METACARPAL RADIOGRAPHIC INDICES IN THE ASSESSMENT OF BONE STRENGTH AND FRACTURE RISK

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THE AUTHOR

The author is currently a Consultant Rheumatologist in the Department of Rheumatology, NHS Bolton, Bolton, Greater Manchester. The work towards this thesis was undertaken when he was a Clinical Research Fellow at the University of Sheffield while on 'out-of-programme' leave from the Manchester Rheumatology Specialist Registrar Rotation, Greater Manchester.

STATEMENT OF ATTRIBUTION

The contributions to the various projects of this thesis were as follows:

Chapter 4: The baseline hand radiographs of the nested case-control cohort (from HIPS) were identified by me, and scanned on the Pronosco X-posure system by me.

Chapter 5: Linda Reaney, research nurse, WHO Collaborating Centre, had scanned the hand radiographs from the VOT cohort on the Pronosco X-posure system (before I started my fellowship).

Chapter 6: Linda Reaney, research nurse, WHO Collaborating Centre, had scanned the baseline hand radiographs from the HIPS cohort on the in-house SMCM system (before I started my fellowship).

Chapter 7: The DXR and SMCM cohorts were the same as those in Chapters 4&6, and had hand radiographs scanned as noted in chapter 4 and 6 above.

For all the projects, I transferred the above, unprocessed data from the original databases into the SPSS statistical package, and processed and analysed the data with Dr McCloskey's guidance where necessary. Other baseline and fracture data (including vertebral morphometry in VOT) were already available as previously inputted by dedicated research personnel for HIPS and VOT for the respective trials.

Sreekanth Vasireddy

ABSTRACTS PUBLISHED ARISING FROM THIS RESEARCH

1. Vasireddy S, Reaney L, Charlesworth D, Kanis JA, McCloskey EV. Effect of medical risk factors on DXA measurements and metacarpal radiographic indices. Rheumatology 2004; 43 (Suppl.2): ii56. **Poster presentation, BSR AGM, Edinburgh, April 2004.**

2. Vasireddy S, Bal S, Reaney L, McGurk C, Kanis J, McCloskey E. Metacarpal BMD and cortical index are significant predictors of hip fracture. J Bone Miner Res 2003; 18 (suppl. 2):S65. **Plenary poster presentation, ASBMR AGM, San Antonio – Oct 2003.**

3. Vasireddy S, Bal SK, Reaney L, Kanis JA, McCloskey EV. Semi-automated metacarpal morphometry (metacarpal cortical index) predicts fracture risk in elderly women. J Bone Miner Res 2003; 18(7):1374. **Poster presentation, Bone and Tooth Society Meeting, Sheffield, June 2003.**

4. Vasireddy S, Haigh C, Adams JE, Jalava T, McCloskey E. Digital x-ray radiogrammetry (DXR) of the metacarpals in the prediction of vertebral fracture and monitoring bone density in a study of clodronate therapy. Osteoporos Int 2003; 14 (Suppl 4): S6. **Oral communication at the 9th Bath Conference on Osteoporosis, June 2003.**

5. Vasireddy S, Cliffe J, Charlesworth DK, Jalava T, Kanis JA, McCloskey EV. Fracture incidence in elderly women with self-reported OA, RA, or

current corticosteroid use: analysis from the MRC HIPS study. Rheumatology 2003; 42 (Suppl): 112. **Poster presentation, BSR AGM, Manchester, April 2003.**

6. Vasireddy S, Haigh C, Reaney L, Adams J, Selby PL, Bal SK et al. Digital x-ray radiogrammetry indices, particularly MCI, can predict vertebral fracture risk in osteoporotic women. J Bone Miner Res 2002; 17 (suppl. 1):S186. **Poster presentation, ASBMR AGM, October 2002.**

SUMMARY OF THE THESIS

Osteoporotic fractures are associated with morbidity and increased mortality, and treating fractures is an increasing expenditure for national health systems. Targeting fracture preventative measures appropriately starts with finding those at risk of fracture, services for which can be expensive and poorly available. Metacarpal morphometry can potentially be an inexpensive and widely available method of skeletal strength assessment. In this study a semi-automated metacarpal morphometry (SMCM) technique and a fully automated digital x-ray radiogrammetry (DXR) technique were studied for fracture prediction ability.

DXR was studied in a nested case-control setting with hip fracture patients and controls (Hip fracture Prevention Study, HIPS), and DXR bone mineral density (BMD) and DXR metacarpal index (MCI) were found to predict hip fracture risk (odds ratio, OR 1.79 and 1.72 respectively for 1 standard deviation (SD) decrease in measurement). DXR was also studied in a prospective setting for vertebral fracture prediction (Vertebral Osteoporosis Trial), and DXR-BMD and DXR-MCI were found to predict vertebral fracture risk (OR 1.56 and 1.81 respectively). SMCM was studied in a prospective setting (HIPS), and average MCI of 6 metacarpals (AMCI) was found to predict all fracture risk and hip fracture risk (OR 1.30 and 1.42 respectively), but not clinical vertebral fracture risk. In all these settings however, hip, spinal and forearm DXA measures had similar or higher point estimates for the respective fracture risk predictions. There was a trend for disproportionately greater bone loss with age at the metacarpals by MCM measures, compared to hip or forearm DXA measures, especially when associated with other medical conditions such as rheumatoid arthritis.

Although MCM measures were not superior to DXA measures in fracture risk prediction, there may be a useful role for them in epidemiological studies or providing a clinical service where access to DXA is limited.

1 INTRODUCTION

The research towards this dissertation was conceived and undertaken between November 2001 and October 2003 at Sheffield, United Kingdom while I was a clinical research fellow at the University of Sheffield.

1.1 UNIVERSITY OF SHEFFIELD MEDICAL SCHOOL

The medical school traces its roots back to the Sheffield School of Medicine founded in 1828, which became part of the University College Sheffield founded in 1897. This eventually became the University of Sheffield following a Royal Charter granted in May 1905.

At present the Medical School has more than one thousand students training at various undergraduate and postgraduate levels. Following the 2008 Research Assessment Exercise, the government's independent Research Rating for the school is 5 - indicating that most of its research is of international standing, and all is of at least national importance, leading to the ranking of 11th out of 20 Russell Group medical schools.

The School's activities integrate teaching, research and the practice of medicine, in collaboration with the Primary and the Secondary care providers in the region. As such, several departments are clinically integrated with the Sheffield Teaching Hospitals NHS Foundation Trust. The two main hospital sites of the Trust in Sheffield are the Royal Hallamshire Hospital and the Northern General Hospital. Both these hospital sites also house several departments and laboratories affiliated to the medical school. Generally, these departments are integrated in such a

way with the clinical departments that they are not only involved in teaching and research, but also provide frontline clinical services.

1.2 SHEFFIELD METABOLIC BONE UNIT AND THE WORLD HEALTH ORGANISATION COLLABORATING CENTRE FOR METABOLIC BONE DISEASES

When this research was started in 2001, the WHO Collaborating Centre for Metabolic Bone Diseases (University of Sheffield, Director: Prof. John Kanis) was based in the Sheffield Metabolic Bone Unit at the Royal Hallamshire Hospital site. The research was undertaken under the supervision of Dr. Eugene McCloskey, who was at the time Senior Research Fellow affiliated to the WHO Collaborating Centre for Metabolic Bone Diseases.

The Centre had several University employees engaged in research, who simultaneously also provided a regional clinical service for patients attending for the diagnosis and management of osteoporosis and other metabolic bone diseases. Facilities included several scanners for assessment of bone, and full haematology and biochemistry laboratory facilities through the Hospital for the assessment of bone including bone turnover markers.

Scanning systems available at the Centre included dual-energy x-ray absorptiometry (for research and clinical use), ultrasound (for research), digital x-ray radiogrammetry (for research) and a semi-automated metacarpal morphometry system (for research).

At the time this research was started, a clinical service for osteoporosis and other metabolic bone diseases was also being provided from the Sorby Wing, Northern General Hospital site by the team led by Prof. Richard Eastell, head of the Academic Unit of Bone Metabolism, University of Sheffield.

1.3 METABOLIC BONE CENTRE, NORTHERN GENERAL HOSPITAL

A review of the osteoporosis clinical services for the region in 2002 resulted in a decision to merge the services delivered from the Royal Hallamshire Hospital and the Northern General Hospital sites in 2003.
Both clinical services, along with staff offices and the clinical research fellows' office, were moved to a newly refurbished block on the Northern General Hospital site in mid-2003.

1.4 CLINICAL RESEARCH FELLOWSHIP & DISSERTATION

Most of the work, including the analyses, for this research was performed when I was based at the Royal Hallamshire Hospital. During this time I also had twice weekly booked clinic lists towards subspecialist clinical training in bone medicine. Some of the final analyses and most of the writing up of the dissertation took place when I was based at the Northern General Hospital site. During this time I also gave medical support to the

Clinical Trials Unit of the Metabolic Bone Centre in recruiting patients etc, along with occasional clinical work.

All the main analyses from this research were submitted, accepted and presented at various national or international bone meetings, and published as abstracts in the relevant supplements as listed at the beginning of the dissertation.

The several analyses that comprise this work are grouped into four main projects. This thesis is organised into several chapters: background, leading on to the hypothesis and objectives; followed by description of the four projects; and ending in a final summary and overall conclusions. Although the background chapter is applicable to the whole thesis, each of the projects is also written up to be individually complete and independently read, incorporating an abstract and introduction relevant to that project. Where this has entailed repetition, every effort has been made to ensure that this is relevant and kept to a minimum.

"EndNote 5" software ((ISI ResearchSoft, Berkeley, USA; licensed by University of Sheffield) was used through out to incorporate references in the text and collate them in the 'References' chapter at the end of the dissertation.

2 BACKGROUND

2.1 NORMAL BONE AND OSTEOPOROSIS

The skeletal system is comprised of bone and cartilage, which are specialised connective tissues. It serves three main functions: integral to posture and locomotion; protection of vital organs and bone marrow; and a reserve of ions in calcium and phosphate metabolism essential for maintaining homeostasis.

2.1.1 NORMAL BONE ANATOMY

Bone can be classified in several ways depending on the aspect of bone that is being described or studied (Soames 1995). Developmentally, bone formation can happen in two ways: a) 'intramembranous', by direct transformation of condensed mesenchymal tissue or b) 'endochondral', preceded by a cartilage model which is later replaced by bone (Soames 1995). Based on shape, bones have been classified as: a) flat bones, eg. skull, pelvis and ribs; b) long (or tubular) bones, eg. long tubular bones of the limbs, and small tubular bones of the hands and feet, such as the phalanges, metacarpals, and metatarsals; and c) irregular bones, bones of the face and vertebral column. Other types are 'short' bones of the carpus and tarsus, and sesamoid and accessory bones (Soames 1995).

The 'intramembranous' development is typically seen in flat bones such as the skull. Although typically long bones are taught in medical school to be a result of 'endochondral' development, long bone development actually involves both types of processes (Baron 1999).

Gross inspection of a long tubular bone typically reveals the following structure: the epiphyses, which are the two wider extremities; the

diaphysis, a nearly cylindrical tube in the middle; and the metaphysis, a developmental zone between the epiphysis and diaphysis. In a longitudinal section, the outer layer of the bone is a thick dense layer of calcified tissue called the 'cortex' (compact bone), and this is thickest in the diaphysis enclosing the medullary cavity housing the bone marrow. The cortex becomes progressively thinner towards the metaphysis and epiphysis, with the internal space filled by a network of thin calcified trabeculae called 'trabecular bone' (cancellous bone). The bone is therefore in contact with soft tissues on two surfaces: an external or 'periosteal' surface, and an internal 'endosteal' surface, both of which are lined with osteogenic cell layers, the 'periosteum' and the 'endosteum' (Baron 1999).

2.1.2 NORMAL BONE HISTOLOGY

Bone is composed of a number of different types of cells embedded in a calcified matrix. The matrix consists of collagen fibres (type I, 90% of total protein) oriented in a preferential fashion in a ground substance primarily composed of glycoproteins and proteoglycans. Calcium hydroxyapatite crystals, in spindle or plate shapes are found on the collagen fibres, within them and in the ground substance usually oriented in the same direction as the collagen fibres (Soames 1995; Baron 1999).

The cell types include osteoprogenitor stromal cells which give rise to other bone cells, osteoblasts which lay down bone, osteocytes within bone, osteoclasts which erode it, and lining cells on bone surface. The osteoblast arises from the stromal cell, is a bone-lining cell and is responsible for the production of collagen and ground substance of the

matrix (Lian, Stein et al. 1999). The osteoclast is a giant multinucleated cell (4-20 nucleii), is a bone lining cell, and is responsible for bone resorption (Soames 1995; Baron 1999). Osteocytes are cells which were originally osteoblasts which became trapped in the bone matrix they produced but these cells are in contact through cell processes and gap junctions with other osteocytes and bone-lining cells including osteoblasts, through a network of thin canaliculi permeating the entire bone matrix. The actions of biomechanical forces on bone are sensed by this osteocyte syncytium within bone via the canalicular network and intercellular gap junctions (Baron 1999; Clarke 2008).

2.1.3 BONE PHYSIOLOGY AND REMODELLING

Osteoblasts are found in clusters of cuboidal cells along the bone surface, usually 100-400 cells per bone-forming site. A mature, active osteoblast secretes type I collagen and specialised bone matrix proteins as osteoid in the direction of the mineralising front of the issue. A number of hormones, cytokines and other polypeptide skeletal growth factors are involved in the regulation of bone formation by their complex actions on osteoprogenitor cells and osteoblasts (Lian, Stein et al. 1999; Caetano-Lopes, Canhao et al. 2007).

Osteoclasts are found singly or in clusters of up to 5 cells, in contact with a calcified bone surface in a bed of elliptic or fusiform spindle shaped lining cells. Activated osteoclasts actively synthesize and secrete lysosomal enzymes and metallo-proteinases into a sealed off compartment on the adjacent bone surface along with acidification of the compartment. The

low pH dissolves the crystals exposing the matrix, which allows the enzymes to degrade the matrix components (Baron 1999).

Osteoblasts also influence bone resorption through receptor activator of nuclear factor-kappaB (RANK) ligand (RANKL) that links to its receptor, RANK, on the surface of osteoclasts and osteoclast-precursor cells, inducing their differentiation and fusion. Osteoblasts secrete a soluble decoy receptor (osteoprotegerin, OPG) that blocks RANK/RANKL interaction by binding to RANKL and, thus, prevents osteoclast differentiation and activation. Therefore, the balance between RANKL and OPG determines the formation and activity of osteoclasts (Hsu, Lacey et al. 1999; Caetano-Lopes, Canhao et al. 2007).

Bone "remodelling" is a process involving the coordinated actions of osteoclasts, osteoblasts, osteocytes within the bone matrix and osteoblast-derived lining cells that cover the surface of bone resulting in the removal of old bone and synthesis of new bone, thereby maintaining the structural integrity and the dynamic nature of the skeleton. The process is accomplished by assembly of osteoclasts and osteoblasts into discrete temporary anatomic structures called basic multicellular units (BMUs) (Jilka 2003). Remodelling starts with signals that initiate osteoclast formation followed by osteoclast-mediated bone resorption, a reversal period, and then a period of bone matrix formation mediated by osteoblasts, followed by mineralisation of the matrix (Mundy 1999; Sims and Gooi 2008).

2.1.4 BONE EVOLUTION WITH AGE

During growth, bone modelling and continuous remodelling optimize strength, by depositing bone where it is needed, and minimize mass, by removing it from where it is not. Cortical bone forms around 85% of total bone in the body of an adult. In adulthood cortical bone is removed mainly by endosteal resorption and resorption within the haversian canals. The latter leads to increased porosity of the bone. However, periosteal bone formation continues throughout life resulting in the increase in diameter of cortical bone, which confers a geometric property of increased rigidity reducing the fragility of slenderness (Rubin and Rubin 1999; Seeman 2008). Cancellous bone comprises around 15% of the skeleton, and remodeling is considered to be subtly different to the process in cortical bone. Bone remodeling cells in cancellous bone are in intimate contact with the cells of the marrow cavity, which produce potent osteotropic cytokines. These can potentially affect remodeling in cancellous bone, while systemic osteotropic hormones such as parathyroid hormone and 1,25-dihydroxy vitamin D3 have been thought to affect the remodeling process to a greater extent in cortical bone (Mundy 1999).

The net mass of bone is maintained at a relatively stable level by bone remodelling in younger adults. However, this balance is disturbed as age progresses: cortical bone loss probably begins to occur after the age 40 years, with cancellous bone loss probably beginning somewhat earlier, with variable acceleration of the bone loss at the time of menopause (Mundy 1999; Martin and Seeman 2008; Seeman 2008).

2.1.5 OSTEOPOROSIS

When the imbalance in bone formation and resorption persists (either age related, or due to other conditions), the continuing bone loss eventually results in osteoporosis.

In 1993 a consensus conference defined osteoporosis as a metabolic bone disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk (Consensus Development Conference) (1993). In 2000 a National Institutes of Health (NIH) consensus development conference defined osteoporosis as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture (NIH Consensus Development Panel) (2001).

For purposes of demographics and prevalence estimates, the World Health Organisation (WHO) classified patients according to bone mineral density (BMD) values and published the information in 1994 (Kanis 1994). These reference ranges are based on population distributions and were not specifically developed for clinical decision-making in the treatment of individual patients. According to this classification, the general diagnostic categories are:

- *Normal:* BMD or bone mineral content (BMC) not more than 1 SD below the young adult mean (T-score above -1).
- *Osteopenia (or low bone mass):* BMD or BMC between 1 and 2.5 SD below young adult mean (T-score between -1 and -2.5).

- *Osteoporosis:* BMD or BMC 2.5 SD or more below the young adult mean (T-score at or below -2.5).
- *Severe osteoporosis (or established osteoporosis):* BMD or BMC 2.5 SD or more below the young adult mean in the presence of one or more fragility fractures.

Osteoporosis is the commonest metabolic bone disease in the UK and other developed countries. Osteoporotic fractures increase with age with hip fractures showing a rising incidence in the 70s, vertebral fractures in the 60s and wrist fractures in the 50s (Wasnich 1999). In this setting, understanding the issues surrounding bone strength and fracture risk have become subjects of interest for study and research, with the eventual objective that better understanding will lead to better preventative and treatment strategies for reducing fracture risk.

2.2 BONE STRENGTH AND FRACTURE RISK

Bone strength and risk of fracture (or ultimate failure of bone) have an inverse relationship: the lower the bone strength, the higher the risk of the bone failing under a given stress or strain (Rubin and Rubin 1999). It might therefore be assumed that the understanding of bone strength can give insights into fracture risk and vice-versa. However, in a clinical setting, the relationship may not be so straightforward, and issues affecting bone strength may not be the only factors influencing fracture risk. Conversely, issues affecting fracture risk may not all be relevant to the determination of bone strength. Nevertheless, modification of bone strength remains the

main objective in identifying or designing interventions to reduce fracture risk (Friedman 2006).

2.2.1 DETERMINANTS OF BONE STRENGTH

Traditionally, BMD measurement has been used as a surrogate marker for prediction of fracture risk and to decide on treatment. However, there has been long recognition that BMD measurements only account for 60-70% of the variation in bone strength. Bone strength is now known to be determined by its material and structural properties such as bone geometry, cortical thickness and porosity, trabecular bone morphology, and intrinsic properties of bony tissue (Ammann and Rizzoli 2003). This realization has led to the development of the concept of bone quality which can be understood as an umbrella term that describes the set of characteristics that influence bone strength and explains the interrelationships of these characteristics (Felsenberg and Boonen 2005). Currently therefore, bone strength can be thought of as a composite expression of bone mineral density, bone quality, and bone geometry with respect to biomechanics.

2.2.2 GENETIC AND CLINICAL FACTORS

Although bone quality is a relatively recent concept, several genetic and clinical factors have already been known to influence BMD and fracture risk. For example, age, gender, ethnicity, family history (particularly maternal hip fracture), smoking, alcohol consumption etc have been shown to be risk factors for fracture (Wasnich 1999). Some of these factors not only influence BMD, but are also known to influence fracture

risk independent of BMD. Several of these factors have been incorporated in a tool for fracture risk assessment (FRAX™) (Kanis, Burlet et al. 2008; Kanis, Johnell et al. 2008). Extra-skeletal factors can also influence fracture risk: for example, falls risk has been shown to be associated with fracture risk independent of BMD (Sambrook, Cameron et al. 2007; Kayan, Johansson et al. 2009).

