush	**0.08°**	**-1.60%**	**1.66°**	**0.01°**	**0.10°**	**0.10%**	**-1.08°**

Forefoot Kinematics

After wearing FFO or cushioning insoles (Cush) for three months, a cross-sectional comparison was made of forefoot kinematics for the shoe-only (shod) condition and while wearing foot orthoses (Table 5.7). Again, any differences between the two orthotic types, either in head to head comparison or in terms of the difference from the shoe-only condition, were minimal. In no case, did the mean of one group lay beyond the bounds of the comparator 95% CI.

There was a trend towards a later maximum forefoot inversion in the FFO group (+11.5%) compared to the shoe-only condition but this is again not definitive as only a few participants exhibited a shift in the timing of peak inversion to the end of stance. Smaller increases in maximum forefoot inversion were noted in the Cush group (4.9%) compared to the shoe only. There were also some changes in the mean timing of maximum forefoot dorsiflexion when wearing the foot orthoses compared to shod motions. In the FFO group there was a mean reduction (-6.8%) of forefoot dorsiflexion and in the Cush group an increase (+3.1%) of forefoot dorsiflexion, although these differences were not supported by a differentiation in the CI between groups. These results should be interpreted with caution in light of the variability in the forefoot data previously noted.

Table 5.7: Forefoot kinematics shod and wearing both types of foot orthoses at the three months follow-up

	Frontal Plane Heel Strike	Max Forefoot Inversion	Time of Max Forefoot Inversion	Forefoot Frontal ROM	Sagittal Plane Heel Strike	Max Forefoot Dorsiflexion	Time of Max Forefoot Dorsiflexion	Forefoot Sagittal ROM
ORTHOSES: FFO								
Mean Shod	8.09°	9.43°	22.40%	6.01°	-3.43°	3.13°	50.00%	6.85°
(CI)	(2.4 to 13.8)	(4.1 to 14.8)	(4.3 to 40.5)	(4.5 to 7.6)	(-7.7 to 0.8)	(-0.2 to 6.4)	(47.9 to 52.1)	(4.3 to 9.4)
Mean FFO	6.31°	7.52°	33.90%	4.29°	-6.10°	0.70°	43.20%	6.75°
(CI)	(1.2 to 11.5)	(2.1 to 13.0)	(14.8 to 53.0)	(2.8 to 5.8)	(-10.4 to -1.8)	(-2.4 to 3.8)	(32.3 to 54.1)	(4.7 to 8.8)
Mean Difference Shod & FFO	**-1.78°**	**-1.90°**	**11.50%**	**-1.72°**	**-2.67°**	**-2.43°**	**-6.80%**	**-0 .10°**
ORTHOSES: Cush								
Mean Shod	7.64°	8.32°	20.70%	6.81°	1.53°	7.92°	46.70%	7.66°
(CI)	(3.9 to 11.3)	(4.6 to 12.1)	(1.5 to 39.9)	(4.6 to 9.0)	(-3.5 to 6.6)	(2.3 to 13.5)	(35.8 to 57.7)	(6.0 to 9.3)
Mean Cush	7.67°	8.67	25.60%	6.12°	-0.48°	6.74°	49.80%	7.53°
(CI)	(2.4 to 13.0)	(3.7 to 13.6)	(5.1 to 46.2)	(4.6 to 7.6)	(-6.6 to 5.6)	(1.5 to 12.0)	(47.5 to 52.1)	(5.5 to 9.6)
Mean Difference Shod & Cush	**0.03°**	**0.35°**	**4.90%**	**-0.70°**	**-2.01°**	**-1.18°**	**3.10%**	**-0.13°**

5.6 Chapter Five Discussion

In this chapter we aimed to explore gait analysis to understand the biomechanical effect of foot orthoses in-shoe. To measure in-shoe foot kinematics, a new gait shoe was developed and tested by comparing outputs from a group of participants with foot pain and a normal control group. Following this a subset of participants with foot pain was examined longitudinally, by comparing outputs derived from walking shoe-only (shod) in comparison to wearing foot orthoses (within-shoe).

5.6.1 Gait Shoe Development

The results of the preliminary gait shoe study (discussed in Section 5.4.4) suggested that temporal and spatial gait parameters and some aspects of multi-segment foot kinematics can be measured reliably in-shoe, allowing comparisons between healthy and pathological groups. The hindfoot and forefoot kinematics were compared at 50% of stance, as the OFM has shown to be sensitive to comparative changes between healthy and pathological groups [183]. The foot pain group demonstrated reduced hindfoot dorsiflexion and increased hindfoot eversion when walking both barefoot and shod. Forefoot dorsiflexion was reduced in both shod and barefoot conditions in the foot pain group. These are similar patterns to comparative studies investigating pes planus versus controls, which showed reduced hindfoot and forefoot dorsiflexion, increased forefoot abduction and greater hindfoot eversion [183, 184].