2.2.3 MEDICAL HISTORY

In addition to the factors mentioned above, several medical conditions or history also have an influence on BMD and fracture risk. Similar to the factors discussed above, these factors may influence fracture risk through their effect on BMD and/or independently. Rheumatoid arthritis has been shown to be associated with reduced BMD and increased fracture risk (Coulson, Reed et al. 2009). Glucocorticoid treatment in the medium to long term has long been known to reduce BMD and also be a risk factor for fracture independently of the BMD reduction, probably through effects on bone quality (van Staa, Geusens et al. 2005; van Staa 2006; Civitelli and Ziambaras 2008). On the other hand, a history of osteoarthritis is associated with increased BMD at the spine and hip and reduced fracture risk (Liu, Peacock et al. 1997; Blain, Chavassieux et al. 2008; Roux, Fechtenbaum et al. 2008). Patients who have been affected by stroke and Parkinson's disease have been shown to be at risk of decreasing BMD and increased fracture risk (Poole, Reeve et al. 2002; Sato, Metoki et al. 2003; Watanabe 2004; Bezza, Ouzzif et al. 2008). Some of the increased fracture risk associated with these neurological conditions is independent of BMD and has been attributed to increased falls risk. Both type 1 and

type 2 diabetes mellitus have been shown to be associated with increased fracture risk, although type 2 diabetes could be associated with increased BMD (Hofbauer, Brueck et al. 2007; Sta Romana and Li-Yu 2007; Rakel, Sheehy et al. 2008). The increased fracture risk in type 2 diabetes therefore has been thought of as a reflection of bone quality and/or extra-skeletal factors such as increased falls risk (Hofbauer, Brueck et al. 2007; Rakel, Sheehy et al. 2008). Hyperthyroidism has been shown to be associated with decreased BMD and increased fracture risk (Linde and Friis 1979; Burman 1997; Bassett, O'Shea et al. 2007). There is little published on the effect of adult onset hypothyroidism on BMD and fracture risk in the literature. However, in a small study, despite treatment with thyroxine, young women with congenital hypothyroidism have been shown to have decreased BMD compared to controls (Kempers, Vulsma et al. 2006).

2.2.4 AREAL PROPERTIES OF BONE

Issues of bone strength and fracture risk can also be viewed from the standpoint of the biomechanical properties of bone. Several interdependent concepts have been studied in this respect to elucidate the structural risks associated with metabolic bone diseases. Broadly, as a biomechanical concept, bone strength can be thought of as a composite of the material properties and the areal properties of bone (Rubin and Rubin 1999).

Material properties such as stiffness and toughness determine the structural quality of the bone. They are determined by the collagen and mineral matrix components and the organisation of the micro-architecture.

In osteoporosis, the collagen and mineral components are affected influencing the material properties of bone (Burr 2002).

Areal properties such as size, density, architecture and geometry are as important as material properties in determining bone strength and risk of skeletal failure i.e., fracture. In addition to density, traditionally measured as BMD, size and bone geometry may have a role in the higher fracture incidence in women (Looker, Beck et al. 2001). In an analysis from the Study of Osteoporotic Fractures, femur geometry variables were found to be predictive of hip fracture (Kaptoge, Beck et al. 2008). Geometric properties of bone can not only have an association with fracture risk, but interestingly, may also have a heritable basis. A recent study which included geometric properties concluded that both men and women with a positive maternal history of osteoporosis may be at greater risk of femur neck fracture owing to thinner cortices and lower BMC, which in turn results in potentially greater cortical instability at this skeletal site (Looker and Beck 2004).

2.3 ASSESSMENT OF FRACTURE RISK

In addition to the costs and morbidity associated with osteoporotic fractures, there is a recognised association with increased mortality (Johnell, Kanis et al. 2004). Assessment of fracture risk has therefore become very important for accurate identification of individuals to target preventative strategies at both an individual and community level. Hip and vertebral fractures are the two most studied osteoporotic fracture types in this respect.

2.3.1 HIP FRACTURES

Hip fracture is the most serious outcome of osteoporosis, and this is becoming more frequent than before because the world's population is ageing and because the frequency of hip fractures is increasing by 1-3% per year in most areas of the world (Cummings and Melton 2002). Hip fracture is also the costliest to treat. In a recent study of the costs of non-vertebral fractures, the most costly non-vertebral fracture sites were, in decreasing order, hip, femur, and tibia fractures (Ohsfeldt, Borisov et al. 2006). BMD measurement is the traditionally used to assess hip fracture risk, and awareness has improved that an incident hip fracture can be predictive of future fracture risk. Despite this, even after hip fracture BMD measurement uptake has been found to be poor (Murray, McQuillan et al. 2005). In addition to BMD, the shape and structure of the proximal femur also help to determine how forces act in the hip in a fall and their measurement can aid the prediction of hip fracture (Gregory and Aspden 2008). Therefore, it is possible that methods of assessing hip fracture risk other than BMD may improve on uptake of measurement and therefore intervention.

2.3.2 VERTEBRAL FRACTURES

Vertebral fracture is the most common osteoporotic fracture (Wasnich 1996). Even as early as the 1980s, an increase in the incidence and prevalence of vertebral fractures compared to the 1950s was documented (Bengner, Johnell et al. 1988). In addition to the morbidity associated with clinical fractures, vertebral fractures in general have also been found to be associated with increased mortality. In an analysis from the Study of

Osteoporotic Fractures, women with radiographic evidence of vertebral fractures were found to have an increased mortality rate, particularly from pulmonary disease and cancer (Kado, Browner et al. 1999). However, vertebral fracture has been more difficult to define in clinical practice as the majority of vertebral fractures are silent (Ziegler, Scheidt-Nave et al. 1996; McKiernan 2009). While BMD measurement can predict vertebral fracture, prevalent vertebral fracture itself has been shown to be predictive of further future vertebral fracture (Ross, Genant et al. 1993; Lunt, O'Neill et al. 2003), and other osteoporotic fractures (McCloskey, Vasireddy et al. 2008). In this setting, identification of vertebral fracture itself has become important in improving fracture risk assessment and methods such as vertebral fracture assessment (VFA) have been studied with this objective (McCloskey, Vasireddy et al. 2008; Schousboe, Vokes et al. 2008). Both BMD measurement or VFA still require direct scanning or imageing of the vertebrae themselves on large devices limiting their accessibility, which leaves scope for development of smaller, portable devices or technologies to predict vertebral fracture risk by scanning or measuring bone fragility at more remote or peripheral sites.

2.3.3 MODALITIES OF SKELETAL STRENGTH MEASUREMENT AND THEIR LIMITATIONS

Several modalities have been developed to assess skeletal strength with varying degrees of success in predicting fracture risk. Some of the main ones are discussed below. Each method, based on the underlying technology, aims to measure one or more aspects of bone strength discussed above.

Dual-energy x-ray absorptiometry (DXA): The best documented single risk factor for fracture is BMD. DXA is widely regarded as the gold-standard technology for the measurement of BMD. However, BMD measured by DXA is an areal measure expressed in gram/cm^2 and not a volumetric measure. It does not discriminate between density differences caused by volume changes, and those caused by changes in mineralization. As such, it does not fully reflect material property changes in ageing or osteoporotic bone that contribute to fracture risk (Nielsen 2000; Burr 2002). It has been found that systematic inaccuracies in DXA BMD measurements may exceed +/-20% at typical in vivo lumbar vertebral sites. These inaccuracies have been thought to arise principally from absorptiometric disparities between the intra- and extraosseous soft tissues within the DXA scan region of interest (Bolotin 2001). There are also non-technical limitations. DXA is one of the more expensive of current technologies in terms of capital costs and running costs. The equipment is large and installation needs to meet certain specifications. Because of the size, lack of portability is an issue (Miller and Bonnick 1999).

Quantitative computed tomography (QCT): QCT has been an established technique for measuring BMD in the axial spine and peripheral skeleton (forearm, tibia). However, QCT availability and utilisation is less common than DXA in the UK. Although QCT can determine in three dimensions the true volumetric density (mg/cm^3) of trabecular or cortical bone at any skeletal site, because of the high responsiveness of spinal trabecular bone and its importance for vertebral strength, QCT has been principally employed to determine trabecular BMD in the vertebral body

and assessment of vertebral fracture risk (Guglielmi and Lang 2002). Interestingly, in a recent study of postmenopausal women with osteoporosis induced by long-term glucocorticoid treatment who were also receiving hormone replacement therapy (HRT), BMD of the lumbar spine as measured by QCT, but not DXA, was found to be an independent predictor of vertebral fractures (Rehman, Lang et al. 2002). Like DXA, QCT also has limitations in terms of high capital costs and running costs, large size and lack of portability.

Quantitative ultrasound (QUS): Ultrasound devices routinely measure two parameters: broadband ultrasound attenuation (BUA) and speed of sound (SOS). Several QUS devices are now available for clinical use for measuring various parameters at skeletal sites with different contents of trabecular and cortical bone. Small size and portability are a major attraction of these devices. QUS has been shown to detect bone fragility and predict fracture risk as well as DXA. There is in fact evidence documenting the ability of QUS to predict osteoporotic fracture risk and to give further BMD-independent information on bone (Malavolta, Mule et al. 2004). However, diagnosis of osteoporosis by QUS remains contentious, but the problems are thought to be due more to the limitations of the present T-scores rather than to the technique (Gonnelli and Cepollaro 2002). In addition, standardization of instruments is still one of the major limitations of this technique at present (Malavolta, Mule et al. 2004).

Other modalities: Several other modalities and devices have been developed, most of which aim to measure bone strength or fragility at peripheral sites and predict fracture risk. Their main strengths are lower

capital costs and running costs, smaller size which means no elaborate installation requirements and allowing portability. However, these are relatively new on the market, and there is limited information regarding their clinical applications, particularly with respect to their performance in predicting fracture risk compared to established technologies discussed above. Technologies include peripheral instantaneous X-ray imager (PIXI, not manufactured at present) (Lawrenson, Nicholls et al. 2006); peripheral quantitative computed tomography (pQCT) (Sawada, Morishige et al. 2007); and digital x-ray radiogrammetry (DXR) which is based on morphometry of metacarpals.

2.4 THE METACARPALS AND METACARPAL MORPHOMETRY

The primary function of the forelimb is locomotion in most mammals. The forelimb has been successfully adapted in mammals of all sizes for the various environments they inhabit: terrestrial, arboreal, aquatic, and airborne. In primates, the forelimbs have developed such that speed and stamina have been sacrificed for an increased range of movement, which in turn has provided increased manual dexterity. This is best developed in humans, man being one of only a few mammals who are truly bipedal and for whom the forelimb serves almost no locomotive function (Gough-Palmer, Maclachlan et al. 2008). Another feature not seen in the other primates that serves to improve fine manipulation is a more progressive and uniform decrease in the size of the hand bones from proximal to

distal: although the metacarpals are smaller than those of the chimpanzee, the terminal phalanges and apical tufts are comparatively large (Susman 1979; Gough-Palmer, Maclachlan et al. 2008).

2.4.1 METACARPAL ANATOMY

The five metacarpals in each hand are numbered in lateromedial order, i.e., the thumb metacarpal is labelled I and the little finger metacarpal is labelled V. They are small tubular bones, with a distal head, shaft and expanded base. Their rounded heads articulate with the proximal phalanges and form the knuckles. At their bases, they articulate with the distal carpal row and each other except I and II. The shafts have longitudinally concave palmar surfaces, forming hollows for the palmar muscles. There is a distal triangular area on the dorsal surface which continues proximally as a round ridge. The medial four metacarpals diverge somewhat, radiating gently proximodistally. The first metacarpal is more anterior and rotated medially on its axis through 90 degrees, allowing the thumb to flex medially across the palm and rotated into opposition with each finger. The second metacarpal has the longest shaft which is prismatic in section and longitudinally curved, convex dorsally and concave towards the palm (Soames 1995). Due to similarities in size and anatomical appearance, in terms of comparative anatomy, human metacarpals II-V form two sets composed of II-III, and IV-V (Susman 1979). However, the shafts of both the third and fourth metacarpals are similar to the shaft of the second metacarpal (Soames 1995).

2.4.2 TUBULAR BONE GEOMETRY AND BIOMECHANICS

The biomechanical properties of tubular bone can be thought of in terms of the properties of a cylindrical object. The ability of a cylinder to resist bending and/or torsion is strongly dependent on the distance of the material relative to the center of the cylinder. For the same cross sectional area, therefore, a cylinder with a larger radius or diameter will demonstrate a greater resistance compared to one with a smaller radius/diameter (Rubin and Rubin 1999).

The mechanical strength of a tubular bone in bending can be estimated by the area moment of inertia (I) = 1/4 x pi x (R^4 - r^4) (where R= external radius, and r= internal radius). Mechanical strength of bone can therefore be considered as dissociated from bone density, since radiological density is different from inertia. When the cross-sectional area is constant (C = R^2 - r^2) in this equation, moment of inertia can be expressed by the equation of (I) = 1/4 x pi x ($2Cr^2$ + C^2). Moment of inertia increases with increases of the external and internal radii (Chigira 1996). Subtle changes in the cross-sectional geometry of a bone will therefore contribute significantly to the bone's structural properties. In this context, subtle increases in the radii of tubular bones achieved through periosteal expansion, may to a certain degree compensate for the bone loss and cortical thinning that parallels the ageing process, and these changes have therefore been considered an adaptation process to ageing (Chigira 1996; Rubin and Rubin 1999).

As metacarpals are small tubular bones, these biomechanical properties apply to them as well. Geometric measures of metacarpals, therefore, can offer a way of quantifying mechanical strength and risk of fracture.

2.4.3 TRADITIONAL METACARPAL MORPHOMETRY

The skeletal system is metabolically active and bone and mineral metabolism, mainly through calcium and phosphate levels in the extracellular compartment, plays a vital role in maintenance of the normal homeostasis. This is regulated both by local hormonal influences (eg. Cytokines) and by systemic hormones (eg. Parathyroid hormone) (Mundy 1999). As the whole skeletal system is in contact with the extracelluar compartment, all bones are subject, to greater or lesser extent, to the same systemic factors influencing bone strength. Therefore, in theory, bone strength measurement at any one site is also likely to reflect bone strength at other sites in general, and hence fracture risk. Peripheral bones such as metacarpals are small and easily accessible to measurement, and it would be cost-effective and cost saving if measurement of bone strength or fracture risk at the metacarpals can be shown to predict fracture risk at significant sites such as the hip and spine. Barnett and Nordin first proposed morphometric measurements of the midshaft of the second metacarpal to diagnose osteoporosis (Barnett and Nordin 1960). Measurements were performed on posteroanterior radiographs of the hand using a ruler and callipers, or with a graduated magnifying glass, of the total and medullary widths (Figure 2.1). The measurement originally called the "hand score", and later the "Barnett-Nordin index" or the metacarpal cortical index (MCI), was expressed as the cortical thickness of the radial side plus the cortical thickness of the ulnar side divided by the outer diameter of the bone expressed as a ratio

(Figure 2.2). In other words, MCI = radial + ulnar cortical thickness/total bone width (Nielsen 2001).

Figure 2.1. Traditional metacarpal morphometry using Vernier callipers.

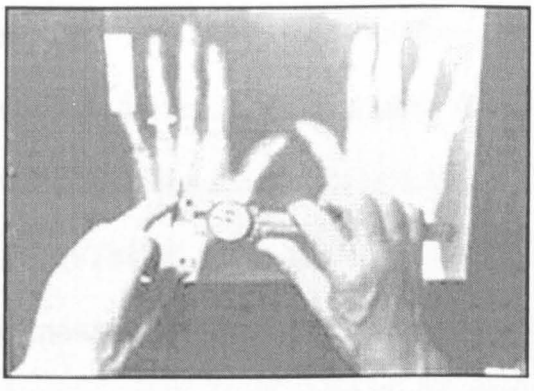
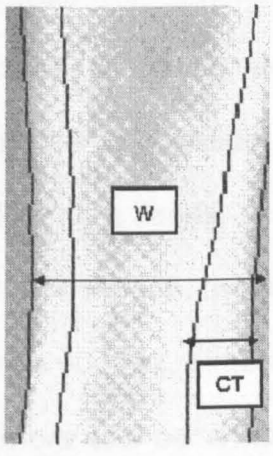


Figure 2.2. Schematic of the metacarpal mid-shaft on a radiograph illustrating the concepts of cortical thickness (CT) and total bone width (W) measurement.



Other metacarpal measures that can also been calculated from the same measurements of total and medullary widths or cortical thicknesses

(medullary width = total bone width – [ulnar+radial cortical thickness]), are the cortical area (CA) and the area ratio. In this measure, the metacarpals are regarded as cylindrical, and the cortical area (CA) is calculated as the difference between the total area (TA = π x (total width/2)^2), and the medullary area (MA = π x (medullary width/2) ^{2}), i.e. CA = TA – MA. The area ratio is expressed as the ratio of cortical area to the total area, i.e., area ratio = CA/TA. Both cortical area and area ratio have been used as metacarpal morphometry measures in different studies as measures to reflect bone strength (Wishart, Horowitz et al. 1993; Kiel, Hannan et al. 2001). As the basic measurements used in arriving at MCI and metacarpal area ratio are the same, they have been considered interchangeable and essentially synonymous (Nielsen 2001).

The second metacarpal was originally chosen because its variability of morphology and length was smaller than that of the other metacarpals (Nielsen 2001). In an analysis from the Baltimore Longitudinal Study of Ageing, radial cortical thickness of the second metacarpal was found to be 11-12% greater in men and 10-12% greater in women than ulnar cortical thickness in both the left and right hands. In men, radial cortex decreased linearly from age 40 to 89. For women, there was a sharp decline in radial thickness from age 50 to age 60 (Fox, Kimura et al. 1995).

Precision and accuracy errors can be an issue with manual techniques. One study showed that the intra-observer variability of traditional MCI measurement of a single metacarpal approximated 10% of the normal MCI (Naor, Di Segni et al. 1972). High variability among operators has also been reported (Nielsen 2001). However, counting six metacarpals (II – IV

both sides) in the same x-ray has been shown to reduce precision error to compare favourably with the precision of other densitometric techniques (Horsman and Simpson 1975).

Metacarpal bone loss might have little clinical relevance, if not related to bone loss at other bone sites, as metacarpal fractures are relatively rare and create modest treatment problems. A significant relationship between MCI and vertebral biconcavity in osteoporotic patients was reported as early as 1971 by Dequeker and colleagues, paving way for further studies (Dequeker, Franssens et al. 1971). Metacarpal morphometry was also subsequently shown to correlate well with bone density at the forearm and vertebral sites (Wishart, Horowitz et al. 1993).

2.4.4 SEMI-AUTOMATED MORPHOMETRY

Traditional metacarpal morphometry saw a decline in popularity with the development of more sophisticated technologies such as single energy x-ray absorptiometry (SXA) and subsequently DXA, and more recently ultrasound. However, availability of these newer technologies remains limited as discussed previously. While metacarpal morphometry has the potential to be widely available and incur low costs, the traditional radiogrammetry with the measurement of metacarpal cortical bone widths using fine needle callipers and hand radiographs is a tedious and time consuming task. This is a serious limitation to its widespread use. Therefore, efforts have been made since the 1990s to partially or fully automate the measurement process.

A semi-automated method called computed x-ray densitometry using a computed densitometric machine (Bonalyser, Teijin Ltd, Tokyo) was

reported showing good correlation (0.663) with lumbar BMD measured by DXA (Yamamoto, Yuu et al. 1994). In another study the same year, the method was shown to have low precision errors (coefficients of variation (CV) 0.2-1.2% for metacarpal BMD and 0.4-2.0% for MCI, respectively), with a more rapid analysis, within 3 minutes, comparing favourably with the previous methods (Matsumoto, Kushida et al. 1994). An analysis from the Hawaii Osteoporosis study reported another technique called computer assisted radiographic absorptiometry where metacarpal BMD measured from hand radiographs, and quantitative ultrasound (calcaneal BUA) were found to be similarly significant predictors of nonspine fracture, vertebral fracture, and overall fracture risk (Huang, Ross et al. 1998).

In Sheffield, an in-house semi-automated technique was also developed in the WHO Collaborating Centre. In this method, the hand radiograph was placed on a back-lit digitizing tablet and points were placed on the metacarpal using a click button cross-wire cursor to measure distances. For example, the distance between points A & B were measured by clicking on point A and moving the cursor over the digitising tablet to point B and clicking a second time. A software program was developed to automatically record the distance between the two clicks. During the measurement of length of the shaft, the technique included a facility for automated computation of the mid-point. At the midpoint of the shaft, the cursor was dragged along the outer (periosteal) and inner (endosteal) edge of the radial and ulnar cortices of the metacarpal, with multiple sampling of coordinates along the cortical edges with the 3 closest coordinates on each side of the midline being used to compute metacarpal

bone width and cortical thickness. The program algorithm allowed for a set sequence of clicks to record several measurements in sequence without any further operator input, with the captured measurements being automatically fed into an electronic database. MCI of the second metacarpal measured with this technique was found to correlate well (correlation coefficient 0.62) with MCI measured with the Bonalyzer, and also forearm and hip BMD, and a 1 standard deviation reduction in measurement was significantly associated with prevalent vertebral fracture risk similar to forearm BMD and Bonalyzer, but not as good as hip BMD (Dey, McCloskey et al. 2000). However, no studies have been published regarding the ability of these semi-automated techniques in predicting future fracture risk, i.e., relationship with incident fracture on longitudinal follow-up.

2.4.5 DIGITAL X-RAY RADIOGRAMMETRY (DXR)

Although semi-automated methods have been developed as above, full automation of the measurement process in metacarpal morphometry has been attempted aiming to make it simpler, faster and more precise. Fully automating the process also makes possible the measurement of multiple metacarpals at the same time and multiple sites from each metacarpal, with the assumption that a summative measurement is likely to be more reflective of bone strength and therefore more predictive of fracture risk compared to a single, point measurement from a single site of one or more metacarpals.

Thodberg and Rosholm described the development of digital x-ray radiogrammetry (DXR) technology, and they identified the main element of

this method as the reconstruction of the metacarpals, more specifically the metacarpal shafts, in a computerized electronic image using the concept of the active shape model (ASM) (Thodberg and Rosholm 2003).

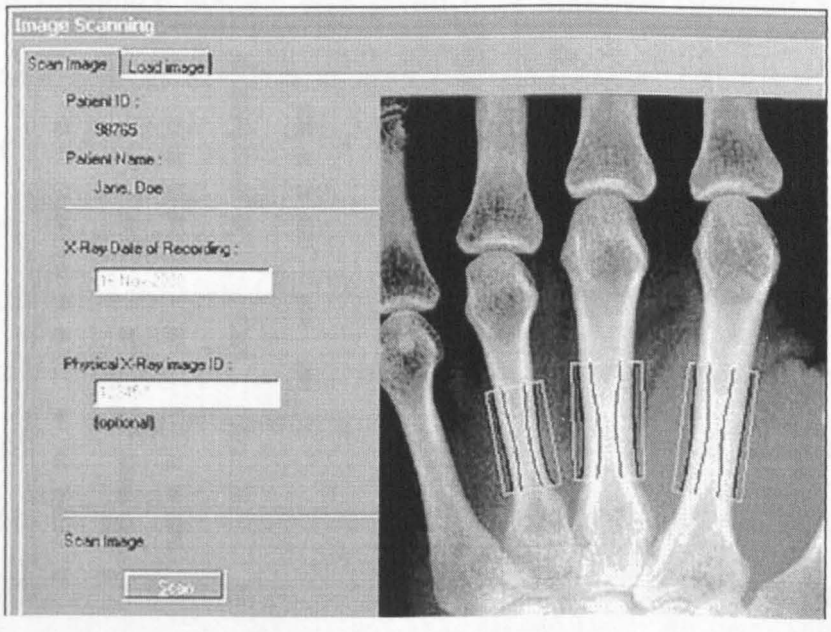
ASM was described in the mid 1990s as a method of model-based vision and image interpretation, specifically aiming at situations where objects of the same class are not identical, and where recognizing and locating by rigid models is inappropriate: for example, medical applications where the shape of organs can vary considerably through time, and between individuals. The method involves building models by learning patterns of variability from a training set of correctly annotated images, allowing the ASMs to deform to fit the data only in ways consistent with the training set (Cootes, Taylor et al. 1995).

Thodberg and Rosholm reported that the standard ASM was unable to locate the metacarpal shafts in the direction along the bones. Therefore, they reported that ASM was extended with a translation operator, which solved the problem (Thodberg and Rosholm 2003). The ASM works by detailed edge finding of cortex, and this was achieved by dynamic programming to determine average cortical thickness (*t*), and average bone width (*W*).

DXR was developed commercially for metacarpal morphometry and marketed as the Pronosco X-Posure System (Sectra Pronosco, Denmark). The process involves digitising of a single plain radiograph of the hand using a high-resolution flat-bed scanner, followed by a completely automated image analysis of the digitised image. The system itself checked the quality of the scanned images and interrupted the

examination in case of inadequate quality. The ASM algorithm was adapted to find the diaphysis of the middle three metacarpals in the hand, following which regions of interest (ROI) were determined automatically for each metacarpal (Jorgensen, Andersen et al. 2000; Thodberg and Rosholm 2003). The algorithm placed the three ROIs in a coupled fashion by sliding them in a partly fixed configuration along the bone shafts to a position identified by the minimum combined bone width. The heights of the ROIs were fixed to 2.0 cm, 1.8 cm, and 1.6 cm for the 2nd, 3rd, and 4th metacarpal respectively. The analysed images and their ROIs were displayed on the computer monitor (Figure 2.3).

Figure 2.3. Computer screen image of DXR regions of interest in the 2nd to 4th metacarpals.



In version 2.0, the BMD was calculated using the cylindrical-tube bone model, DXR-BMD = $c\,\pi\,t\,(1 - t/W)$, where c is a constant representing the

average *mineral mass / unit volume* of bone (Rosholm, Hyldstrup et al. 2001; Thodberg and Rosholm 2003). The constant c was determined so that DXR–BMD on the average was equal to that of the mid–distal forearm region measured with the Hologic QDR 2000 densitometer (Hologic Inc., Bedford, USA) (Böttcher, Pfeil et al. 2006). The MCI of each metacarpal was calculated using the traditional principle as described, but using the average cortical thickness *t,* and bone width *W,* as MCI = *2t / W.* DXR-MCI was calculated as the weighted average of the three metacarpals as follows: $(MCI_2+MCI_3+0.5MCI_4)$ / 2.5. The fourth metacarpal was given a lower weighting in calculating the average cortical thickness and bone width for computing both indices due to a lower precision in measuring the fourth metacarpal "and an inferior clinical importance" (Böttcher, Pfeil et al. 2006).

Since the Pronosco system was given FDA approval (Version 1 in 1999 and Version 2.0 in 2000) and was marketed, DXR has been used in research resulting in some further published studies. For example, DXR has been found to be an effective and sensitive modality for monitoring periarticular osteoporosis in hands, which is among the earliest features of rheumatoid arthritis, preceding bone erosions (Jensen, Klarlund et al. 2004; Bottcher, Pfeil et al. 2006). However, there have been only two studies published with respect to fracture prediction ability. In an analysis from the Study of Osteoporotic Fractures, DXR was shown to predict hip, vertebral and wrist fractures in elderly women (Bouxsein, Palermo et al. 2002). In a subgroup analysis from the third Copenhagen City Heart Study, DXR-BMD was found to be predictive of humeral, vertebral, wrist

and hip fractures in decreasing order (Bach-Mortensen, Hyldstrup et al. 2006).

Interestingly, before the era of DXR, in a study of another automated computerized radiogrammetry of the second metacarpal compared with forearm and spine absorptiometry, Deriquebourg and colleagues commented that radiogrammetry was by no means the best method to evaluate bone mass; that its automation did not improve the correlation with osteodensitometric values. They felt that radiogrammetry was still of interest in mass screening, particularly when other more expensive techniques or methods of bone mass measurement are not readily available, and that automation just makes it simpler, faster, and more precise, rendering its use easier on a larger scale (Derisquebourg, Dubois et al. 1994).

In this context, as discussed above, there is limited information published regarding bone strength assessment and, particularly, relevant fracture predictive ability for both semi-automated (Dey, McCloskey et al. 2000) and fully automated metacarpal morphometry techniques (Bouxsein, Palermo et al. 2002; Bach-Mortensen, Hyldstrup et al. 2006) compared to the more extensive information published about other established modalities such as DXA. There is, therefore, a need for further robust data and analyses in this respect to assess whether metacarpal radiographic indices could be recommended for use on a wider scale and as investigation of choice.

3 HYPOTHESIS AND OBJECTIVES

The various projects contributing to this dissertation were driven by the following hypothesis and objectives.

3.1 HYPOTHESIS

Metacarpal radiographic indices:

- are able to predict future fracture risk
- are comparable to other established skeletal measures in their ability to assess skeletal strength and predict future fractures.

3.2 OBJECTIVES

The objectives of the various projects, therefore, were to evaluate:

- the ability of semi- and fully-automated MCM techniques to predict future (incident) hip, vertebral and other fractures.
- the fracture risk prediction of MCM in comparison to established techniques such as DXA.
- the correlation between various MCM measures, and between MCM measures and DXA measurements at other sites.
- the interaction between MCM and a history medical risk factors.

4 DXR IN THE PREDICTION OF HIP FRACTURES

4.1 ABSTRACT

Introduction: Hip fracture is the most expensive osteoporotic fracture type to manage. A combination of assessments of skeletal strength and extra-skeletal risk factors optimises the identification of future fracture risk. While hip bone mineral density (BMD) remains the reference standard, other more widely applicable skeletal measures may be of value. In this study the ability of metacarpal BMD and metacarpal cortical index (MCI) measured by digital x-ray radiogrammetry (DXR) were compared to that of hip BMD to predict incident hip fractures.

Methods: A nested case-control design was used within the context of a large prospective study cohort comprising 5212 women aged 75 years or older (mean 80 years, range 75-100) enrolled to a double-blind placebo-controlled study of the bisphosphonate, clodronate (Bonefos®). This analysis included 153 women who sustained incident hip fractures and 532 randomly selected controls who remained free of hip fracture during a median follow-up of 4 years. Baseline BMD at the total hip and distal forearm were measured by DXA (Hologic QDR4500 and Osteometer DTX200 respectively). Bilateral hand radiographs obtained at baseline were analysed using DXR to produce automated measures of metacarpal BMD (DXR-BMD) and DXR-MCI.

Results: The hip fracture group had significantly lower hip BMD, forearm BMD and DXR indices at baseline than controls. There was no significant difference between the fracture and control groups with respect to clodronate treatment. In univariate logistic regression analysis, the odds ratios (OR, 95%CI) for hip fracture per 1SD decrease in DXR-BMD and

DXR-MCI of 1.79 (1.47-2.19, P<0.001) and 1.72 (1.41-2.11, P<0.001) respectively were similar to that of forearm BMD of 1.90 (1.55-2.34, P<0.001) while a similar decrease in total hip BMD demonstrated a larger gradient of risk of 2.33 (1.87-2.90, P<0.001). DXR indices remained significant predictors of hip fracture following adjustment for clinical predictors (age and body weight) (1.46, 1.17-1.81, and 1.43, 1.15-1.76, respectively) but were not independent of forearm BMD or hip BMD. Following adjustment for the clinical variables, the ORs for the DXR indices remained comparable to that of forearm BMD (1.51, 1.19-1.91) but was lower than that for total hip BMD (1.98, 1.56-2.50).

Conclusions: In this study DXR indices were found to be significant predictors of hip fracture independently of other extra-skeletal clinical risk factors. Hip BMD remained the strongest predictor of hip fracture. In the absence of access to DXA, metacarpal indices may prove useful skeletal measures for fracture prediction to include in the risk assessment of individuals.

4.2 INTRODUCTION

Osteoporosis and fragility fractures cause significant morbidity, and the principal underlying skeletal cause is reduced BMD. However, extra-skeletal risk factors also predispose to fracture occurrence. Therefore a combination of assessments of skeletal strength and extra-skeletal risk factors optimises the identification of future fracture risk.

Hip fracture is not only associated with significant morbidity but also mortality (Browner, Pressman et al. 1996; Johnell, Kanis et al. 2004). While single measures of skeletal strength such as hip BMD by DXA have been shown to predict site specific and remote fracture risk (Marshall, Johnell et al. 1996), and remain the reference standard for skeletal strength assessment, the scanner required to perform the measurements requires significant space and other resources to operate. It is also unclear if combined measures of skeletal strength are of more value in fracture prediction than single measurements. Other methods of skeletal strength assessment incorporating composite measures may be of value and more widely applicable in predicting fracture risk (Gluer, Wu et al. 1993; Gatti, Sartori et al. 2001).

Metacarpal morphometry was described in 1960 as a method of skeletal strength assessment from hand radiographs, but did not gain mainstream recognition as the traditional manual technique was a tedious and time consuming process (Barnett and Nordin 1960; Horsman and Simpson 1975). Semi-automated MCM techniques have since been described showing ability in predicting fracture risk (Dey, McCloskey et al. 2000). More recently digital x-ray radiogrammetry (DXR) has been developed

where these measurements have been fully computerised and automated, significantly reducing both the time and effort involved (Jorgensen, Andersen et al. 2000).

DXR has been shown to be comparable to other peripheral measures such as quantitative ultrasound in the detection of osteoporosis (Boonen, Nijs et al. 2005). However, the ability of DXR to predict fracture risk itself has not been widely reported previously. The aim of the current study was therefore to determine the ability of DXR indices to predict hip fracture risk, and to compare their performance to that of DXA measurements.

4.3 METHODS

4.3.1 SUBJECTS

MRC Hip fracture Prevention Study (HIPS): HIPS was a single-centre study based at Sheffield, UK between 1996 and 2002. The aim was to identify risk factors for hip fracture in elderly caucasian women combined with a randomised placebo-controlled trial of oral clodronate (Bonefos®) for fracture prevention.

A total of 5212 community dwelling women aged 75 years or over were recruited to the study. Following baseline assessments of risk factors, the women were randomised to receive oral clodronate 800mg or an identical placebo for 3 years and were followed for up to a further 2 years.

4.3.2 DESIGN

This particular analysis was designed as a nested case-control study within the HIPS cohort. The group had been pre-selected for the purpose of several analyses and included 153 women who sustained low-trauma hip fracture along with 534 randomly selected controls who did not sustain hip fracture during the study period.

4.3.3 MEASUREMENTS

Data including medical and fracture history were collected at enrolment from all subjects. Height and weight were recorded and baseline hand radiographs were performed.

4.3.3.1DXA at baseline:

Subjects had hip and forearm BMD by DXA on a Hologic QDR4500 (Hologic Inc., Bedford, USA) and an Osteometer DTX200 (Osteometer Meditech Inc., Hawthorne, USA) respectively.

4.3.3.2DXR indices:

The Sectra/Pronosco X-posure System™ (Sectra, Denmark), Version 2.0, was used to obtain measurements from hand radiographs taken at baseline. These comprised DXR-MCI and DXR-BMD as described below:

DXR-MCI: The cortical index (CI) of a tubular bone is calculated as: CI = 2t / W, where t = cortical thickness and W = bone width of said bone. MCI is calculated as a weighted average of the CI's of the middle 3 metacarpals: MCI = $(CI_2+CI_3+0.5CI_4) / 2.5$ (Bouxsein, Palermo et al. 2002; Thodberg and Rosholm 2003).

DXR-BMD: This is computed using the formula for tubular bones as: DXR-BMD = $c \pi t (1 - t/W)$, where c is a constant representing the average *mineral mass / unit volume* of bone (Rosholm, Hyldstrup et al. 2001).

Both measurements were obtained from the non-dominant side with automated output.

4.3.3.3Fracture data

All subjects were followed up at 6 monthly intervals by study nurses. As part of the follow-up data collection, all incident fracture data were also collected. All reported fractures were independently confirmed and classified by verifying the x-ray or x-ray report. Hip fractures were further classified according to x-ray or x-ray report as 'femoral neck' or 'trochanteric' fractures.

4.3.3.4Statistics

Data were collected on databases derived from the Microsoft Office Access database software. These were subsequently tranferred to, and processed and analysed in the SPSS Version 11.x statistical package. Baseline characteristics were studied using ANOVA. Gradients of risk for incident hip fracture for 1 standard deviation decrease in measurement of skeletal strength were studied using univariate and multivariate regression. Correlations between the various skeletal measures were studied using Pearson corrleation coefficients and measures of agreement by the kappa coefficient. A P value of <0.05 was considered statistically significant.

4.4 RESULTS

The median duration of follow-up during the study was 4 years. The proportion of subjects who received clodronate was similar between the hip fracture group and control group (46% vs. 50%, not significant).

4.4.1 BASELINE CHARACTERISTICS (TABLE 4.1)

Women who had incident hip fractures were on average 1.6 years older at baseline than those who did not ($P<0.001$). They also had lower body weight and body mass index (BMI, $P<0.001$), and although there was an approximately 1cm difference in mean height, this was not significantly different. All mean skeletal strength measures including DXA and DXR indices were significantly lower in the hip fracture group ($P<0.001$), except mean metacarpal bone width which was not significantly different.

Table 4.1. Comparison of baseline characteristics (mean ± SD).

	Fracture group (n=153)	Control group (n=534)	P (ANOVA)
Age (years)	80.9±4.4	79.3±3.8	<0.001
Height (cm)	155.1±6.0	156.2±6.5	0.069
Weight (kg)	59.3±9.7	65.9±12.5	<0.001
BMI (kgm^{-2})	24.6±3.9	27.0±4.7	<0.001
Total hip BMD (gcm^{-2})	0.658±0.127	0.766±0.142	<0.001
Femoral neck BMD (gcm^{-2})	0.564±0.093	0.659±0.129	<0.001
Trochanteric BMD (gcm^{-2})	0.500±0.110	0.587±0.123	<0.001
Ward's area BMD (gcm^{-2})	0.360±0.108	0.462±0.140	<0.001
Forearm BMD (gcm^{-2})	0.302±0.070	0.346±0.076	<0.001
DXR BMD (gcm^{-2})	0.408±0.053	0.439±0.055	<0.001
DXR MCI	0.296±0.050	0.322±0.051	<0.001
Cortical thickness (cm)	0.121±0.019	0.132±0.020	<0.001
Bone Width (MC 2-4, cm)	0.819±0.044	0.822±0.049	0.595
Clodronate treated (%)	70 (46)	269 (50)	0.359*

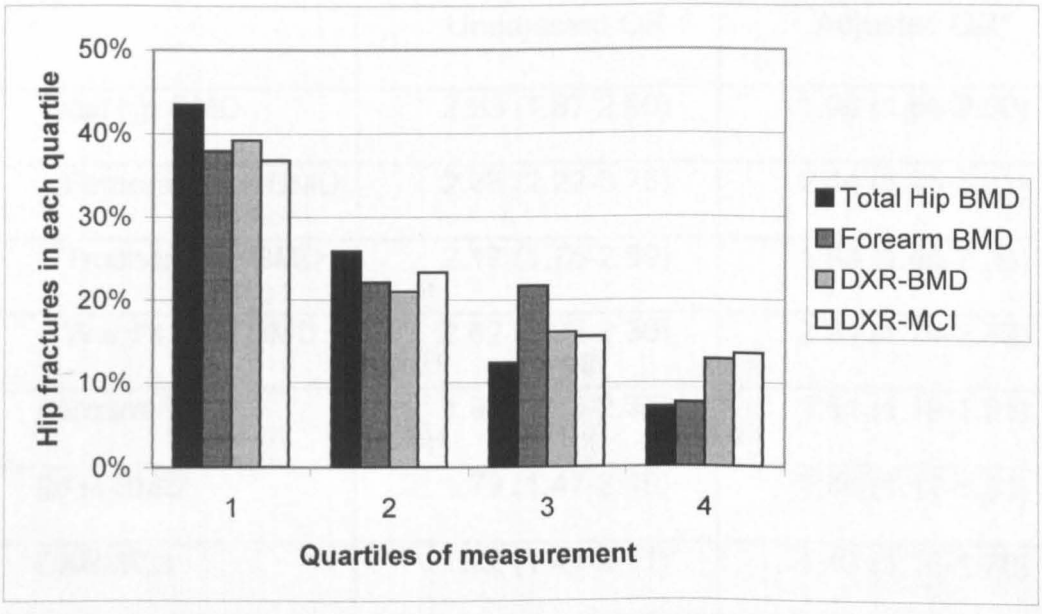
*Chi-square test.