The new gait shoe showed good ability to retain subtle differences in gait parameters and hindfoot kinematics between barefoot and shod conditions and kinematic patterns were comparable with those reported in the literature. No meaningful comparison can be made between barefoot and shod outputs derived from the forefoot transverse plane motions, due to wide variability that was shown in this study that is comparable to other foot studies [184].

5.6.2 Comparison of Gait Parameters and Foot Kinematics between Shoe-Only and Orthoses Conditions

A comparison of the mean and CI was made between the follow-up gait analyses firstly shod and then wearing the functional orthoses (FFO), and secondly shod and then wearing the cushioning (Cush) orthoses.

The comparison of the temporal and spatial gait parameters showed no systematic changes at follow-up. A comparison between gait parameters shod and wearing either type of foot orthoses showed only minor changes that indicating that walking parameters were not affected by wearing foot orthoses for three months in this patient group.

The orthoses did not have any systematic effect on hindfoot or forefoot peak angles in either FFO or Cush orthoses groups when compared to shod measurements. The Cush and FFO orthoses showed very little effect on the comparative mean hindfoot or forefoot kinematics, only minor decreases in the frontal and sagittal planes were noted with wide CIs. The FFO group showed small trends that suggest a relative increase in the time to maximum hindfoot eversion and time to maximum forefoot inversion, with a small reduction in the time to maximum forefoot dorsiflexion. These trends were not seen the in the Cush group.

These weak trends do not suggest the walking with FFO (compared to shod-only) caused a systematic effect on the kinematic data for the hindfoot or forefoot. The inherent variability of the forefoot data also precludes any conclusive statements about any systematic effect associated with functional orthoses use.

A comparison of the in-shoe and orthoses multi-segment kinematics has been made in the literature (see Table 5.1), although not all studies reported the same variables making direct comparisons to previous literature difficult. In addition, there was only one clinical study of midfoot OA, the remaining five studies (summarised in Table 5.1) were conducted in healthy groups

using different multi-segment models. Pre-fabricated and custom orthoses in otherwise healthy individuals have been reported to reduce maximum navicular eversion [380] and reduce internal tibial rotation [241]. Factors not observed in the current study. Other studies aligned more closely with the findings outlined in this chapter showed minor and clinically irrelevant changes in hindfoot eversion (-0.3° to 0.2°) and fo refoot plantarflexion (0.4°) [241, 378, 379].

In the midfoot OA study [387], foot orthoses were worn for one month and very small reductions in hindfoot maximum eversion (-1.1°) were reported wearing a flat, firm carbon fibre orthoses, while the customised orthoses also reduced hindfoot eversion (-2.6°), reduced hindfoot dorsiflexion (-0.7°) and reduced forefoot abduction (-2.9°) [387]. Few comp arisons can be made between the current study and midfoot arthritis study [387] as we did not report hindfoot eversion or forefoot abduction due to the previously reported between-day and off-set variability [375].

Our data confirmed the small kinematic changes in the forefoot but calls into question the clinical relevance given the large degree of variability. Rao *et al.* (2010) further detailed findings supposedly indicative of small changes (<1.6°) in forefoot kinematics, but concerns over t he high variability of the forefoot data (shown in this study) preclude any meaningful comparison [387].

The results of this study and previously published orthoses studies report changes in hindfoot and forefoot kinematics that may be undermined by the between-session and between-day reliability errors. This is exemplified in Table 5.1 where half of the studies reported little or no change (+1° to -1°) in segmental kinematics. A multi-segment kinematic reliability study has shown between-session same-day errors in the hindfoot sagittal (1.4°), forefoot sagittal (2.3°) and forefoot frontal (5.1°) plane motions [373] that are larger than the results reported in this chapter. The study by Chevalier *et al.*

(2012) is one of the few studies to have reported the forefoot values in detail, although the methodology was case driven to compare different types of foot orthoses [388]. Interestingly this study showed there were changes in the participant response to the orthoses that were more consistent in the hindfoot and forefoot sagittal plane than in the transverse and frontal planes [388].

After wearing the orthoses for three months, a comparison between the in-shoe and the insole kinematics showed the FFO affected more slightly more of the kinematic variables than the Cush orthoses but that no effects were systematic or clinically meaningful. The underlying premise of supplying a cushioning 4mm flat insole was that it would not affect foot kinematics and might act and an explanatory control for any effects seen in the FFO group. Instead the cushioning group showed a greater variability of means and CI of the foot kinematics. In this small sub-study, there was no evidence for any systematic influence on foot kinematics in either treatment group.

The results in this study are supported by the many studies of foot orthoses in normal populations which suggest foot orthoses can cause small, non-significant changes in foot motions. A conclusion supported by the large degree of subject-specific variability in foot motions (found in this study) that can confound foot orthoses investigations.

5.7 Limitations

Some of the challenges and limitations of repeated multi-segment angular measurements were discussed in Chapter Two. This is one of the first prospective studies of multi-segment foot kinematics to show the effect of orthoses on foot kinematics in a unique pathological group. This study would have been strengthened if we had the resource to recruit and analyze a larger cohort of data, as this would have narrowed confidence estimates and may have allowed the use of inferential statistics. The kinematic analysis was however, intended to act solely as a confirmatory counterpoint to the novel MR imaging data detailed in Chapter Four and so resources were directed primarily at the MR imaging study.