4.4.2 DISTRIBUTION OF FRACTURES BASED ON SKELETAL STRENGTH

Data for all 4 skeletal measures were divided into quartiles of strength (1=lowest and 4=highest) and fracture distribution in each quartile was studied. For all measures, the highest incidence of fracture was in quartile

1 and the lowest incidence in quartile 4. The steepest distribution was in total hip BMD with less steep but similar distributions among forearm BMD and the 2 DXR indices (Figure 4.1).

Figure 4.1. Proportion of hip fractures in each quartile of measurements of total hip BMD, forearm BMD, DXR-BMD and DXR-MCI in the whole study group (n=687). (Quartile 1=lowest and quartile 4= highest).



4.4.3 GRADIENTS OF RISK FOR HIP FRACTURE FOR 1 SD DECREASE IN MEASUREMENTS (TABLE 4.2 & Fig 4.2A)

Total hip and forearm DXA measurements as well as DXR-BMD and DXR-MCI measurements were converted to standard deviation units against the mean values of each measure for the whole cohort (Z scores). In univariate analysis of Z scores using logistic regression, all 4 skeletal measures were significant predictors of hip fracture expressed as odds ratios (OR's) and 95% confidence intervals. After adjusting for age and body weight in a forward-conditional logistic regression model, all the

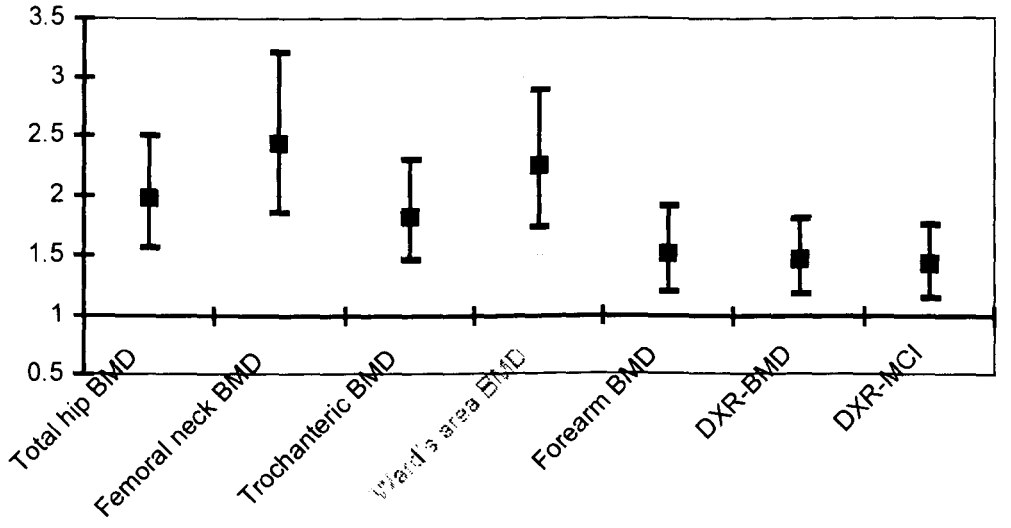
measures remained significant predictors of hip fracture. Total hip BMD (and its subregions) had the highest odds ratios with both the DXR indices having OR's similar to that of forearm BMD (Table 4.2 & Figure 4.2A).

Table 4.2. Unadjusted and adjusted (for age and weight) odds ratios (95% confidence intervals) for all hip fractures (n=153) for a 1 SD decrease in measurements of bone strength (P≤0.001 for all).

	Unadjusted OR	Adjusted OR*
Total hip BMD	2.33 (1.87-2.90)	1.98 (1.56-2.50)
Femoral neck BMD	2.88 (2.22-3.73)	2.44 (1.85-3.21)
Trochanteric BMD	2.17 (1.75-2.69)	1.83 (1.46-2.30)
Ward's area BMD	2.62 (2.05-3.36)	2.24 (1.74-2.89)
Forearm BMD	1.90 (1.55-2.34)	1.51 (1.19-1.91)
DXR-BMD	1.79 (1.47-2.19)	1.46 (1.17-1.81)
DXR-MCI	1.72 (1.41-2.11)	1.43 (1.15-1.76)

*Forward-conditional logistic regression.

Figure 4.2A. Adjusted OR's (point estimates) and 95% CI (high and low lines) from Table 4.2 plotted as a graph.



4.4.4 FEMORAL NECK VS. TROCHANTERIC FRACTURES

The hip fracture group was subclassified into femoral neck and trochanteric fracture subgroups (baseline characteristics, Table 4.3). One patient was excluded as the type of fracture was not classified. The trochanteric fracture group had significantly lower DXR-BMD (P=0.039) and mean metacarpal cortical thickness (P=0.046), but there was no difference in mean metacarpal bone width (P=0.84). The trochanteric fracture subgroup also showed non-significant trends towards greater age, lower mean body weight, BMI, total hip and forearm BMD, and DXR-MCI.

Table 4.3. Comparison of femoral neck and trochanteric fracture sub-groups (mean ± standard deviation).

	Femoral neck (n=106)	Trochanteric (n=46)	P (ANOVA)
Age (years)	80.6±4.3	81.7±4.6	0.185
Height (cm)	155.0±5.9	155.2±6.1	0.871
Weight (kg)	59.6±10.0	58.2±8.9	0.424
BMI (kgm^{-2})	24.7±4.0	24.2±3.6	0.464
Total hip BMD (gcm^{-2})	0.666±0.136	0.638±0.102	0.225
Femoral neck BMD (gcm^{-2})	0.567±0.099	0.556±0.077	0.489
Trochanteric BMD (gcm^{-2})	0.510±0.117	0.477±0.090	0.091
Ward's area BMD (gcm^{-2})	0.364±0.117	0.350±0.087	0.478
Forearm BMD (gcm^{-2})	0.307±0.067	0.289±0.076	0.166
DXR-BMD (gcm^{-2})	0.414±0.051	0.395±0.055	0.039
DXR-MCI	0.301±0.049	0.284±0.050	0.053
Cortical thickness (cm)	0.123±0.019	0.116±0.020	0.046
Bone Width (MC 2-4, cm)	0.819±0.042	0.820±0.049	0.840

4.4.5 GRADIENTS OF RISK OF FEMORAL NECK AND TROCHANTERIC FRACTURE FOR 1 SD DECREASE IN MEASUREMENTS (TABLE 4.4):

After adjustment for age and body weight in a forward-conditional logistic regression model, all 4 skeletal measures were significantly predictive of both femoral neck and trochanteric hip fracture expressed as OR's (95%

CI). Similar to the whole hip fracture group, hip BMD and its subregions had the highest OR's with forearm BMD having OR's similar to the two DXR indices for both fracture subtypes. The point values for OR's were also somewhat higher for the trochanteric fracture subgroup for all 4 measures.

Table 4.4. Odds ratios (95% confidence intervals), adjusted for age and weight, for femoral neck and trochanteric fractures for a 1 SD decrease in measurements of bone strength (forward-conditional logistic regression, all P<0.05).

	Femoral neck (n=106)	Trochanteric (n=46)
Total hip BMD	1.83 (1.42-2.37)	2.45 (1.72-3.48)
Femoral neck BMD	2.32 (1.71-3.15)	2.95 (1.92-4.53)
Trochanteric BMD	1.67 (1.31-2.13)	2.08 (1.47-2.95)
Ward's area BMD	2.13 (1.61-2.81)	2.38 (1.58-3.59)
Forearm BMD	1.47 (1.12-1.92)	2.07 (1.44-2.98)
DXR-BMD	1.36 (1.07-1.73)	2.02 (1.40-2.93)
DXR-MCI	1.34 (1.06-1.70)	1.97 (1.36-2.85)

4.4.6 MULTIVARIATE ANALYSIS

All variables that were significantly different at baseline between the hip fracture group and the controls were entered into a multivariate forward-

conditional logistic regression model to determine independent predictors of hip fracture. In this model, age, weight and total hip BMD were independently associated with fracture risk (Table 4.5).

Table 4.5. Independent predictors of hip fracture. Mutivariate analysis.

	Odds Ratio, 95% CI
Age (yrs)	1.06, 1.01-1.11*
Weight (kg)	0.98, 0.96-0.995*
Total hip BMD (1 SD decrease)	1.98, 1.56-2.50*
Forearm BMD (1 SD decrease)	0.92, 0.66-1.29
DXR-BMD (1 SD decrease)	1.16, 0.70-1.91
DXR-MCI (1 SD decrease)	0.99, 0.62-1.60

*Forward-conditional logistic regression, $P<0.02$.

Amongst the skeletal measures only, to identify if any of the peripheral measures predicted fracture risk independent of total hip BMD, each of the measures was put through a forward-conditional regression model with total hip BMD. After adjusting for total hip BMD in the regression model, forearm BMD as well as both the DXR indices were no longer significantly associated with fracture risk (Table 4.6).

Table 4.6. Multivariate analysis: gradients of fracture risk for 1 SD decrease in measurement adjusted for total hip BMD (odds ratios, 95% CI).

	Odds Ratio, 95% CI	P
Forearm BMD	1.06, 0.77-1.45	0.736
DXR-BMD	1.28, 0.78-2.10	0.324
DXR-MCI	0.93, 0.58-1.49	0.771

4.4.7 ASSOCIATION MEASURES BETWEEN THE DXA AND DXR INDICES

Correlation Coefficients:

Pearson correlations were calculated between hip BMD and the other 3 skeletal measures and are summarised in Table 4.7. Total hip BMD had slightly better correlation with forearm BMD and DXR indices compared to femoral neck BMD.

Table 4.7. Correlation (Pearson coefficients) between the various skeletal measures (all P<0.01).

	Forearm BMD	DXR-BMD	DXR-MCI
Total hip BMD	0.67	0.57	0.54
Femoral neck BMD	0.59	0.50	0.46
Forearm BMD	-	0.71	0.68
DXR-BMD	-	-	0.90

Scatter Plots:

Using the SPSS software, scatter plots with fit lines were constructed to study the associations between the various skeletal measures (Figures 4.2-4.4). T scores were computed from BMD data using previously published normative data for peak bone mass in a young adult for DXR-BMD (Black, Palermo et al. 2001), and the manufacturer's normative data for DXA. Using the traditional definition of osteoporosis as T score ≤ - 2.5, reference lines were created on the scatter plots.

Figure 4.2. Scatter plot correlating total hip DXA T- scores and forearm DXA T-scores.

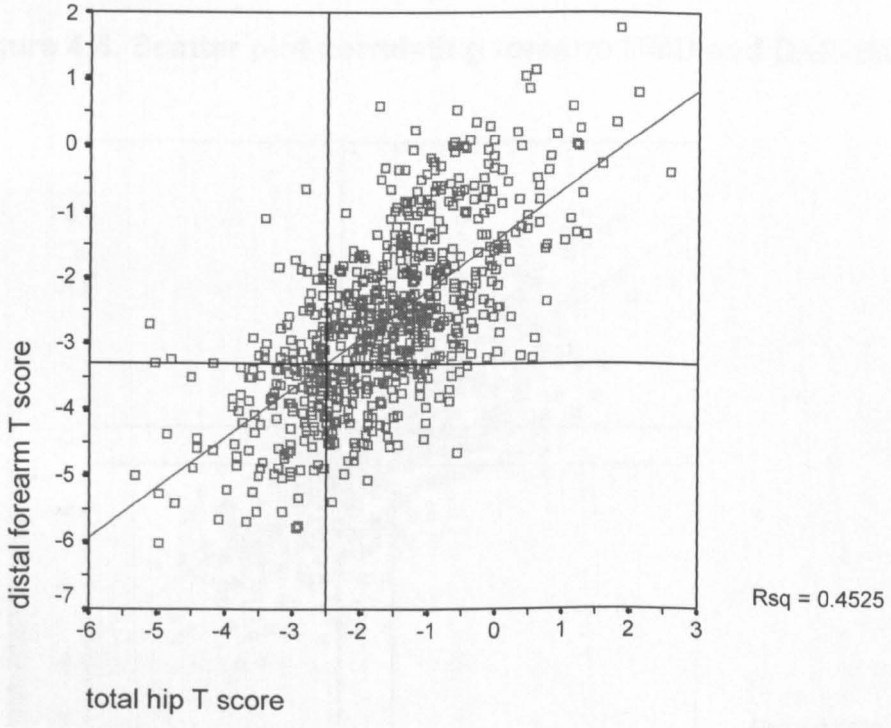


Figure 4.3. Scatter plot correlating total hip DXA T scores and DXR-BMD T scores.

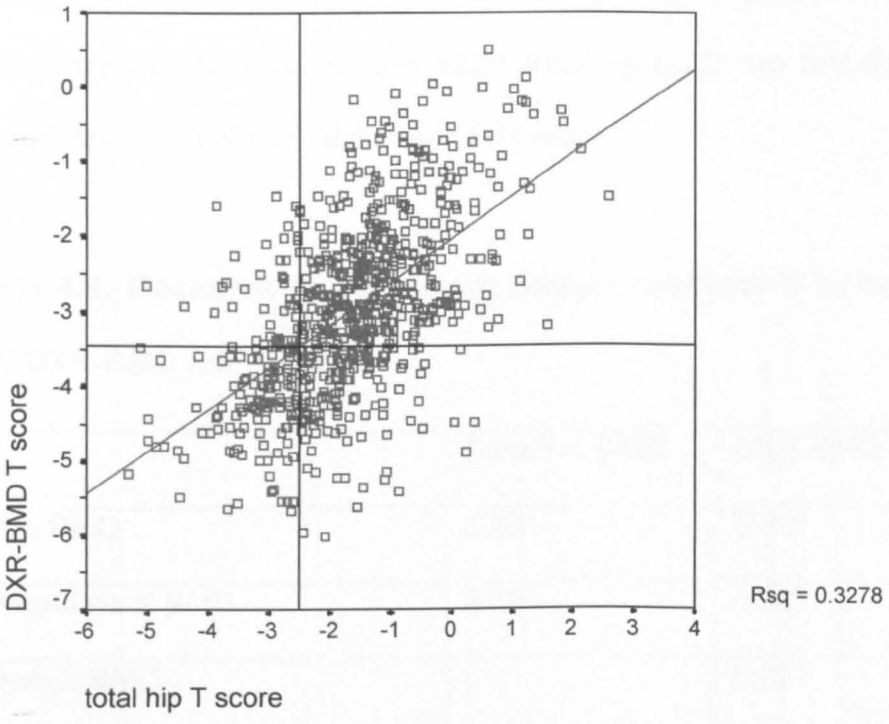
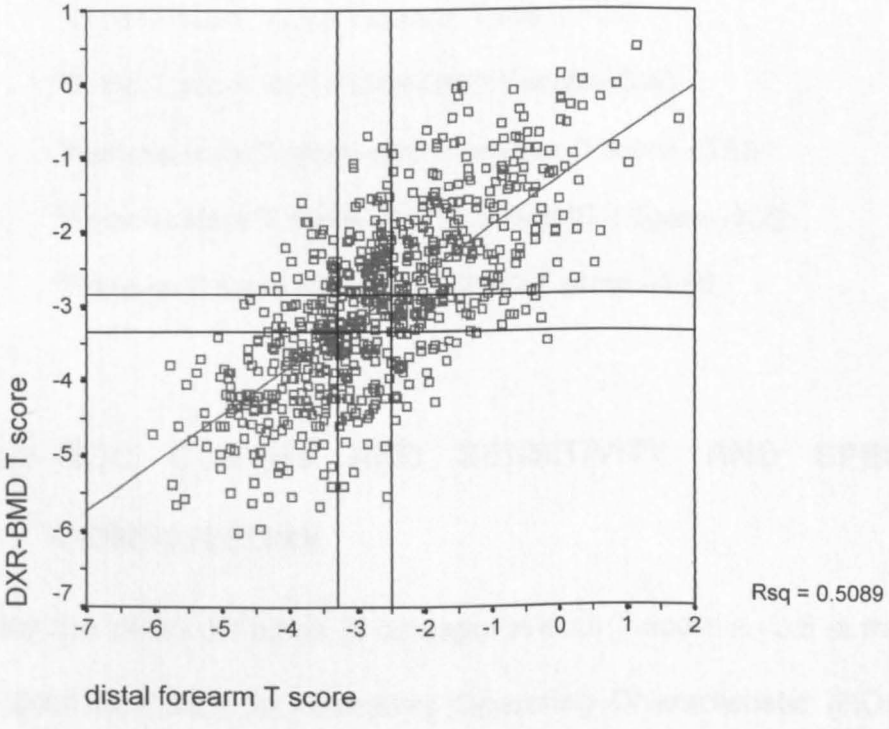


Figure 4.4. Scatter plot correlating forearm BMD and DXR-BMD.



Kappa Coefficients:

Data from the reference lines were used to compute measures of agreement (kappa coefficients) on the diagnosis of osteoporosis (Table 4.8). Compared to femoral neck BMD, total hip BMD had slightly stronger agreement with forearm BMD and DXR-BMD.

Table 4.8. Measures of agreement (kappa coefficient) between DXA and DXR-BMD (all P<0.05)*.

	Forearm BMD	DXR-BMD
T. hip BMD	0.39[1]	0.40[2]
Femoral neck BMD	0.38[3]	0.36[4]
Forearm BMD	-	0.45[5]

*Definition of osteoporosis based on fit- and reference lines of scatter plots as below:

[1]T. hip T score –2.5 = Forearm T score –3.3

[2]T. hip T score –2.5 = DXR-BMD T score –3.45

[3]Femoral neck T score –2.5 = Forearm T score –3.05.

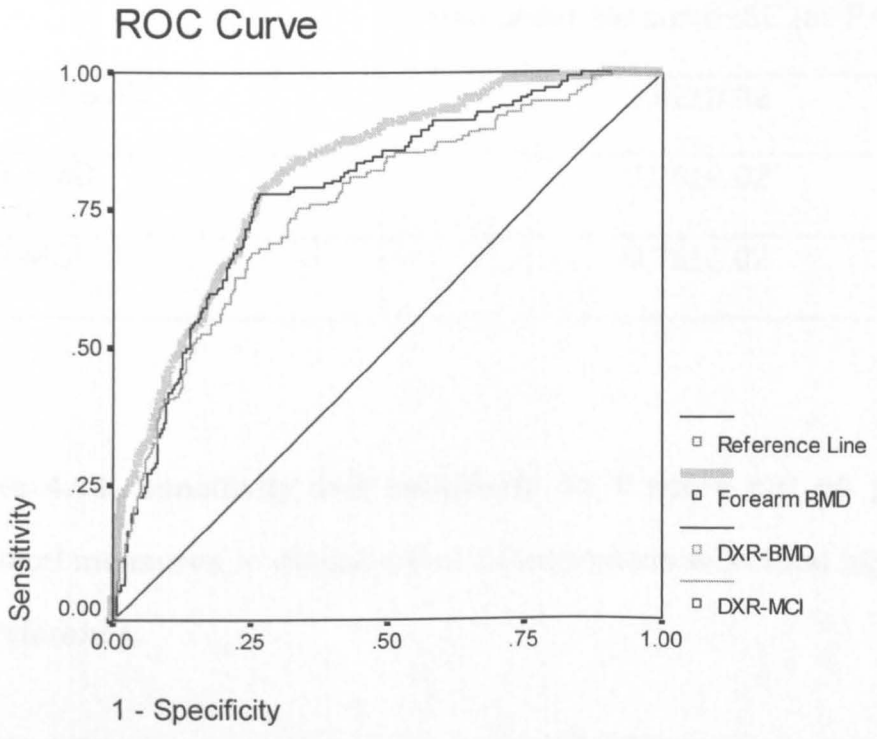
[4]Femoral Neck T score –2.5 = DXR-BMD T score –3.25.

[5]Forearm T score –2.5 = DXR-BMD T score –2.85.

4.4.8 ROC CURVES AND SENSITIVITY AND SPECIFICITY COMPARISONS

Using the WHO definition of osteoporosis as T score ≤ -2.5 at the total hip by DXA as reference, Receiver Operating Characteristic (ROC) curves were produced for forearm DXA and the DXR indices (Figure 4.5).

Figure 4.5. ROC curves of the skeletal measures with total hip BMD as reference for the diagnosis of osteoporosis.



The 'area under the curve' calculations were similar and statistically significant (P<0.001) for all the three measures (Table 4.9). Using coordinates of the curve, sensitivity and specificity of forearm BMD and DXR-BMD T scores were calculated at various thresholds including thresholds that were used in computing the kappa coefficients. These were broadly similar although forearm BMD seemed to have slightly higher specificity than DXR-BMD at similar thresholds (Table 4.10).

Table 4.9. Area under the curve for skeletal measures in diagnosis of osteoporosis with total hip BMD as reference (T score≤ -2.5).

	Area under the curve±SE (all P<0.001)
Forearm BMD	0.82±0.02
DXR-BMD	0.78±0.02
DXR-MCI	0.76±0.02

Table 4.10. Sensitivity and specificity by T score cut off points of skeletal measures in diagnosis of osteoporosis with total hip T score as reference.

	T score	Sensitivity (%)	Specificity (%)
Forearm BMD	-2.5	90.7	51.2
	-3.00	82.1	69.7
	-3.3	66.7	77.4
DXR-BMD	-2.5	91.4	41.9
	-3.00	79.6	60.2
	-3.45	71	76.1

4.5 DISCUSSION

In this study the ability of DXR indices to predict future hip fracture was compared to that of DXA measures. DXR indices were significantly lower

at baseline in the hip fracture group compared to controls independent of age and body weight. While total hip BMD remained the strongest predictor of hip fracture, the OR's for 1 SD decrease in measurement of the DXR indices were significant and similar to that of forearm BMD. The correlations between hip BMD and the DXR indices were similar to that of hip and forearm BMD. With hip BMD as reference standard, forearm BMD and DXR-BMD had similar sensitivity and specificity in diagnosing osteoporosis.

4.5.1 BASELINE CHARACTERISTICS

Similar to findings in previous studies, in this study incident hip fracture was associated with greater age (Zain Elabdien, Olerud et al. 1984; Bouxsein, Palermo et al. 2002) and low body weight or BMI (Johnell, Gullberg et al. 1995; Bouxsein, Palermo et al. 2002). The differences between the fracture and control groups in the DXR indices seem to be a reflection of significantly lower mean cortical thickness of the scanned metacarpals rather than the mean bone width which was similar in both groups. This may represent endosteal bone resorption reflecting true loss of bone mass while a change in bone width may reflect a change in geometry-related bone strength. Although Bouxsein and colleagues reported on DXR indices, no data or comment were included in their report regarding measured cortical thickness and bone width.

The trends for greater age, lower body weight and lower DXA measures noted in the trochanteric fracture group compared to femoral neck fracture group were reported previously (Mautalen, Vega et al. 1996; Stewart, Porter et al. 1999), although these were not significant in our study.

Bouxsein and colleagues reported on the hip fracture subtypes, but no data on age or body weight or indeed mean values of DXA or DXR were included in the subtype analysis. While DXA measures did not distinguish between the two subtypes in the current study, DXR-BMD was significantly lower at baseline in the trochanteric subgroup. This is in keeping with previous reports that peripheral BMD measures were lower at baseline in trochanteric fractures compared to femoral neck fractures (Mautalen, Vega et al. 1996; Stewart, Porter et al. 1999). In fact, women sustaining trochanteric fractures were reported to have lower bone mass at the hip by DXA, distal radius by peripheral QCT, and tibia by QUS, while those sustaining femoral neck fractures had low BMD primarily at the hip suggesting more generalised skeletal loss in women sustaining trochanteric fractures (Augat, Fan et al. 1998).

4.5.2 PREDICTING FUTURE HIP FRACTURE

Total hip BMD and its subregions remained the strongest predictors of hip fracture in this study with unadjusted OR's of 2.33 for total hip BMD and 2.88 for femoral neck BMD. This site specificity is in keeping with the report by Bouxsein and colleagues, where femoral neck BMD was the strongest predictor of hip fracture with an age-adjusted relative hazard (RH) of 3.0 for 1 SD decrease in BMD, (Bouxsein, Palermo et al. 2002), and also the meta-analysis by Marshall and colleagues, where hip BMD measurement was found to be the strongest predictor of hip fracture with a relative risk of 2.6 for 1 SD decrease in BMD (Marshall, Johnell et al. 1996).

In the current study, hip and forearm DXA, as well as the DXR-BMD & DXR-MCI were significant predictors of both trochanteric and femoral neck fractures although all were better predictors of trochanteric fracture (OR's 2.45, 2.07, 2.02 and 1.97 respectively) than femoral neck fractures (OR's 1.83, 1.47, 1.36 and 1.34 respectively). However, Bouxsein and colleagues reported that while forearm BMD, and DXR indices predicted trochanteric fractures significantly (RH's 1.9-2.3), they did not predict femoral neck fractures (1.0-1.3, not significant) (Bouxsein, Palermo et al. 2002). This may be because the mean age of their hip fracture cohort was 75.5 years, while our cohort was older with a mean age of 80.9 years and consequently likely to be more osteoporotic in general. As no mean values for the skeletal measures were reported for the fracture subtypes by Bouxsein and colleagues, this can only be speculated. Interestingly, in the only other study published of DXR-BMD in predicting osteoporotic fractures, Bach-Mortensen and colleagues found that the trend in DXR-BMD decrease with hip fracture did not reach statistical significance (P=0.052), but this could have been because of the relatively small number of incident fractures in their study (total of 245 women who suffered fracture) (Bach-Mortensen, Hyldstrup et al. 2006).

4.5.3 DIAGNOSIS OF OSTEOPOROSIS

The correlations between total hip BMD and DXR indices were significant in this study although the magnitude was less than 0.6. Femoral neck BMD had weaker correlation with DXR-BMD similar to those reported previously by Bouxsein and colleagues (0.5 in both studies). The correlation between forearm BMD and DXR indices was somewhat better

around 0.7, and this was similar to that reported by Bouxsein and colleagues (0.68 with distal radius BMD, and 0.75 with proximal radius BMD). In fact, in the present study forearm BMD correlated better with DXR-BMD than with total hip BMD (0.71 vs. 0.67 respectively). The strongest correlation in our study was between DXR-BMD and DXR-MCI (0.9), comparing well with that reported by Bouxsein and colleagues (0.87). This was as expected as both measures are computed using the same measurements captured on radiogrammetry.

Recently, a threshold T score of -1.53 by DXR-BMD (using an earlier version 1 of Pronosco X-posure system) was reported as having a sensitivity of 79.6% and specificity of 76.3% in diagnosing osteopenia using total hip BMD as reference standard (T score < -1) (Ward, Cotton et al. 2003), but no specific values were reported for the sensitivity and specificity in diagnosing osteoporosis itself. In our study DXR indices had similar sensitivity and specificity in diagnosing osteoporosis to that of forearm BMD at various thresholds with total hip BMD as reference. While the measures of agreement with total hip BMD were only moderate for the various skeletal measures (kappa <0.5), the area under the curve (AUC) for DXR-BMD was 0.78 which was comparable to 0.84 reported by Ward and colleagues with the earlier Version 1.

4.5.4 POTENTIAL LIMITATIONS

The present study was designed as a nested case-control study in the context of a larger prospective cohort study. The smaller group was selected to perform several analyses in addition to the primary objectives in a cost effective manner. The relatively small number of fractures studied

meant that while the point estimates of the various OR's reached statistical significance, the confidence intervals were relatively wide. Although analysing the whole cohort would have possibly provided a more robust database and tighter confidence intervals for the OR's, it is unlikely to have significantly added to the overall findings, as the findings were largely in keeping with those reported by Bouxsein and colleagues who reported on a similar nested case-control group chosen from a much larger cohort of over 9000 subjects.

Our study was also a setting for a placebo controlled trial of clodronate which could be a potential confounder. However, at baseline a similar proportion of the hip fracture and control group had received clodronate with no statistically significant difference. It is, therefore, likely that the findings are generalisable in the context of hip fracture prediction.

The ability of DXR indices in predicting hip fracture risk in the long term is not known. In our study, the median duration of follow-up was 4 years comparable to that reported by Bouxsein et al (4-5 years). However, single peripheral measurements may predict long term risk: for example, forearm BMD was reported to predict fractures over 25 years (Duppe, Gardsell et al. 1997). It is possible that DXR indices may also have such predictive ability as they seem to be comparable to forearm BMD over the shorter follow up in this study.

In this study, a later version of the Pronosco X-posure system (Version 2.0) was used where the DXR indices were computed using measurements from the second to fourth metacarpals only. The initial version 1 employed measurements from the metacarpals, radius and ulna

for computing DXR-BMD (Jorgensen, Andersen et al. 2000; Bouxsein, Palermo et al. 2002), raising the possibility that measurements may not be comparable between the two versions. However, Black and colleagues compared the association with fracture risk for DXR-BMD computed from metacarpals to that computed from metacarpals, radius and ulna and found them to be similar (Black, Palermo et al. 2001). This suggests that the findings from the present study are comparable to measurements in previous studies using the initial version as well.

4.6 CONCLUSIONS

In this analysis, DXR indices were found to predict future hip fracture risk. While hip BMD remains the strongest predictor of hip fracture, DXR indices are at least as able as forearm BMD in predicting fracture risk and in diagnosing osteoporosis. DXR may have a significant role in the more widespread provision of osteoporosis diagnostic services, either as a stand-alone assessment of risk where DXA facilities are not available, or as a screening tool to target axial measurements of BMD.

5 DXR IN THE PREDICTION OF VERTEBRAL FRACTURES

5.1 ABSTRACT

Introduction: Vertebral fracture is the commonest osteoporotic fracture type. It is not yet clear whether combined measures of skeletal strength are of more value in the prediction of fracture risk than a single measurement alone. The aim of this study was to determine the ability of two new simple measurements derived from hand radiographs to predict future vertebral fractures, and to compare their performance with that of DXA measurements at the spine and hip in women with osteoporosis.

Methods: This analysis was performed on data from the Vertebral Osteoporosis Trial (VOT). 538 women fulfilling the WHO criteria for osteoporosis (spine or hip T-score <-2.5) and/or with at least one prevalent vertebral fracture were recruited to a 3-year double-blind, controlled study. The women received either clodronate 800mg daily by mouth (Bonefos®) or an identical placebo and all patients received a calcium supplement of 500mg daily. Bone density (BMD) was measured at the spine and hip by DXA at baseline. Prevalent and incident vertebral fractures were identified by morphometric evaluation of lateral spine radiographs obtained at baseline and annually thereafter. Hand radiographs obtained at baseline were analysed using the Pronosco X-posure system^{TM} to derive DXR-BMD and metacarpal cortical index (DXR-MCI).

Results: 90 women (17%) experienced one or more incident vertebral fractures during the study. At baseline, these women were significantly older and had significantly lower mean values of BMD at the lumbar spine, hip, DXR-BMD and DXR-MCI ($P \leq 0.001$ for all). In univariate analysis, the gradients of risk per 1SD decrease (Odds Ratio, 95%CI) for incident

vertebral fractures were similar for lumbar spine BMD and DXR-MCI (1.82, 1.37-2.43 and 1.81, 1.37-2.39 respectively), and were slightly higher than that for DXR-BMD and total hip BMD (1.56, 1.23-1.96, and 1.46, 1.16-1.96 respectively). In a multivariate forward conditional regression model, the baseline presence of vertebral fracture, spine BMD and DXR-MCI were all significant independent predictors of future vertebral fracture with ORs of 6.84, 3.66-12.78 for prevalent vertebral fracture; 1.56, 1.17-2.07 for lumbar spine BMD; and 1.47, 1.04-2.07 for DXR-MCI.

Conclusions: In this study, DXR-BMD and DXR-MCI were found to be predictors of future vertebral fracture risk in women with osteoporosis that are similar in performance to lumbar spine or hip BMD. Moreover, DXR-MCI may capture a component of risk for incident vertebral fractures that is not accounted for by other measures of BMD. DXR measures may have wide applicability in the management of osteoporosis since hand radiographs are relatively inexpensive and involve low doses of radiation.

5.2 INTRODUCTION

Vertebral fracture is the commonest type of osteoporotic fracture (Wasnich 1996). It has been found to be not only associated with increased morbidity but also mortality (Kado, Browner et al. 1999). However, the majority of vertebral fractures are silent, and this can pose problems at the clinical practice level in identifying those at risk (Ziegler, Scheidt-Nave et al. 1996; McKiernan 2009).

Reduced bone mass measured as bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) has been shown to be an independent risk factor for fracture in several studies (Marshall, Johnell et al. 1996). DXA is currently the most commonly used measure of bone mass and it has been shown that single BMD measurements at a particular skeletal site is predictive of over-all fracture risk (relative risk RR 1.5 per 1 standard deviation (SD) decrease in measurement) with optimal prediction for the site of measurement (RR 2-3 per 1SD decrease) (Marshall, Johnell et al. 1996). Cadaveric studies demonstrate that BMD as measured by DXA determines only 50-80% of skeletal strength at identical or closely related sites, and only 20-35% at distant sites, supporting the concept that BMD is site specific to a large extent (Cheng, Lowet et al. 1998; Eckstein, Lochmuller et al. 2002). Other characteristics of the bone may determine a proportion of skeletal strength, as is shown by some differences in fracture prediction using quantitative ultrasound (QUS) (Gluer, Wu et al. 1993). Therefore, it has been proposed that composite measures of skeletal strength may be of greater value in general fracture prediction

than single site measurements, especially when these are from peripheral sites (Gatti, Sartori et al. 2001).

Metacarpal morphometry by radiogrammetry is a non-invasive measure of skeletal strength from hand radiographs first described in 1960 (Barnett and Nordin 1960). There was little development in this modality of skeletal measurement until Horsman and Simpson described the 'six metacarpal hand index' in 1975 (Horsman and Simpson 1975). Traditional radiogrammetry never gained mainstream recognition as it was tedious and time consuming with measurements of metacarpal cortical thickness and bone width undertaken using fine needle callipers on hand radiographs. In the last 15 years, semi-automated techniques for metacarpal morphometry have been developed (Matsumoto, Kushida et al. 1994; Dey, McCloskey et al. 2000). More recently digital x-ray radiogrammetry (DXR) has been described where these measurements have been fully automated to significantly reduce both time and effort (Jorgensen, Andersen et al. 2000). DXR estimates skeletal strength from automated measurements of bone dimensions on hand radiographs and is expressed as composite indices such as DXR-BMD and metacarpal cortical index (DXR-MCI). So far, however, there have been only two studies published of the fracture predictive ability of DXR (Bouxsein, Palermo et al. 2002; Bach-Mortensen, Hyldstrup et al. 2006). This study was aimed at determining the ability of DXR indices to predict future vertebral fracture occurrence in osteoporotic women, and comparing their performance with that of DXA measurements at the spine and the hip.

5.3 METHODS

5.3.1 SUBJECTS

Vertebral Osteoporosis Trial (VOT): The VOT was a multicentre trial of clodronate (Bonefos®, Schering/Leiras Oy, Finland) for vertebral fracture prevention in women with osteoporosis (spine or hip T Score ≤ -2.5 by DXA) and/or one or more vertebral fractures confirmed by plain radiograph.

5.3.2 DESIGN

VOT was designed as a randomised, placebo-controlled trial. Patients were recruited and followed up at 5 centres in the United Kingdom. They received daily oral clodronate 800mg or placebo for 3 years. All received a daily calcium supplement equivalent to 500mg of elemental calcium during the 3 years.

5.3.3 DXR INDICES

Subjects had plain hand radiographs taken at study entry. DXR indices were computed for each patient from the non-dominant hand on the plain radiographs using a commercially available DXR system (Sectra/Pronosco X-posure System™, Version 2.0, Sectra, Denmark). These comprised DXR-MCI and DXR-BMD as described below:

5.3.3.1DXR-MCI:

The cortical index (CI) of a tubular bone is calculated as: CI = 2t / W, where t = cortical thickness and W = bone width of said bone. In DXR the

computation of MCI is fully automated and is calculated as a weighted average of the CI's of the middle 3 metacarpals: MCI = $(CI_2+CI_3+0.5CI_4) / 2.5$ (Bouxsein, Palermo et al. 2002; Thodberg and Rosholm 2003).

5.3.3.2DXR-BMD:

This is computed using the formula for tubular bones as: DXR-BMD = $c \pi t (1 - t/W)$, where '*c*' is a constant representing the average *mineral mass / unit volume* of bone (Rosholm, Hyldstrup et al. 2001).

5.3.4 OTHER MEASUREMENTS

Patients had height and weight measured at baseline. Lumbar spine (L2-L4 vertebrae) and total hip BMD were recorded in each patient at baseline and yearly follow-ups by DXA scanners at the study centres (Hologic QDR 4500A, Hologic Inc., Bedford, USA). All the values were standardised subsequently across the study centres using the European spine phantom.

5.3.5 FRACTURES

Patients were followed up at 6-monthly intervals. Standard lateral radiographs of the thoracic and lumbar spines were obtained at baseline and annually thereafter. Baseline radiographs were put through vertebral morphometry using the semi-automated McCloskey method (McCloskey, Spector et al. 1993) and prevalent vertebral fractures were identified based on the computed vertebral height ratios. Only vertebrae that were normal at baseline were included in the evaluation for incident fractures on follow-up radiographs. Incident fractures had to fulfil the criteria for a

prevalent fracture and show a minimum decrease in height from the baseline film of 15% equalling 4.6mm or more (McCloskey, Selby et al. 2001).

5.3.6 STATISTICAL ANALYSIS

Primary data were previously captured on Microsoft Access® based databases. For the purposes of this project, this data were transferred to, and were processed and analysed in the SPSS Version 11 statistical package. Baseline data of those who had a new vertebral fracture during the study period were compared to those who did not, using analysis of variance (ANOVA) and Chi-square tests. ROC curves were produced to study the relationship between measured skeletal indices and vertebral fracture incidence. Gradients of risk for 1 standard deviation (SD) decrease of each skeletal strength measurement and independent contribution to fracture risk was determined using univariate and multivariate regression models. Correlations between spine and hip BMD and DXR indices were calculated using Pearson coefficients.

5.4 RESULTS

Of the total of 593 women enrolled in the VOT, 538 (91%) had baseline hand radiographs available for evaluation by DXR, and were included in the present analysis. Ninety patients (16.7%) had one or more incident vertebral fractures during the study period. In the cohort, 243 patients had a prevalent vertebral fracture at baseline, of whom 76 went on to develop a new fracture; of the 295 who did not have a prior history, 14 developed vertebral fractures during the study period (relative risk = 6.6).

5.4.1 BASELINE CHARACTERISTICS

The baseline characteristics of those with new vertebral fractures ('new-fracture group') are compared to rest of the cohort without a new vertebral fracture ('non-fracture group') in Table 5.1. The new-fracture group were significantly older, and had significantly lower mean values for lumbar spine BMD, total hip BMD, DXR-BMD, and DXR-MCI. A significantly higher proportion of the new-fracture group had a history of prior vertebral fracture (84.4% vs. 37.3%, P<0.001). Although the new-fracture group were slightly shorter and lighter, there was no significant difference in mean body mass index (BMI) compared to the non-fracture group.

Table 5.1. Baseline characteristics.