Methodologically, this study was limited by the lack of an explicit repeated measures study with short-term re-measurement of kinematics prior to any treatment effect. A repeated measure sub-study may have enabled the identification of discrete kinematic measures for the cross-sectional comparisons unique to this population. To overcome this, pre-specified variables were chosen, based on published reliability studies of multi-segment kinematic models but we recognize this limitation.

This study was limited somewhat in scope by the use of a convenience clinical sample. The incidence of midfoot pain and BMLs were not known at the start of recruitment. Therefore, a specific sample was chosen to explore a unique research question in a prospective investigation within the constraints of the sample rather than trying at this early stage to understand the pathology of midfoot pain at a population level.

Finally, in common with all studies employing marker-based motion analysis, the results of this study were confounded by the systematic error introduced by skin artefact and marker placement, all of which can introduce variability. This is a particular problem in the foot as the angular excursions are small

and therefore the error margins are often large relative to the anatomical motion under investigation.

5.8 Conclusion

This study set out to explore whether orthoses can alter gait parameters and foot kinematics. A novel gait shoe was developed and tested that can be used when measuring multi-segment foot kinematics and was demonstrated to be capable of producing comparable kinematics both barefoot and in-shoe. A direct comparison between gait parameters and hindfoot kinematics in pathological and normal groups showed that barefoot differences were maintained in-shoe. In the forefoot, there was some indication the gait shoe had an effect on kinematics, limiting the total range observed. Forefoot kinematics were subject to large variability in this study, as in previous reports, therefore clinical data for the forefoot should be interpreted with caution.

The results of this study and previous studies were undermined by the variability in the observed segmental kinematics and the small excursions of the segmental motions being evaluated. As such a small number of pre-specified kinematic variables were chosen for investigation and conservative descriptions were used to understand the data.

In the current study there was no strong evidence of any systematic pattern in the kinematic effect of functional foot orthoses versus the cushioning insoles. This supports to some extent previous assertions in the literature that the mechanical effects of foot orthoses may occur less through major changes in joint motions and possibly more through the internal distribution of forces within the foot.

Chapter Six:

Discussion

6.1 Introduction

The body of work described in this thesis aimed to explore the mechanism of action through which functional foot orthoses may act on mechanical midfoot pain. This included studies that explored the effect of foot orthoses on resulting foot motion and internal bone stress. The direct measurement of bone stress is invasive, therefore in this thesis BML volume (measured on MR imaging) is proposed as surrogate measurement of internal bone stress. The combination of MR imaging and gait analyses in a foot study has not been undertaken previously and is a novel approach to understanding the biomechanical mechanism of foot orthoses on foot pain and bone stress.

6.2 Addressing the Objectives

This thesis addressed the main aim and objectives of described in Section 1.2.

Objective one: to identify a method to quantify BML volume in the midfoot bones. Four different studies were planned and completed to investigate different methods of quantifying volumes of signal on MR images. Segmentation methods using manual and automated signal tracing methods were investigated in a phantom study and then applied to foot images. Compared to automated tracing, the seed-growth techniques, to define the volume of the BMLs, proved to be unreliable. In the final study the automated tracing method was used to segment the foot bones, this was combined with the subtraction of bone marrow signal and this showed good inter-rater reliability to capture BML volume in the midfoot. This method was applied in Chapter four.

Objective two: to identify patterns of BMLs, which are observed with MR resonance imaging, in patients with mechanical medial midfoot pain. Baseline analysis of the foot pain group and the patterns of BMLs were described in Chapter Four. The intermediate cuneiform, medial cuneiform and second metatarsal were the most common sites for BMLs, locations that are similar to that reported in bone marrow oedema syndrome and pathological bone response patterns in military and sports studies [123, 126].

Objective three: to explore the association between mechanical medial midfoot pain and distribution of BMLs. Baseline analyses in Chapter Four showed a poor relationship between the severity of reported foot pain and total BML volume, and foot pain and the number of bones involved. While this was observed in a small sample and the data need to be interpreted cautiously, these findings corroborate previous research in both knee BMLs and foot BMLs, which reported low to moderate relationships between pain and the size of BMLs [289, 361, 389].

Objective four: to explore the effect of in-shoe foot orthoses on patterns of BMLs in the medial midfoot region. Changes of BML patterns over a period of 12 weeks were described in Chapter Four: there was evidence to suggest that the functional foot orthoses reduced BML volume in the medial midfoot bones, more than that seen in the cushioning insole group.

Objective five: to explore the effect of in-shoe foot orthoses on foot pain and impairment. The comparative effect on patient reported outcome of two types of orthoses intervention over 12 weeks (a functional foot orthosis and a cushioning insole) were reported in Chapter Four. While only an exploratory study, the results suggested a greater decrease in foot pain and the severity of pain impairment in the functional foot orthoses group, compared to the cushioning insole group.