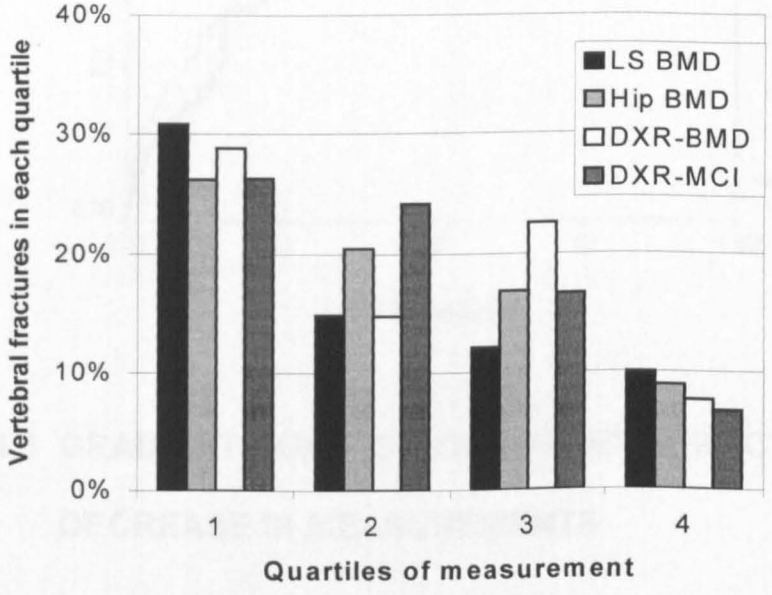
	New vertebral fracture(s) (n=90)	Rest of cohort (n=448)	P (ANOVA)
Age (years)	70.5±7.1	66.6±8	<0.001
Height (cm)	154.6±6.7	156.5±6.4	0.015
Weight (kg)	58.9±11.7	61.1±11.2	0.091
Body mass index (kg/m^2)	24.6±4.3	24.9±4.2	0.49
L2-L4 sBMD (mg/cm^2)	625±125	684±112	<0.001
Total hip sBMD (mg/cm^2)	608±102	651±115	0.001
DXR-BMD (gcm^{-2})	0.42±0.05	0.44±0.05	<0.001
DXR-MCI	0.31±0.05	0.34±0.06	<0.001
Prior vertebral fracture (%)	76 (84.4)	167 (37.3)	<0.001[a]

[a]Chi-square test.

5.4.2 PERFORMANCE ACCORDING TO QUARTILES OF MEASUREMENTS AND ROC CURVES

Measurements from the four skeletal measures were converted into quartiles and the distribution of the incident vertebral fractures was studied amongst the quartiles (Figure 5.1). For all four measures the highest incidence was in the lowest strength quartiles and lowest incidence in the highest strength quartiles ($P<0.05$ for all measures by Chi-square test).

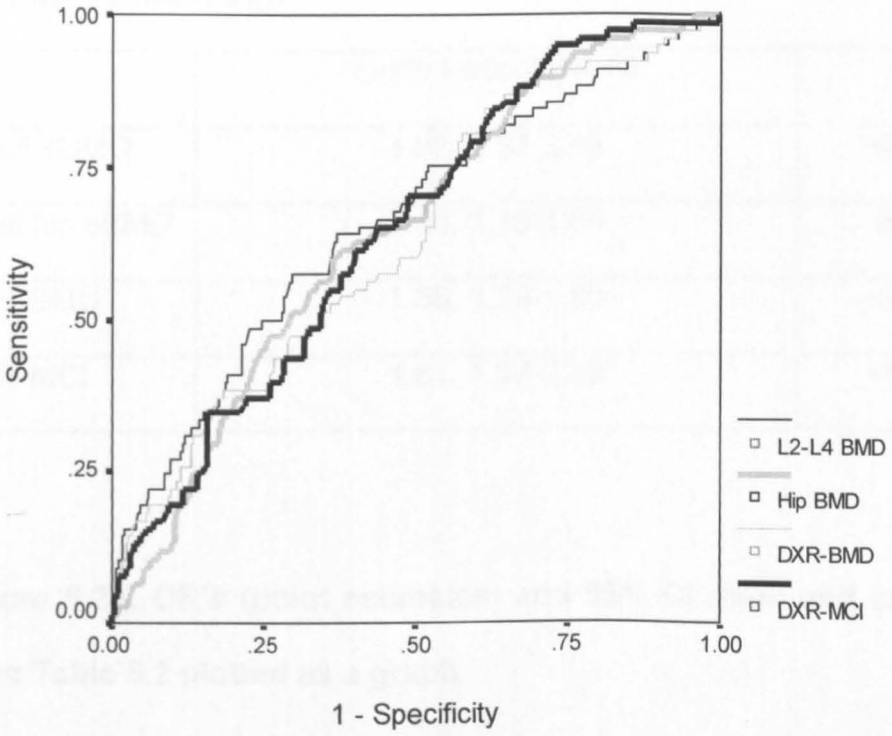
Figure 5.1. Incident vertebral fractures according to quartiles of measurements for each skeletal measure (Quartile 1 = lowest).



Receiver Operating Characteristic (ROC) curves were plotted using SPSS software to assess and compare the sensitivity and specificity of the skeletal measures in predicting incident vertebral fractures (Figure 5.2). The area-under-the curve (AUC) was highest for lumbar spine BMD (0.66),

but this was more or less similar to that of DXR-MCI (0.65). The AUC's for hip BMD and DXR-BMD were slightly lower (0.64 for both).

Figure 5.2. Receiver Operating Characteristic (ROC) curves for incident vertebral fracture based on the four skeletal measures.



5.4.3 GRADIENTS OF RISK OF INCIDENT FRACTURE FOR 1SD DECREASE IN MEASUREMENTS

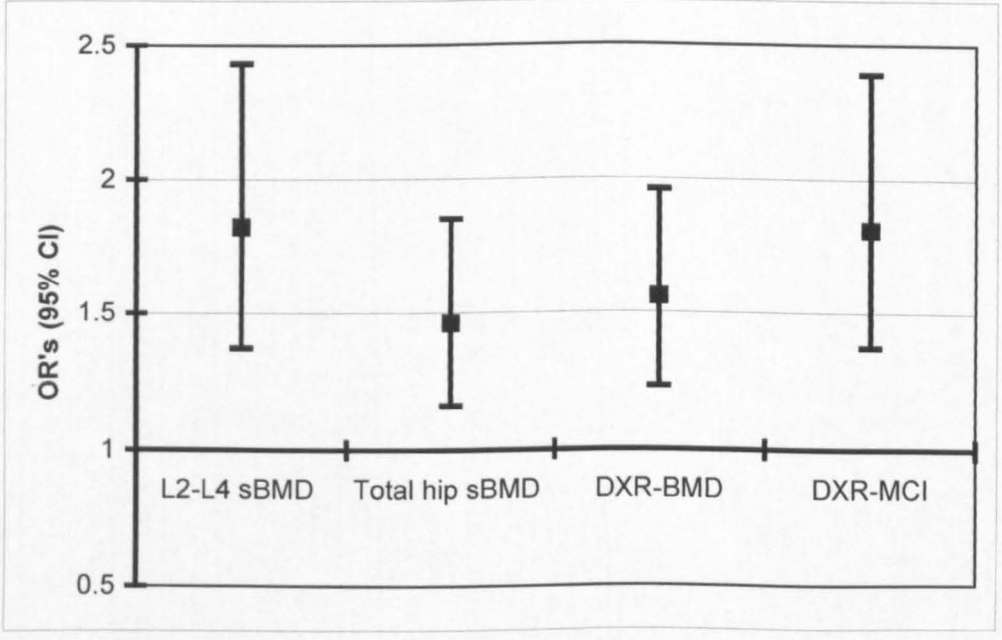
The absolute values of the skeletal strength measures were converted to standard deviation (SD) units. These values were entered into univariate regression models to derive the gradients of risk for incident vertebral fracture for 1 SD decrease in the measurements expressed as odds ratios (OR, 95%CI, Table 5.2). The point estimates of the gradients of risk per 1SD decrease were similar for lumbar spine BMD and DXR-MCI (1.82 and

1.81 respectively), and these were slightly higher than that for total hip BMD and DXR-BMD (1.46 and 1.56 respectively).

Table 5.2. Gradients of risk for incident vertebral fracture for 1 SD decrease in measurement (Univariate analysis, odds ratio, 95% confidence intervals).

	Odds Ratio, 95% CI	P
L2-L4 sBMD	1.82, 1.37-2.43	<0.001
Total hip sBMD	1.46, 1.16-1.85	0.001
DXR-BMD	1.56, 1.23-1.96	<0.001
DXR-MCI	1.81, 1.37-2.39	<0.001

Figure 5.2A. OR's (point estimates) and 95% CI (high and low lines) from Table 5.2 plotted as a graph.



5.4.4 INDEPENDENT PREDICTORS OF FUTURE FRACTURE RISK

All the variables found to be significant in univariate analyses, including all the four skeletal strength measures, were entered into multivariate regression models (Table 5.3). In a forward conditional logistic regression model, lumbar spine BMD, DXR-MCI, and a history of prior vertebral fracture at baseline were found to be independent predictors of future vertebral fracture ($P<0.05$ for all three). Of the three, prior history of vertebral fracture had the strongest association with future vertebral fracture risk with an OR of 6.84.

Table 5.3. Multivariate analysis (forward-conditional regression): Independent predictors of future vertebral fracture (odds ratio, 95% confidence interval).

	Odds Ratio, 95% CI	P
Age (yrs)	1.01, 0.96-1.05	0.84
Height (cm)	1.01, 0.96-1.06	0.78
L2-L4 sBMD (1SD decrease)	1.56, 1.17-2.07*	0.003
Total hip sBMD (1SD decrease)	1.03, 0.74-1.45	0.85
DXR-BMD (1SD decrease)	0.80, 0.43-1.50	0.48
DXR-MCI	1.47, 1.04-2.07*	0.027
Prior vertebral fracture	6.84, 3.66-12.78*	<0.001

*Independent predictors

5.4.5 ASSOCIATION BETWEEN SKELETAL MEASURES

The strength of association between any two skeletal measures was studied using Pearson correlation coefficients (Table 5.4). As expected correlation was highest between the two DXA measures (0.61), and between the two DXR measures (0.89). Although they had similar predictive ability for future vertebral fracture in univariate analysis, the correlation was the least between lumbar spine BMD and DXR-MCI (0.34). However, all correlations were statistically significant (P<0.001).

Table 5.4. Correlations amongst the various skeletal measures (Pearson coefficients, all P<0.001).

	T.hip sBMD	DXR-BMD	DXR-MCI
L1-L4 sBMD	0.61	0.37	0.34
T. hip sBMD	-	0.53	0.51
DXR-BMD	-	-	0.89

5.5 DISCUSSION

In this study, low values of two DXR indices, DXR-BMD and DXR-MCI, were found to be associated with a significantly increased future risk of vertebral fracture. Their predictive abilities were similar to that of hip BMD and lumbar spine BMD respectively. DXR-MCI was able to predict vertebral fractures independently of other skeletal strength measures, including lumbar spine BMD.

5.5.1 COMPARISONS AT BASELINE

Women in the new-fracture group were significantly older than those in the non-fracture group in this analysis. This is consistent with what is already known regarding the relationship of vertebral fracture with age: for example, in a Finnish cohort, Santavirta and colleagues reported that in both sexes, the prevalence of thoracic vertebral fractures increased with age – after 40 years of age in men and after 55 years of age in women (Santavirta, Konttinen et al. 1992); and data from the European Prospective Osteoporosis Study (EPOS) also confirmed the rise in

incidence with age (EPOS 2002). However, the question of whether or not age is a risk factor for prevalent or incident vertebral fracture independent of BMD was not addressed in these two studies. In the current analysis, in multivariate regression models, age was not found to be a significant independent predictor of fracture risk suggesting that any association is no more than a reflection of lower bone density noted with older age. Although the mean body weight was lower in the new-fracture group, this was not statistically significant. The mean height was also somewhat lower in the new-fracture group (154.6cm vs. 156.5cm, P=0.015), but this could probably be a reflection of the fact that a significantly greater proportion in this group had a vertebral fracture at baseline (84.4% vs. 37.3%, P<0.001), and probably had already lost some height by the time of the baseline measurement. In fact, the mean BMI of both groups was nearly identical (24.6 vs. 24.9). This is similar to the analysis from EPOS in which Roy and colleagues reported a trend in both men and women, where increasing body weight and body mass index were associated with a reduced risk of vertebral fracture, although, apart from body mass index in men, the confidence intervals embraced unity (not significant) (Roy, O'Neill et al. 2003). In the current analysis, those with prevalent vertebral fracture at baseline had a much higher risk of new vertebral fracture than those without a baseline vertebral fracture (relative risk = 6.6). This is in keeping with previously published studies where prevalence of vertebral fracture was found to be a risk factor for not only future vertebral fracture (Ross, Genant et al. 1993; Lunt, O'Neill et al. 2003) but also non-vertebral fracture (McCloskey, Vasireddy et al. 2008).

The non-fracture group had significantly greater mean values ($P<0.001$) than the new-fracture group in all 4 skeletal measurements with differences in the lumbar spine BMD (0.68 g/cm^2 vs. 0.62 g/cm^2 respectively, 9.7% difference), and DXR-MCI (0.34 vs. 0.31 respectively, 9.7% difference), being of greater magnitude than the differences in total hip BMD (0.65 g/cm^2 vs. 0.61 g/cm^2 respectively, 6.6% difference), or DXR-BMD (0.44 g/cm^2 vs. 0.42 g/cm^2 respectively, 4.8% difference). The magnitude of the difference between the two groups is similar in DXR-BMD and hip BMD, with both the differences being lower than with spine BMD; this is probably because both are 'remote' measurements with respect to the vertebral site. However, the difference between the two groups in mean DXR-MCI values (which is also a 'remote' index for the vertebral site) was as high as that with the spine BMD, suggesting that DXR-MCI may capture a component of skeletal strength not accounted for by the other measures. In the nested case-control analysis reported by Bouxsein and colleagues, mean lumbar spine BMD, DXR-BMD and DXR-MCI were similarly higher in the control group (0.869 g/cm^2, 0.495 g/cm^2 and 0.374 respectively) compared to the vertebral fracture group (0.753 g/cm^2, 0.459 g/cm^2 and 0.340 respectively). Although these values are not directly comparable to the current analysis, as the cohort characteristics and the measuring devices including the Pronosco system (Version 1) were different, there was no comment made regarding the magnitude of the differences in the various measures between the vertebral fracture and control groups (Bouxsein, Palermo et al. 2002).

5.5.2 FRACTURE RISK BY UNIVARIATE ANALYSIS

The finding that spine BMD is somewhat more specific than hip BMD for predicting risk of fracture at the vertebral site (site specificity) is as expected based on the previously published meta-analysis by Marshall and colleagues where a 1 SD reduction in spine bone density measurement was associated with a relative risk of 2.3 (1.9-2.8) for vertebral fracture (Marshall, Johnell et al. 1996). Bouxsein et al, however, reported a slightly higher predictive ability of femoral neck BMD over lumbar spine BMD for vertebral fracture in their analysis (age-adjusted OR's 2.5 and 2.3 respectively) (Bouxsein, Palermo et al. 2002). In the current analysis, lumbar spine BMD and DXR-MCI fared equally well, the OR's being 1.8 for both measures. DXR-BMD achieved a gradient of risk somewhat lower than that for spine BMD or DXR-MCI. In fact, the gradient of risk was similar to the other remote index, total hip BMD (OR's 1.6 and 1.5 respectively). In contrast, Bouxsein et al reported lower predictive ability of DXR-BMD and DXR-MCI (OR's 1.9 and 1.8 respectively) compared to DXA measures (above), although these are not directly comparable as the cohorts and measures were different to the current analysis, and OR's for all four measures were already age-adjusted in their report (Bouxsein, Palermo et al. 2002). Bach-Mortensen et al also reported an OR of 2.0 for 1SD reduction in DXR-BMD for vertebral fracture, although no other skeletal measures were compared in their analysis of post-menopausal women from the Copenhagen City Heart Study (Bach-Mortensen, Hyldstrup et al. 2006). There is some evidence that bone geometry, particularly for compact skeletal segments, is a

determinant of its strength at least as important as bone density (Gluer, Wu et al. 1993; Gatti, Sartori et al. 2001). While DXR indices might capture a component of bone strength determined by other areal properties of bone, the similar OR's for DXR-MCI and lumbar spine DXA are more likely to be a statistical quirk in view of the relatively modest number of incident fractures studied, as the point estimates are within the CI's of the other two measures.

5.5.3 INDEPENDENT PREDICTORS ON MULTIVARIATE ANALYSIS

In multivariate regression models, hip BMD and DXR-BMD were not independently related to fracture risk with OR's of 1.0, 0.7-1.4; and 0.8, 0.4-1.5 respectively. In fact, in a forward-conditional logistic regression model only spine BMD, DXR-MCI and baseline history of prior vertebral fracture were significantly and independently associated with fracture risk ($P<0.001$). Bouxsein and colleagues did not report any analysis for independent predictors for fracture among the skeletal measures they studied. The finding of lumbar spine BMD as an independent predictor in the present study is as expected, as it is the local index of skeletal strength. History of prior vertebral fracture has also been shown to be a risk factor for future fracture in previous studies and is therefore an expected result in the current analysis. It is difficult to provide a biological explanation for the similar predictive abilities of DXR-MCI and lumbar spine BMD, apart from the suggestion above that DXR-MCI captures a component of skeletal strength determined by bone geometry or other attributes inaccessible to DXA, particularly as the correlation of DXR-MCI

with lumbar spine BMD was the least amongst the skeletal measures in this analysis (Pearson correlation coefficient 0.34).

5.5.4 POTENTIAL LIMITATIONS

The relatively small number of fractures studied meant that while the point estimates of the various OR's reached statistical significance, the confidence intervals were relatively wide. The setting of this study was a controlled trial of clodronate, and the selection of subjects was based on this, rather than a population-based cohort, which could probably have provided a more robust basis for evaluation of DXR. When this project was conceived, and analyses were completed and published as abstracts (Abstracts 4 and 6 listed at the beginning of the thesis), the randomisation information of the trial had remained undisclosed. Subsequent publication from the study confirmed the efficacy of clodronate in reducing the vertebral fracture incidence by 46% (McCloskey, Selby et al. 2004). This fracture-reducing effect of clodronate will need to be taken in to account in assessing the gradients of risk for fracture of the various measures, and it would be interesting to study if there is any effect on odds ratios when adjusted for clodronate treatment in multivariate regression analysis. One possibility is that, in an untreated population the gradients of risk could be greater than the findings presented here. For example, the OR for lumbar spine BMD for vertebral fracture risk in our study (OR 1.6, 1.2-2.1) was lower than the relative risk previously reported by Marshall and colleagues in a meta-analysis of untreated patients (RR 2.3, 2.0-3.5) (Marshall, Johnell et al. 1996), or indeed the OR reported by Bouxsein and colleagues (OR 2.3, 1.8-2.9) discussed earlier, where the subjects were

from the Study of Osteoporotic Fractures which had no treatment intervention (Bouxsein, Palermo et al. 2002).

It is also possible that the spinal and peripheral skeletal strength are altered differently with clodronate treatment affecting the gradients of risk for the various skeletal measures differently. However, in the timescales similar to this study (3 years), any treatment such as clodronate is likely to have only a relatively small impact on a comparison of techniques within the same population as in the current study. It is intended that these issues will be addressed when preparing the analyses for publication in the near future when randomisation data will be available and added to the database and processed appropriately.

5.6 CONCLUSIONS

In this study, DXR-BMD and DXR-MCI were found to be comparable to hip or lumbar spine BMD as indicators of future vertebral fracture risk in osteoporotic women. In addition, DXR-MCI may capture a component of skeletal strength, and risk for vertebral fractures that is not accounted for by the other measures of skeletal strength studied. These simple measures may have wide applicability (especially where DXA is not available) since hand radiographs and DXR are relatively inexpensive.