Objective six: to explore the effect of in-shoe foot orthoses on gait parameters and foot kinematics. Foot kinematics both in-shoe only and shoe plus the orthoses conditions were compared in each intervention group after wearing the orthoses for three months. In this exploratory study, no systematic changes were found in foot kinematics with the use of either functional foot orthoses or the cushioning orthoses when compared to the shoe-only condition.

6.2 Discussion of Major Findings

The Effect of Functional Foot Orthoses on Patient Reported Outcomes

The work in this thesis supports the findings of previous clinical trials, suggesting that functional foot orthoses can reduce foot pain and impairment. Intervention with functional foot orthoses reduced mechanical foot pain, particularly in the first six weeks. Foot pain impairment as measured by the MFPDI reduced in the first six weeks of treatment and was maintained at week 12. In contrast, the cushioning insole (control group) showed a small trend towards reduced foot pain and impairment that was not systematic across the group and by the end of the study there was no systematic effect noted. The small improvements in foot pain and particular improvement of functional impairment noted in the cushioning group may suggest that a cushioning insole could provide some initial clinical benefit. This effect would need to be tested in a larger powered randomised trial.

These short-term reductions in foot pain were similar to those reported previously in an orthoses trial of patients with painful posterior tibial tendon dysfunction [209]. The magnitude of foot pain improvements in this study were however smaller than those reported in previous plantar fasciitis studies [202-204] but greater than those reported in metatarso-phalangeal joint OA [219]. The main aim of this thesis was to explore the mechanism of

action of orthoses on patient reported outcomes, kinematics and imaging outcomes, it was not the aim of this thesis to examine the clinical efficacy of foot orthoses in a clinical trial. Randomisation of treatment allocation was employed to minimise sources of bias and confounding factors. To examine the clinical efficacy of functional foot orthoses on mechanical midfoot pain and patterns of bone stress a powered randomised controlled trial with a longer follow-up would be required.

A clinical presentation of foot pain aggravated by mechanical stress was a pre-requisite for entry into this study. Therefore participants in this study presented with moderate functional impairments at baseline. Although using functional foot orthoses resulted in greater reduction in pain compared to the cushioning insole, they did not have a greater effect on functional impairment, where small reductions in both groups were noted after six weeks. This pattern of response with initial improvements in both intervention groups and then no further effect was similar to that observed in a recent falls intervention trial, which also incorporated functional foot orthoses [390]. The weaker effect of functional foot orthoses to address the functional impairment may have been limited by both the small sample size and shortcomings in the outcome measure. The outcome measure for functional impairment used in this study (a sub-scale of the MFPDI) includes an item to reflect the amount of time per month the foot pain affects an activity [348]. This three point scale (none, some and most of the time) and may lack responsiveness and further work to understand functional impairment outcomes are needed [391].

The Effect of Functional Foot Orthoses on Bone Marrow Lesions

Changes in BML patterns have been illustrated on MR imaging studies after periods of intense physical activity and following the intervention of an intentionally “harmful pronatory” insole [283, 392]. The findings in this thesis demonstrated that MR imaging can detect abnormal bone signal associated with foot pain, which may represent an abnormal physiological response to bone forces. In this study, an intervention with functional foot orthoses

brought about reductions in the total volume of BML compared to the cushioning insole, particularly in the medial midfoot bones.

The exploratory results in this thesis also support previous research data that shows functional foot orthoses have the potential to reduce bone stress injuries. Functional foot orthoses has shown to reduce the incidence of bone stress injuries in prospective trials [205, 393] and experimental studies, where reductions in the metatarsal bone and tibial bone strain have also been shown [296, 364]. *In-vivo* and *in-vitro* bone studies have shown that functional foot orthoses not only reduced vertical loading strain but also torsional rotation strain. The work in this thesis demonstrated a change in bone signal in multiple midfoot bones, thus supporting the theory that functional foot orthoses have the potential to modify the distribution of forces in the bones of the foot.

Bone marrow lesions are an example of how adaptive remodelling of bone can occur as a consequence of mechanical loading. The natural resolution of painful, stress-related BML patterns in the foot can however, take up to one year [121]. Mechanical treatments such as immobilisation and functional foot orthoses can improve resolution rates and also potentially prevent bone stress injuries [282, 288, 289, 394]. The work in this thesis supports previous research adding to the evidence that BMLs have a mechanical influence and that orthotic treatment can potentially change the forces in the foot and alter bone physiology. While an exploratory study, this thesis attempted to address some of the limitations of previous studies by including a comparator control group and validating the imaging quantification methods. In addition this was the first study to assess the pattern of BMLs prior to and following the intervention of functional foot orthoses in pathological group and to note the effect of functional foot orthoses to reduce the volume of BMLs in the medial midfoot bones.