6 SEMI-AUTOMATED METACARPAL MORPHOMETRY IN THE PREDICTION OF FRACTURE RISK

6.1 ABSTRACT

Introduction: The assessment and management of osteoporosis and fractures is expensive for national health systems. To improve fracture prediction in a cost-effective manner, effective utilisation of existing techniques will need to be supplemented by introduction of more affordable and widely available newer techniques. Metacarpal cortical index (MCI) is known to predict future fracture risk. In this study a new, rapid semi-automated technique to derive MCI from hand radiographs using a digitising tablet was evaluated.

Methods: Subjects were 4929 women aged 75 years or older participating in the MRC HIPS study which was designed to evaluate risk factors for fracture combined with a placebo-controlled trial of oral clodronate (Bonefos®) for fracture prevention. Bilateral hand radiographs were obtained at baseline and the measurements were captured using a transparent cross-hair cursor with the films placed on a backlit digitising tablet and stored automatically in an electronic database. The length, total bone width and cortical thicknesses of the second to fourth metacarpals of both hands were measured. The MCI was calculated for both hands separately and an average value was also derived (AMCI).

Results: During a median follow-up of 4 years, 792 women sustained at least one fracture; of these 180 sustained hip fractures and 658 sustained non-hip fractures. At baseline, these women had significantly lower total hip BMD, forearm BMD and AMCI (all $P \leq 0.001$). In univariate analysis the gradient of risk of fracture (odds ratio, 95% CI) for 1 standard deviation decrease in AMCI was 1.42, 1.22-1.65 for hip fractures; and 1.30, 1.20-

1.40 for all fractures. The corresponding ORs for total hip BMD were 2.09, 1.80-2.43 and 1.61, 1.49-1.74 respectively, and for forearm BMD were 1.79, 1.52-2.11 and 1.47, 1.35-1.59 respectively. The gradients of risk with AMCI were either similar or higher than with unilateral MCI. However, SMCM indices were not significantly predictive of incident clinical vertebral fractures. After adjusting for significant extra-skeletal variables, AMCI remained significantly associated with both hip fractures and all fractures. However, after adjusting for total hip BMD, AMCI was not significantly predictive of fracture risk.

Conclusions: AMCI computed using this rapid technique is an indicator of future fracture risk in elderly women in the community. As hand radiographs are inexpensive and easy to access, this technique could have wide applicability in screening and management of osteoporosis in the community, especially where access to DXA is limited.

6.2 INTRODUCTION

Osteoporotic fractures cause significant morbidity and their management is a significant expense in the health systems of developed countries and is likely to become so in developing countries (Genant, Cooper et al. 1999). The prevention of osteoporotic fractures by antiresorptive treatment and other measures is also a considerable expense and this has made identification of those at highest risk of fracture a priority for cost-effective prevention (NICE 2008; Tosteson, Burge et al. 2008). Despite the need, however, availability of, or access to diagnostic services is poor in several parts of the world (Genant, Cooper et al. 1999).

A number of risk factors including low bone mineral density (BMD) predispose to osteoporotic fractures. The currently accepted definition and diagnosis of osteoporosis is based on T score derived from measurements of BMD by dual-energy x-ray absorptiometry (DXA) (Kanis 1994). However, setting up and running a bone densitometry service using DXA requires considerable resources including space and this may be an important limiting factor in providing diagnostic services in resource deprived areas. DXA may also have some limitations as an only assessment tool for osteoporotic fractures (Nielsen 2000). There is some evidence to suggest that composite measures of skeletal strength may be of more value in fracture prediction than single measurements (Gluer, Wu et al. 1993; Gatti, Sartori et al. 2001). Therefore, to improve fracture prediction and prevention in a cost-effective manner, a combined approach is needed involving effective utilisation of existing techniques

and knowledge of risk factors, and also introducing affordable and potentially more widely available techniques.

Metacarpal morphometry (MCM) from hand radiographs (radiogrammetry) was one of the earliest methods described for systematic skeletal strength assessment and diagnosis of osteoporosis (Barnett and Nordin 1960). Traditional radiogrammetry, involved tedious and time consuming measurements of metacarpal dimensions using callipers and subsequent manual calculations. It therefore never gained mainstream recognition, especially with the advent of newer automated technologies such as single energy x-ray absorptiometry (SXA) and later DXA with the capability of measuring BMD at central sites. More recently, with the renewed interest in less expensive and potentially more widely available technologies, semi-automated techniques for MCM have been described which improve on the time and effort involved in obtaining measurements by traditional MCM (Matsumoto, Kushida et al. 1994; Yamamoto, Yuu et al. 1994). A fully automated system of digital x-ray radiogrammetry (DXR) has also been described since (Jorgensen, Andersen et al. 2000) and has been commercially available.

A rapid, semiautomated MCM (SMCM) technique was developed in-house at the WHO Collaborating Centre in Sheffield, involving a back-lit digitising tablet. This technique was compared to a commercially available MCM technique (Bonalyser®, Teijin Corporation, Japan) in a cohort of 178 osteoporotic women (mean age 70 years), and both were found to have similar intra-observer reproducibility of metacarpal cortical index (MCI) of the second metacarpal, which is a principal measure of MCM (Dey,

McCloskey et al. 2000). Although in that study, it was shown to be significantly associated with prevalent vertebral fracture, SMCM has not been tested for prospective incident fracture predictive ability previously. In this study was aimed at an evaluation of this technique in a large prospective setting, including comparisons with DXA and DXR.

6.3 METHODS

6.3.1 SUBJECTS

MRC Hip Fracture Prevention Study (HIPS): HIPS was the largest single centre osteoporosis study in elderly women based at Sheffield, UK. The study aimed to identify risk factors associated with hip fracture and determine the efficacy of clodronate (Bonefos®, Leiras Oy, Finland.), an oral bisphosphonate, in fracture prevention. 5212 community-dwelling caucasian women aged 75 years or over were recruited to the study.

6.3.2 DESIGN

The study was conducted as a randomised, double-blind placebo controlled trial of clodronate. All subjects received either oral clodronate 800mg daily or identical placebo for 3 years and were followed for up to a further 2 years. Extensive baseline data were collected at recruitment and this included height, weight, fracture and medical history and all had baseline measurements and investigations including hand radiographs.

This particular analysis included 4929 subjects (94.6% of HIPS cohort) who had analysable SMCM measurements from baseline hand

radiographs. From the same radiographs, a subgroup of 654 subjects also had DXR measurements of the non-dominant hand.

6.3.3 SEMI-AUTOMATED METACARPAL MORPHOMETRY

This new technique was developed at Sheffield to derive the MCI from hand radiographs. A backlit digitising tablet and a transparent cross-hair cursor with click-buttons were developed to measure distances between two points. For example, the distance between points A & B were measured by clicking on point A and moving the cursor over the digitising tablet to point B and clicking a second time. A software program was developed to automatically record the distance between the two clicks. The program algorithm allowed for a set sequence of clicks to record several measurements in sequence automatically without any further operator input.

The length, diameter (bone width) and the cortical thicknesses of the second to fourth metacarpals of both hands were captured using the cross-hair cursor on films placed on the digitising tablet and stored automatically in an electronic database. The data were subsequently transferred to the SPSS statistical package and processed.

6.3.3.1Metacarpal Cortical Index

The cortical index of a tubular bone has traditionally been calculated as follows: CI= medial+lateral cortical thickness/bone width.

The MCI was calculated as a weighted average of the middle 3 metacarpals as follows: $MCI = (CI_2+CI_3+0.5CI_4)/2.5$.

MCI was coded and analysed by non-dominant and dominant sides (NDMCI & DMCI). Average MCI was then computed as follows: AMCI = (NDMCI+DMCI)/2.

6.3.4 DXA MEASUREMENTS

Baseline BMD by DXA was performed for the hip on a Hologic QDR4500A scanner (Hologic Inc., Bedford, USA), and for the forearm using an Osteometer DTX200 (Osteometer Inc., Hawthorne, USA).

6.3.5 DXR MEASUREMENTS

In the smaller subgroup of 654 patients, the following DXR measurements were obtained using the Pronosco X-posure System Version 2.0 (Sectra Pronosco, Denmark).

6.3.5.1DXR-MCI:

The cortical index (CI) of a tubular bone is calculated as: CI = 2t / W, where t = cortical thickness and W = bone width of said bone. DXR-MCI is computed in an automated sequence as a weighted average of the CI's of the middle 3 metacarpals: MCI = $(CI_2+CI_3+0.5CI_4)) / 2.5$ (Bouxsein, Palermo et al. 2002; Thodberg and Rosholm 2003)..

6.3.5.2DXR-BMD:

This is computed using the formula for tubular bones as: DXR-BMD = $c \pi t (1 - t/W)$, where '*c*' is a constant representing the average *mineral mass / unit volume* of bone (Rosholm, Hyldstrup et al. 2001).

6.3.6 FRACTURES

All subjects were followed up every 6 months by study nurses. Data collected included incident fracture history. All incident fractures which were clinically reported were confirmed independently and classified by reviewing the relevant x-ray or x-ray report.

6.3.7 STATISTICS

The primary HIPS data and the initial data captured from SMCM were collected on databases derived from Microsoft Access. Data were transferred and final processing and statistical analysis was performed using the SPSS Version 11.x statistical package. Baseline characteristics of the whole cohort and fracture subgroups were studied using ANOVA. MCI measurements between left/right and nondominant/dominant side subgroups were compared using paired t-tests. Gradients of risk for incident fracture for 1 standard deviation decrease in measurement of skeletal strength were studied using univariate and multivariate regression. Correlations between the various skeletal measures were studied using Pearson correlation coefficients. A P value of <0.05 was considered statistically significant.

6.4 RESULTS

The median follow up period for the study was 4 years. In the analysed cohort, 792 (16.1%) women sustained at least one fracture during the study. Of these, 180 (3.7%) sustained at least one hip fracture, and 658

(13.3%) sustained at least one non-hip fracture. The non-dominant side for the majority (96%) was the left side as expected.

6.4.1 BASELINE CHARACTERISTICS

At baseline, the fracture groups had significantly lower weight, hip and forearm BMD, and MCI indices (all $P<0.05$) (Table 6.1). The hip and axial (non-vertebral) fracture subgroups were also significantly older (mean 81.0 and 80.2 yrs respectively vs. 79.5 yrs for study cohort, $P<0.001$), while there was no significant difference in the appendicular fracture group. At baseline there was no difference in AMCI between the clodronate and the placebo groups (0.49 ± 0.07 for both). Clodronate treatment had no significant effect on incident hip or other fracture types other than on incident appendicular fracture, where there was a statistically significant decrease.

MCI subtypes: The mean NDMCI was significantly higher compared to the DMCI in the study cohort as a whole (0.51 and 0.47 respectively, paired t-test $P<0.001$). Mean bone width was higher on the dominant side (8.14 vs 8.04, $P<0.001$), but this was off-set by lower mean cortical thickness (1.93 vs. 2.07, $P<0.001$), producing a lower mean DMCI compared to NDMCI. Similarly, mean $NDCI_2$ was higher compared to DCI_2 (0.52 and 0.49 respectively, $P<0.001$). These trends were noted in the individual fracture groups as well with the non-dominant side values being higher than the dominant side.

Table 6.1. Baseline characteristics (mean ± SD).

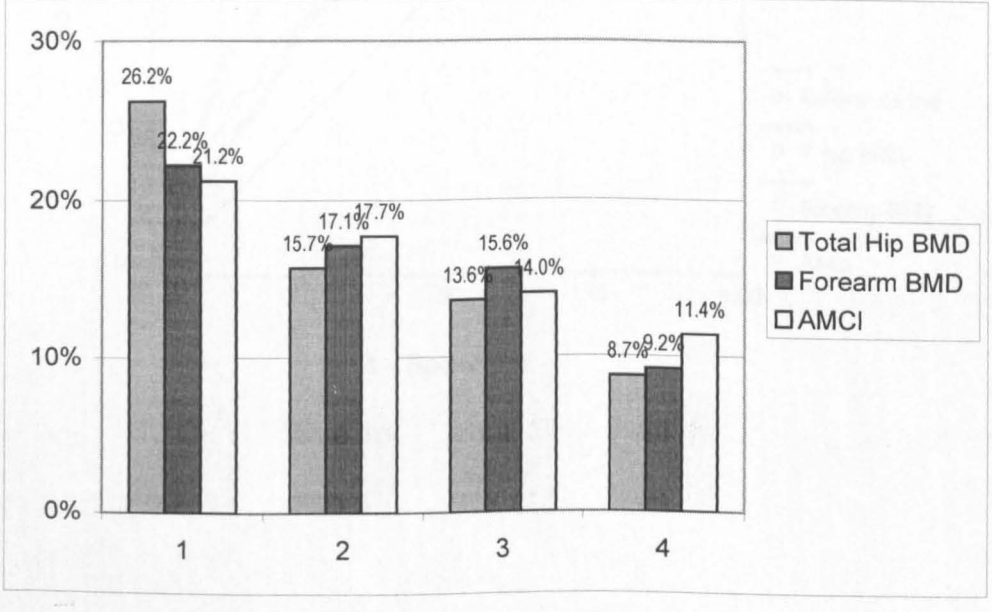
	Study cohort	Hip fractures	Appendicular	Vertebral	Axial (non-vert)	All fractures
Number (%)	4929[a]	180 (3.7)	449 (9.1)	77 (1.6)	189 (3.8)	792 (16.1)
Age (years)	79.5±3.9	81.0±4.6*	79.3±3.8	79.9±3.8	80.2±4.0**	79.9±4.1**
Height (cm)	155.9±6.1	154.9±6.1**	156.2±6.1	154.9±506	155.5±6.4	155.8±6.1
Weight (kg)	65.1±12.0	59.3±10.3*	64.1±10.8	62±9.5**	62.2±12.7*	63.0±11.2*
Body mass index	26.8±4.6	24.7±4.0*	26.3±4.1**	25.8±3.9	25.7±4.7**	25.9±4.3
T. hip BMD (gcm^{-2})	0.75±0.14	0.65±0.13*	0.71±0.14*	0.70±0.13*	0.70±0.15*	0.70±0.14*
Fem neck BMD (gcm^{-2})	0.65±0.12	0.56±0.09*	0.61±0.11*	0.61±0.12**	0.60±0.11*	0.60±0.11*
Forearm BMD (gcm^{-2})	0.34±0.08	0.30±0.07*	0.32±0.07*	0.32±0.07**	0.31±0.08*	0.32±0.07*
AMCI	0.49±0.07	0.47±0.07*	0.48±0.06*	0.49±0.08	0.47±0.07*	0.48±0.07*
NDMCI	0.51±0.08	0.49±0.08*	0.49±0.07*	0.51±0.09	0.49±0.07*	0.49±0.07*
DMCI	0.47±0.08	0.45±0.07*	0.46±0.07**	0.47±0.08	0.45±0.07*	0.46±0.07*
$NDCI_2$	0.52±0.09	0.49±0.09*	0.50±0.09*	0.51±0.1	0.50±0.08*	0.50±0.09*
DCI_2	0.49±0.09	0.47±0.08*	0.48±0.08**	0.50±0.09	0.47±0.08*	0.48±0.08*
Clodronate treated (%)	2466 (50)	84 (47)	200 (45)*	34 (44)	97 (51)	367 (46)**

[a]94.6% of HIPS cohort; ANOVA and Chi-square test (clodronate treatment): *P≤0.001; **P<0.05.

6.4.2 PERFORMANCE ACCORDING TO QUARTILES OF MEASUREMENTS AND ROC CURVES

Total hip BMD, forearm BMD and AMCI measurements were divided into quartiles of skeletal strength (1=lowest) and cumulative incidence of all fractures in each quartile for the three measures are shown in Figure 6.1. This shows the steepest distribution in hip BMD quartiles, suggesting it to be the most discriminating measure. Incidence in quartiles of forearm BMD was similar to AMCI.

Figure 6.1. Cumulative incidence (%) of all fractures in quartiles of hip BMD, forearm BMD and AMCI (1=lowest).



Receiver operating characteristics (ROC) curves were produced for total hip BMD, forearm BMD and AMCI to study their performance in the overall identification of incident fractures (Figures 6.2 and 6.3). The areas-under-the-curve (AUC's) suggest that all 3 measures performed moderately well

in all-fracture identification (Table 6.2). Hip BMD was however somewhat superior when individual fracture types were studied, while the AUC of AMCI for vertebral fracture identification was insignificant.

Figure 6.2. Receiver operating characteristics (ROC) curves for skeletal measures at baseline: performance in identification of incident hip fracture.

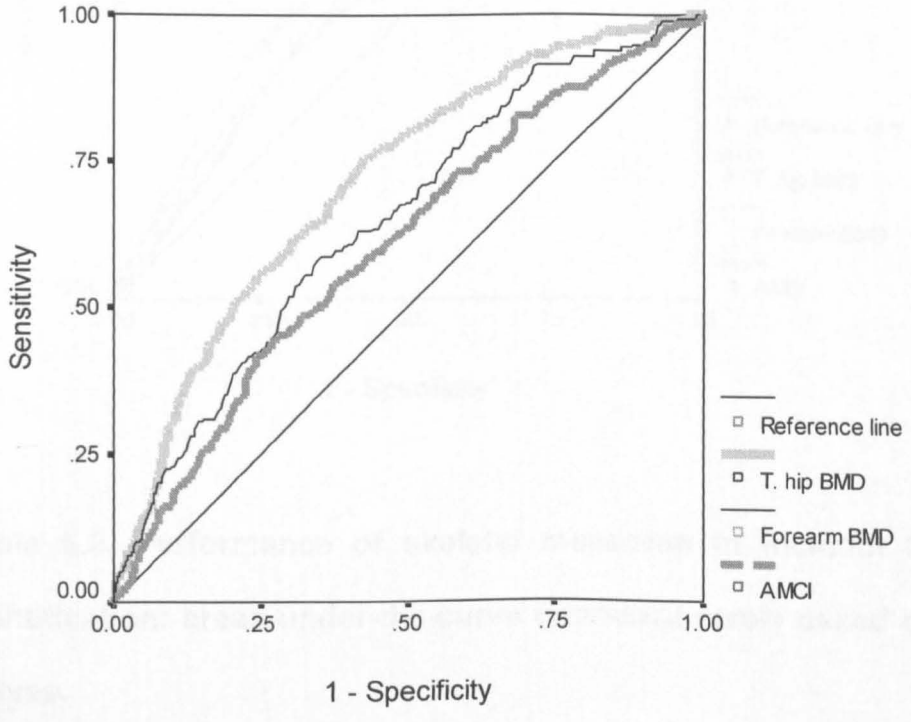


Figure 6.3. Receiver operating characteristics (ROC) curve for skeletal measures at baseline: performance in identification of any fracture (cumulative all-fracture incidence).

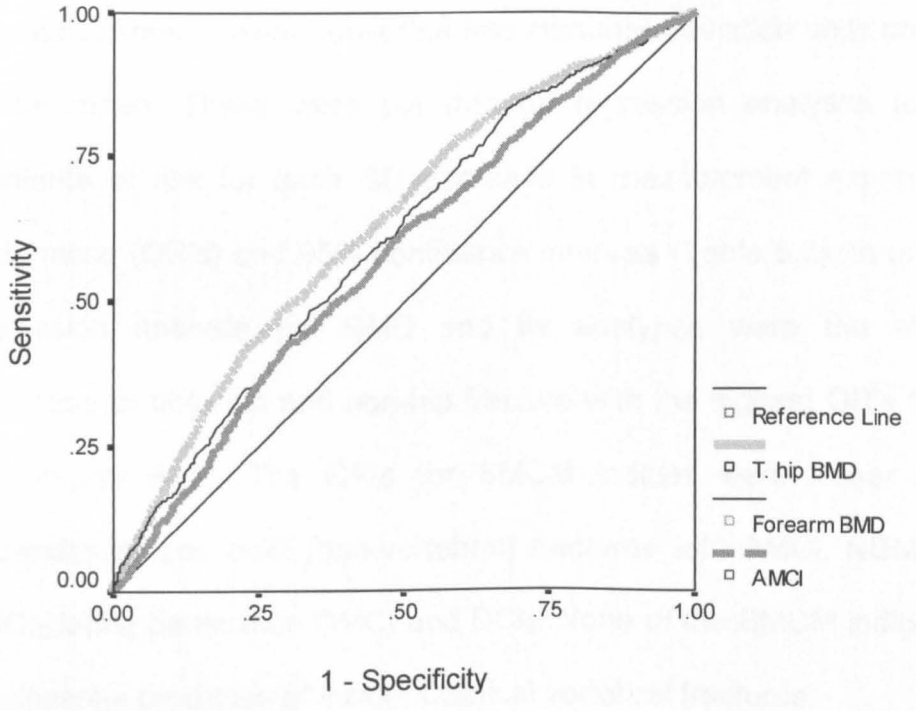


Table 6.2. Performance of skeletal measures in incident fracture identification: areas-under-the-curve (standard error) based on ROC curves.