The Effect of Functional Foot orthoses on Foot kinematics

In this small study, the effect of wearing either functional foot orthoses or cushioning insoles for three months did not result in a systematic effect on foot kinematics (compared to a shoe-only condition). The review of the literature relating to foot kinematics suggests that foot motions can be both highly variable and difficult to measure reliably in both normal and pathological groups [169, 177, 178, 374, 376]. Detailed studies of the efficacy of foot orthoses to modify foot motions have largely been limited to small groups of healthy people, which may respond differently to orthoses than those with foot pain (see Tables 2.3 and 5.1). Kinematic studies are underrepresented in clinical groups of people with foot pain and pathology, where individual responses to orthoses may be more predictable. This is exemplified in studies of rheumatoid arthritis where hindfoot pathology and subsequent deformity alters tibial and hindfoot motion [161, 216].

There were weak trends in some of the kinematic data reported in this thesis suggesting that wearing functional foot orthoses may increase the relative time to maximum hindfoot eversion and time to maximum forefoot inversion, with a small reduction in the time to maximum forefoot dorsiflexion (compared to in-shoe only measurements). These trends were not seen the in the cushioning insole group. The lack of observable systematic change in the treatment groups may be again due to the small sample sizes, and a larger sample would be needed to examine the biomechanical effects in greater detail.

In larger studies, it has been suggested functional foot orthoses may change motions in discrete groups of people and that there may be specific kinematic characteristics that predict those people that may respond. This has been demonstrated in studies of anterior knee pain, were change of foot morphology and peak hindfoot eversion was shown to be a predictor of knee pain improvement [227, 395, 396]. This approach to classification of responders and stratification of groups requires a randomised trial with large samples powered for sub-group modelling. In small exploratory studies (as

in this thesis) the between and within-person variability can confound any change in the mean kinematic patterns. The results of the current study suggest that any further work examining the effect of functional foot orthoses on foot kinematics should include biomechanical stratification methodologies to better understand the different response in foot kinematics within a larger group. In small exploratory studies (as in this thesis) the between and within-person variability can confound any change in the mean kinematic patterns.

6.3 Addressing the Central Aim

This thesis set out to explore whether functional foot orthoses can objectively modify bone stress in the midfoot. The results arising from the studies described in this thesis suggest that the intervention with functional foot orthoses resulted in reduced total BML volume and alteration of specific sites of BML in the bones of the midfoot, in comparison to a control cushioning group. In this thesis no systematic changes of multi-segment foot kinematics were demonstrated with the application of functional foot orthoses compared to the cushioning insole devices.

The theory that functional orthoses may have a more systematic effect on foot forces more than foot kinematics is a paradigm that was proposed in 2001 by Benno Nigg [385]. This theory emerged as kinematic studies have showed inconsistent effects of functional orthoses on hindfoot eversion (as discussed in Section 2.6.2). Combined clinical and biomechanical studies have further undermined the theory that functional orthoses act through altering kinematics, with foot pain reductions not accompanied by systematic changes in hindfoot eversion [220, 230, 238]. The controversy surrounding the biomechanical underpinning of orthoses treatment has led to further investigations of the kinetic effects of foot orthoses.

Increased loading of the medial midfoot and forefoot with fatigue and load carrying has been shown in both *in-vivo* pressure studies and *in-vitro* bone force studies [117, 302, 305, 397, 398]. These experimental studies suggest that bone stress can be associated with repeated application of small increases in local forces as well by a single traumatic event. The capacity of foot orthoses to modify forces has been tested experimentally in cadaveric and human *in-vivo* models, where metatarsal and tibial bones stresses have been shown to decrease immediately on application of foot orthoses [296, 364]. The effect of functional foot orthoses in changing internal bone physiology has not been previously quantified using imaging outcomes. In the foreseeable future MR imaging is unlikely to become mainstream in the clinical management of mechanical foot pain, the technique described in this thesis, is a non-invasive approach that can be applied in larger clinically relevant studies.

In this thesis there were some indications of a change in the distribution of BML patterns between the two orthoses groups, suggesting foot forces may have been altered in a different manner. In the functional orthoses group, the lateral cuneiform and the intermediate cuneiform were the sites where new regions of BML signal were observed. In contrast in the cushioning insole group the BML volume in the lateral cuneiform decreased and new sites of BMLs were observed in the intermediate cuneiform, medial cuneiforms, navicular and first metatarsal of some participants. These patterns may suggest that after three months, the cushioning control group showed a tendency toward sustained medial loading, and a transfer of load laterally. These observations about alterations in the patterns of BMLs should be interpreted cautiously due to the small number of participants and the small number of bones involved. The findings are theoretically plausible and foot orthoses that have been moulded to the forefoot and midfoot have shown greater ability to reduce bone strain and distal foot forces, than non-contoured devices [296, 399]. Future studies to explore these findings further are warranted.

Another intriguing observation in this thesis was the role of the intermediate cuneiform associated with dorso-medial foot pain. More emphasis has been previously placed on the medial cuneiform (which was also commonly involved in this study), due to the role of the medial arch in pes planus deformity and foot pronation [63]. This current study suggested however that the intermediate cuneiform was most susceptible to both resolution and the formation of BMLs in response to altered forces through the use of orthoses. Although force was not measured directly in this study it is hypothesized in this thesis that the intermediate cuneiform is subject to significant local forces, as it is the highest point of the transverse arch of the tarso-metatarsal joints and has the greatest number of ligament attachments [88]. The tarso-metatarsal joints are also subject to 23° to 25°of sagittal plane motions (approximately equal to the talo-crural joint) [400] and this may also influence local stress patterns. In addition the intermediate cuneiform and the second metatarsal (both common sites of bone stress in this thesis) are also prevalent sites of painful joint degeneration [309]. The results in thesis suggest further studies examining the role of the intermediate cuneiform in the function of the foot and pathology are warranted.

6.4 Limitations

Measurement of Bone Stress

In this thesis the effect of foot orthoses on patterns of bone stress was explored. In order to achieve this, in the clinical study, non-invasive methods using MR imaging were chosen. Direct measures of bone stress are highly invasive and usually applied *in-vitro* involving instrumented staples or similar technologies, which are implanted directly into bone. Magnetic resonance imaging has the advantage that it is non-invasive but the measurement of BML volume is recognised as being a surrogate measure of bone stress. Concurrent validation of imaging methods with

direct force measurement in the bones was not feasible in this clinical study due to the implantation of the bone devices.

This development and validation of a measure to quantify BML volume was undertaken as there are no previously validated outcomes of semi-quantitative scoring or signal segmentation methods published in the foot. In Chapter Three, three methods to quantify BML volume were developed and the intra-measurement reliability of one researcher was assessed over two time points. The final method showed acceptable levels of reliability for the segmentation and subtraction of BMLs that was subsequently used in the main intervention study (Chapter Four).

This approach to quantifying BML with subtraction has limitations however, for instance validating the measurement methods on images acquired over two time points would have better evaluated the error associated with repeated imaging. This was not possible however, due to the cost and availability of MR image scanning. The approach of validating two discrete images per person would have accounted for repeated positional error (that can manifest as image partial volume), changes in signal intensity associated with fat-suppression (that can manifest as changes in grey-scale) as well as measurement intra-reliability.

An alternative method not explored in this thesis may have been the exploration of signal intensity as an outcome measure as well as the BML volume. The signal intensity of BML can be evaluated by comparing signal-to-noise ratios and dynamic enhanced imaging. The signal intensity has been shown in studies of inflammatory diseases to be associated with foot pain and osteitis [291], although there appeared to be no added benefit when signal intensity was compared directly in gadolinium versus STIR images [118]. The risks associated with administering the intra-venous contrast agents required for dynamic enhancement were not felt to warrant the small benefits in evaluating BMLs, this is in contrast to the wide-spread

use of contrast agents in quantifying synovial inflammation in rheumatic diseases [327]. While every effort was made to validate the techniques applied in this thesis. It was not the aim of this thesis to develop a new, generalisable imaging outcome measure for BMLs in the foot. Future work could develop the segmentation/subtraction technique described here and validate the outcome more thoroughly for general use.

Kinematic Multi-segment Foot Modelling

At the outset of the current programme clinical studies using multi-segmental foot modelling were novel. Numerous multi-segment foot models have since been developed and published in an attempt to better measure and interpret segmental foot motions but at the time of planning with work there were no published comparative studies to examine the superiority of one foot model over another. The OFM was chosen in this study as this model was widely used with good internal and external validity.

Foot kinematics in this study was investigated at follow-up only, comparing shoe-only and in-shoe with foot orthoses. Baseline between-group comparisons, and baseline to follow-up longitudinal comparisons were not undertaken due to the need for user of orthoses to become accustomed to orthoses use. The published repeatability of the OFM has been reported to be relatively poor [373], but a repeatability study was not undertaken in the work described in this thesis due to lack of time and resources. To overcome this limitation, specific kinematic variables were chosen that had been reported previously to be the most reliable [169, 373], however we recognise that a repeatability study using the precise protocol employed in the current programme would have allowed us to better quantify the magnitude of errors associated with using the Oxford multi-segment foot model in this type of study.

Sample Size and Follow-up

The main methodology in this thesis was an exploratory study, employed to better understand the effect of foot orthoses on biomechanical outcomes. A larger sample would have been beneficial, particularly to investigate the effect of orthoses on individual bone volumes for each group and from baseline to follow-up. A larger sample was not possible due to the high costs of MR imaging and the complexities and amount of image analysis and kinematic data processing required throughout thesis. A longer follow-up period may also have improved the results of this study and enabled examination of resolution rates, however and three months was felt to be appropriate time-frame to examine the mechanism of foot orthoses to establish whether they could exert an influence on BMLs.

6.5 Considerations for Future Research

There are a number of findings in this thesis that have highlighted considerations for future research.

The Role of Functional Orthoses in Altering Foot Kinematics

The functional anatomy of the foot is highly complex due to the number of structures present, the interdependence between functional units and the requirements for precisely timed activities. The effect of foot orthoses on the movement of the foot is not fully understood as current multi-segment models have a number of limitations: in-shoe measurements, skin movement artefact and segmental variability. The results in this, and a growing body of related studies do not support the theory that functional foot orthoses systematically modify foot motions. These studies do however have limitations of relatively small size and many have lacked comparator groups. New models that measure the kinematics of individual bones such as the Anybody Glasgow-Maastricht foot model, may provide insights into individual bone movements, however this model is still in the development

stage and requires CT imaging to define the bone morphology precluding its use in large samples or in patient populations. Future studies of foot kinematics are needed that include clinical cohorts with a control group comparison and which are adequately powered to allow stratification to account for the large amounts of between and within-person variability. The feasibility of a large randomised controlled trial of foot orthoses in people with OA-related midfoot pain, is being planned currently, and includes a gait sub study to enable better understand of the variability in the response of foot motions to foot orthoses in larger numbers of patients.

The Role of Functional Orthoses in Altering Foot Forces

The results of this thesis support the need for future studies to examine the role of functional foot orthoses in altering systematically the pattern of foot forces. Experimental *in-vitro* studies are highly invasive and are not applicable to clinical studies using patients. While not perfect, imaging studies offer a surrogate solution that can use non-invasive techniques. Magnetic resonance imaging of bone pathology may be a method that can be applied in clinical setting to understand how bone stress can be modified. Using imaging to map internal bone movement using co-registration and modelling is one application that has yet to be applied in the foot [401]. These techniques are being developed and applied in conjunction with FE models and biomechanical models. New modelling techniques in the foot that use imaging (MR and CT) to scale the bones of the foot coupled with multiple skin-mounted reflective markers may allow better motion capture of all the 26 bones of the foot and the integration with force data [402]. The application of such models may allow a non-invasive estimation of bone forces, although this will remain limited to modelling rather than direct measurement. Patient specific FE models using imaging may be a future direction to investigate the predictive capacity to understand if changes in BML patterns reflect changes in bones forces. Further studies are needed however, to examine the internal and external validity of these emerging co-registration models as motion capture technology still relies mainly on the

precision and reliability of skin-mounted markers; a well recognised limitations of this approach.

The Role of Functional Orthoses in Altering Bone Physiology

The results of this study support the role of functional foot orthoses in modifying patterns of bone stress (as measured by BML volume). The functional foot orthoses intervention improved outcomes in participants with foot pain and BMLs associated with: i) Bone marrow oedema syndrome, ii) Traumatic BMLs, iii) OA-associated BMLs (not established radiographic foot OA). Although the focus of this thesis was to examine the mechanism of action of foot orthoses on bone stress (as measured by volumes of BMLs), the potential mechanism of functional orthoses to modify pathology requires further research. Further work examining the underlying pathology of bone marrow lesions using, for example, proton magnetic resonance spectroscopy, high-resolution computed tomography or single-photon emission computed tomography, may offer interesting insights into bone activity and trabecular micro-fracture within the spectrum of bone pathology. Given the results in this thesis, further work to examine the role of foot orthoses in modifying the course of foot diseases associated with altered bone physiology are warranted. Future clinical research (a randomised controlled trial with imaging outcomes) is underway to examine the efficacy functional foot orthoses to modify foot pain and localised bone marrow lesions in OA of the midfoot, with the aim of targeting bone disease in OA.

Quantification of BML Measurement

In this thesis the challenges of BML segmentation and measurement were discussed and were addressed in part. Further research is now needed to develop and validate some of the BML signal segmentation and quantification techniques developed in this thesis. Application of the subtraction technique once a bone has been segmented could be developed into an automated approach using signal gradients. In future this may allow the wider use of MR imaging as an outcome measure in clinical and experimental studies, based on standardised protocols and providing

estimates of BML volumes that can be better compared between groups and between studies. Validation of these methods alongside traditional scoring approaches are being considered in the next stage of research in midfoot OA, with the aim of applying interval bones scores (such as those developed in rheumatoid arthritis). Further work comparing low field extremity 0.2T MRI and higher strength 3T images is being planned, applying semi-quantitative scoring and/or segmentation measurements to understand the clinical application of extremity MR imaging of the foot in a patient population.

6.6 Conclusions

Functional foot orthoses are widely prescribed to relieve foot pain. The mechanism of action through which orthoses modify painful foot symptoms is not however, well understood. The work in this thesis explored the role of functional foot orthoses in altering patterns of foot pain, foot impairment, bone stress and foot kinematics. Bone marrow lesion patterns quantified on MR imaging was proposed as a surrogate measure of bone stress in the foot. A reliable method of bone segmentation and BML signal was developed and applied in this thesis. Intervention using functional foot orthoses (for three months) reduced foot pain and modified bone stress in a systematic pattern compared to a control insole. There was no systematic change in foot kinematics associated with wearing either the functional orthoses or cushioning insole in this study. This work adds further evidence to the paradigm that the mechanism of action of functional orthoses is through alteration of internal distribution of force rather than influencing magnitudes of motion. Functional foot orthoses appear to have the potential to reduce foot pain and bone stress in the medial midfoot bones and further work is now required to explore this formally in larger stratified samples, using randomised controlled trial methodology.

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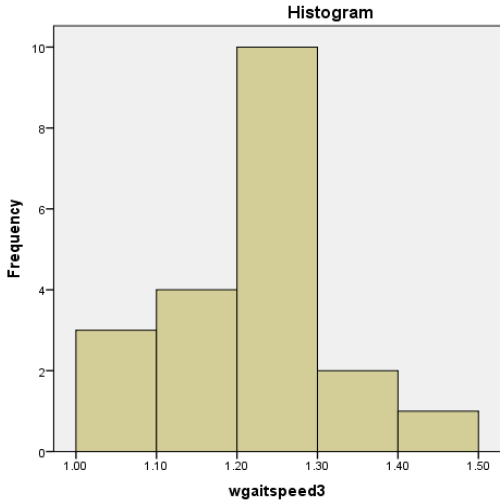
Appendix A:
Histograms of Gait Variables

Distribution graphs for gait analyses were plotted for the 20 participants and the variance and spread of data visually examined for homogeneity in a select number of variables. A selection of three gait variables was chosen to examine the distribution of data out of the possible of 27 gait variables (in all four conditions this would mean a total of 108 histograms). These three variables, walking speed, maximum hindfoot frontal plane motion and total hindfoot sagittal ROM, were chosen as temporal and hindfoot kinematics are published widely in the literature and have homogeneity in larger sample sizes. Histograms for all three variables were plotted for two conditions (1- shod follow-up, 2- insole follow-up). The histograms shown in Figures A1, A2 and A3 displayed some central tendency, however due to the size of the groups, the data rarely showed any or equally tailing, with the data clustering around the central point representing kurtosis in each these four trials for each variable.

Figure A1: Histograms for walking speed for each condition

1 Shod Follow-up	2 Insole Follow-up



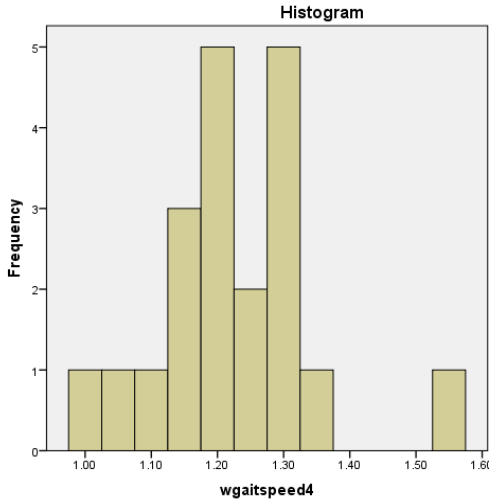
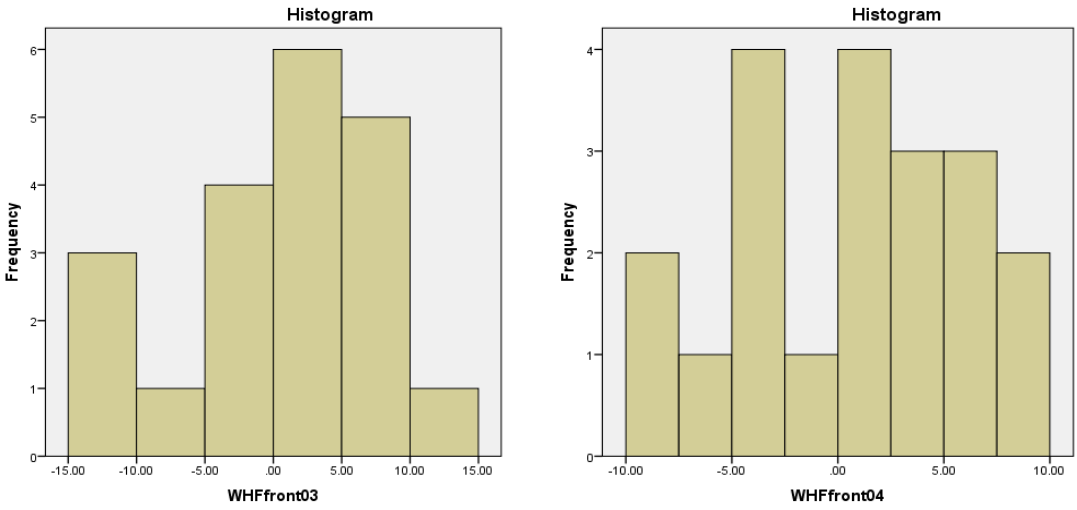


Figure A2: Histograms for maximum hindfoot eversion for each condition

3 Shod Follow-up	4 Insole Follow-up



Due to the small sample of participants in this data set, the distribution (in the three examples of temporal and kinematic gait) was heterogeneous. On the basis of this initial exploration of the data, descriptive statistics rather than inferential statistics were utilised, comparing the median and range of the data in the total group (20 participants) and per insole group (10 participants each group).

Figure A3: Histograms for hindfoot sagittal range of motion for each condition

1 Shod Follow-up	2 Insole Follow-up