	Hip fractures	Appendicular	Vertebral	Axial (non-vertebral)	All fractures
Total hip BMD	0.71 (0.02)	0.60 (0.01)	0.61 (0.03)	0.62 (0.02)	0.63 (0.01)
Forearm BMD	0.65 (0.02)	0.58 (0.01)	0.59 (0.03)	0.61 (0.02)	0.60 (0.01)
AMCI	0.61 (0.02)	0.57 (0.01)	0.51 (0.04)	0.58 (0.02)	0.58 (0.01)

6.4.3 GRADIENTS OF FRACTURE RISK FOR 1 STANDARD DEVIATION DECREASE IN MEASUREMENT

All measurements were converted into standard deviation units compared to the mean. These were put through regression analyses to obtain gradients of risk for each SD decrease in measurement expressed as odds ratios (OR's) and 95% confidence intervals (Table 6.3). In univariate regression analysis hip BMD and its subtypes were the strongest predictors of both hip and non-hip fracture with the highest OR's followed by forearm BMD. The OR's for SMCM indices were lesser for hip, appendicular and axial (non-vertebral) fractures with AMCI, NDMCI, and $NDCI_2$ faring better than DMCI and DCI_2. None of the SMCM indices were significantly predictive of incident clinical vertebral fractures.

After adjustment for significant extra-skeletal variables, hip, appendicular and axial (non-vertebral) fracture prediction remained significant with all the measures (Table 6.4). In all cases, trends noted in univariate analyses were preserved with hip BMD remaining the strongest predictor of hip and other fractures.

Table 6.3. Gradients of fracture risk for 1 SD decrease in baseline measurement expressed as odds ratios, 95% confidence intervals.

	Hip fractures	Appendicular	Vertebral	Axial (non-vert)	All fractures
Total hip BMD	2.09,1.80-2.43	1.42, 1.29-1.52	1.47, 1.18-1.84	1.54, 1.34-1.78	1.61, 1.49-1.74
Femoral neck BMD	2.47, 2.07-2.97	1.42, 1.28-1.58	1.45, 1.13-1.85	1.53, 1.31-1.80	1.64, 1.51-1.79
Forearm BMD	1.79, 1.52-2.11	1.33, 1.20-1.47	1.43, 1.13-1.82	1.52, 1.30-1.78	1.47, 1.35-1.59
AMCI	1.42, 1.22-1.65	1.24, 1.12-1.37	1.06, 0.84-1.32	1.33, 1.14-1.53	1.30, 1.20-1.40
NDMCI	1.38, 1.19-1.61	1.27, 1.15-1.40	1.08, 0.86-1.35	1.28, 1.11-1.48	1.30, 1.20-1.40
DMCI	1.38, 1.19-1.60	1.17, 1.06-1.29	1.03, 0.82-1.28	1.32, 1.14-1.52	1.24, 1.15-1.34
$NDCI_2$	1.41, 1.22-1.64	1.21, 1.09-1.33	1.15, 0.92-1.44	1.28, 1.11-1.49	1.26, 1.17-1.36
DCI_2	1.41, 1.21-1.64	1.15, 1.04-1.26	0.98, 0.78-1.23	1.32, 1.14-1.53	1.22, 1.13-1.31

Table 6.4. Gradients of fracture risk for 1 SD decrease in measurements adjusted for extra-skeletal variables significant in univariate analysis: age, height and weight for hip fracture; BMI and clodronate treatment for appendicular fractures; and age and weight for axial (non-vertebral) fractures (forward-conditional regression). Odds Ratios, 95% confidence intervals.

	Hip fractures	Appendicular	Axial (non-vert)	All fractures
Total hip BMD	1.81, 1.53-2.16	1.42, 1.28-1.56	1.54, 1.34-1.78	1.61, 1.49-1.74
Forearm BMD	1.40, 1.15-1.70	1.33, 1.20-1.47	1.52, 1.30-1.78	1.46, 1.35-1.59
AMCI	1.21, 1.03-1.42	1.24, 1.12-1.37	1.27, 1.09-1.48	1.26, 1.16-1.36
NDMCI	1.19, 1.01-1.40	1.27, 1.15-1.40	1.23, 1.06-1.43	1.26, 1.17-1.36
$NDCI_2$	1.22, 1.04-1.44	1.20, 1.09-1.33	1.23, 1.06-1.43	1.22, 1.13-1.33

6.4.4 INDEPENDENT PREDICTORS OF FUTURE FRACTURE

All variables significant at baseline were entered into multivariate logistic regression models to derive independent associations with fracture risk. Total hip BMD was an independent predictor for all fractures (Table 6.5). In addition, age and weight were independent predictors of hip fracture. Forearm BMD was an independent predictor of axial (non-vertebral) fracture but not of other types. Clodronate treatment was independently associated with reduced appendicular fracture risk. Although independent of age, weight and clodronate treatment as mentioned previously, AMCI was no longer significantly associated with either hip or other fracture type after adjustment for hip BMD.

Table 6.5. Independent predictors of future fracture: multivariate regression analysis.

	Hip fractures	Appendicular	Axial (non-vert)	All fractures
Age (yrs)	1.04, 1.01-1.08*	-	1.02, 0.98-1.05	1.00, 0.98-1.02
Height (cm)	1.02, 0.99-1.05	-	-	-
Weight (kg)	0.98, 0.97-1.00*	-	1.00, 0.98-1.02	1.00, 1.00-1.01
Total hip BMD (1SD decrease)	1.81, 1.53-2.16*	1.42, 1.29-1.57*	1.36, 1.12-1.64*	1.50, 1.35-1.66*
Forearm BMD (1SD decrease)	1.00, 0.78-1.27	1.06, 0.92-1.23	1.24, 1.01-1.51*	1.12, 1.01-1.25*
AMCI (1SD decrease)	1.01, 0.83-1.23	1.07, 0.95-1.21	1.05, 0.88-1.27	1.05, 0.95-1.16
Clodronate rx	-	0.79, 0.65-0.96*	1.07, 0.86-1.43	0.83, 0.71-0.98*

*Forward-conditional regression, $P<0.05$.

6.4.5 ASSOCIATIONS BETWEEN DXA AND SMCM INDICES

The correlation between hip and forearm BMD and SMCM indices was studied using scatter plots (Figures 6.4, 6.5 and 6.6), and Pearson coefficients (Table 6.6). AMCI had somewhat better correlations with both DXA indices than NDMCI although all correlations were significant. AMCI had stronger correlation with forearm than hip BMD.

Figure 6.4. Scatter plot showing correlation between AMCI and total hip BMD by T scores.

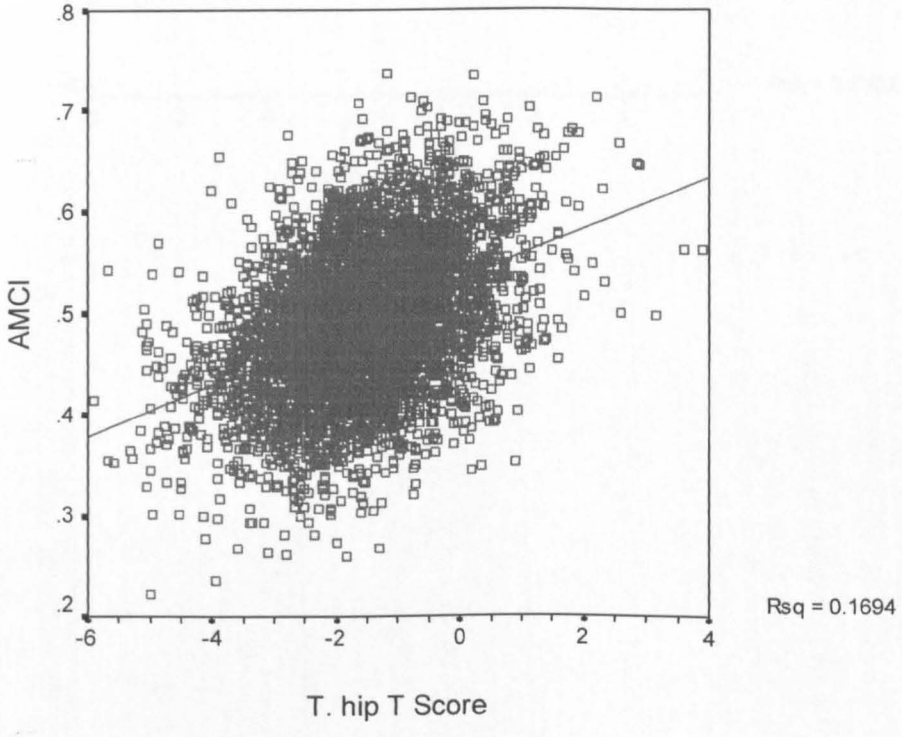


Figure 6.5. Scatter plot demonstrating correlation between AMCI and DXR-MCI.

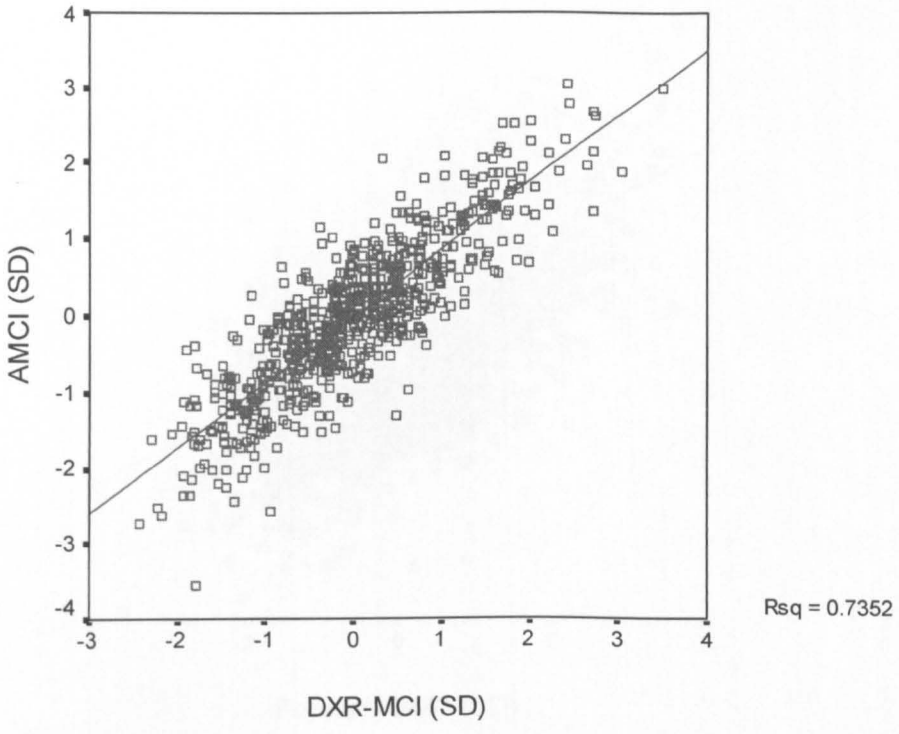


Figure 6.6. Scatter plot demonstrating correlation between AMCI and forearm BMD.

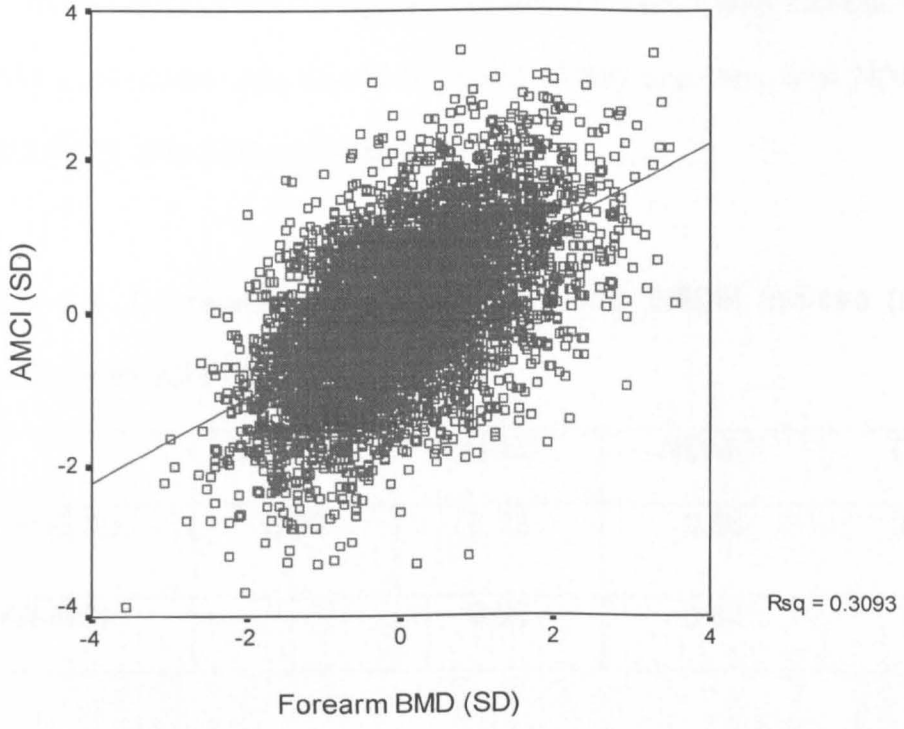


Table 6.6. Correlations between DXA and SMCM indices (Pearson coefficients, all P<0.001).

	Forearm BMD	AMCI	NDMCI
Total hip BMD	0.65	0.41	0.38
Forearm BMD	-	0.56	0.51
AMCI	-	-	0.93

6.4.6 COMPARISONS AND ASSOCIATIONS BETWEEN DXR AND SMCM INDICES

In the study group, 654 subjects also had DXR indices measured from the non-dominant hand. Of the MCM indices, DXR-BMD correlated best with AMCI (0.73) in this subgroup (Table 6.7). There were significant

differences (t-tests P<0.001) between mean DXR-MCI (0.32±0.05) and mean values of AMCI, NDMCI and DMCI (0.49±0.07, 0.51±0.08 and 0.47±0.08 respectively). Although mean DXR-MCI was closest to mean DMCI, correlation was best with AMCI (0.85) and less with NDMCI and DMCI (0.81 and 0.79 respectively).

Table 6.7. Correlations between DXR and SMCM indices (Pearson coefficients, all P<0.001) .

	DXR-MCI	AMCI	NDMCI	DMCI
DXR-BMD	0.90	0.73	0.68	0.67
DXR-MCI	-	0.86	0.81	0.79

6.4.7 DIAGNOSIS OF OSTEOPENIA AND OSTEOPOROSIS BY AMCI

Using the WHO definitions of osteopenia and osteoporosis based on total hip BMD (T scores <-1 and <-2.5 respectively) ROC curves were produced to illustrate the diagnostic ability of AMCI (Figures 6.7 & 6.8). The areas under the curve (AUC's) for diagnosis of both osteopenia and osteoporosis were similar (0.70, SE 0.01). Based on the ROC curves, three thresholds were chosen to derive sensitivity, specificity, positive predictive value and negative predictive value for both diagnoses and findings are summarised in Table 6.8. These suggest that an AMCI > 0.535 rules out osteoporosis with a high negative predictive value (92.1%)

and an AMCI < 0.485 suggests a diagnosis of osteopenia/osteoporosis with a high positive predictive value (81.2%).

Figure 6.7. ROC curve illustrating performance of AMCI in diagnosing osteoporosis (T. hip T score < -2.5).

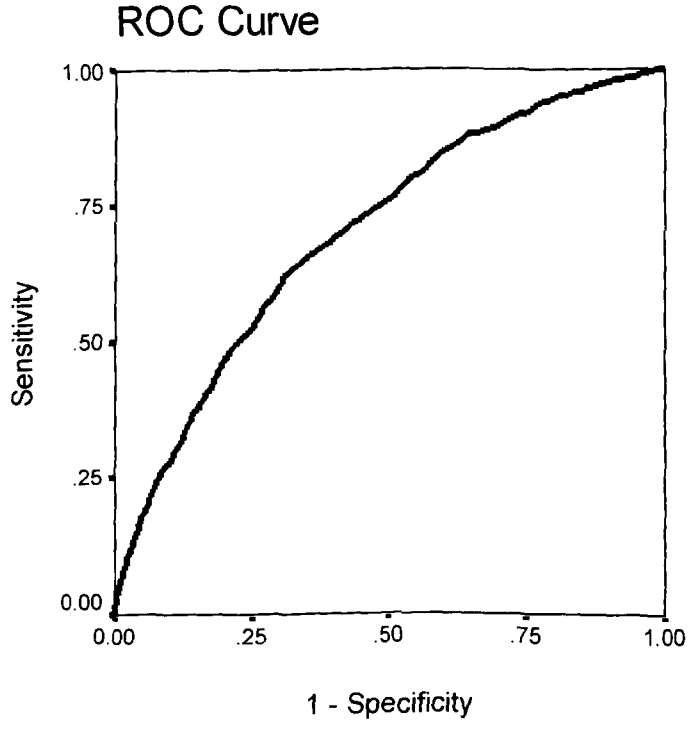


Figure 6.8. ROC curve illustrating performance of AMCI in diagnosing osteopenia or osteoporosis (T. hip T score <-1).

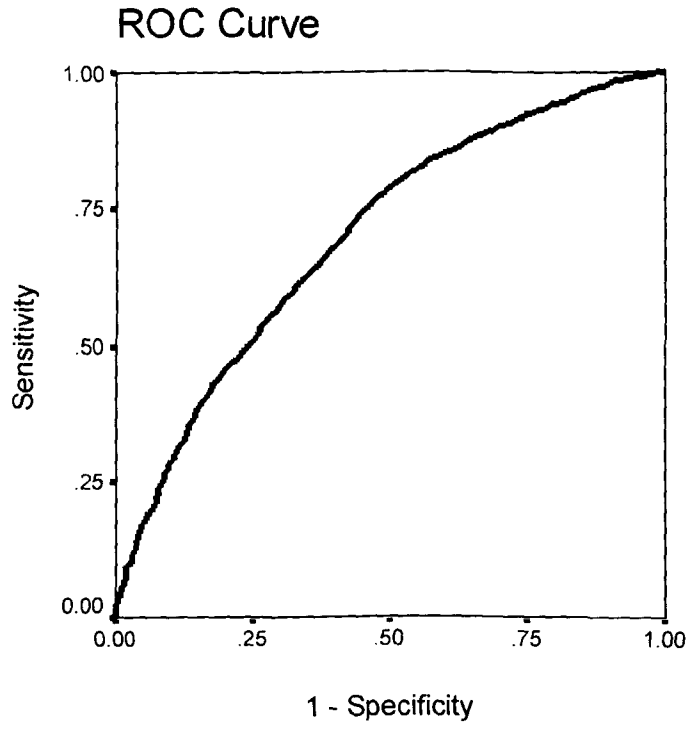


Table 6.8. Performance of various AMCI thresholds in diagnosing osteopenia/osteoporosis (T. hip T score <-1) and osteoporosis (T. hip T score <-2.5). PPV=positive predictive value & NPV=negative predictive value. All values as percentages.

AMCI threshold	Osteopenia				Osteoporosis			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
<0.485	54.3	73.1	81.2	41.3	69.5	59.5	27.5	89
<0.507	67.8	60.6	78.9	45.2	80.3	54.2	24.7	90.4
<0.535	82.0	44.8	76.4	52.1	90.0	29.9	22.2	92.1

6.5 DISCUSSION

In this study the ability of a new SMCM technique in predicting fracture risk was analysed and compared with other measures of skeletal strength. Hip and forearm BMD were significantly lower in all fracture groups. SMCM indices were significantly lower in hip, appendicular and axial (non-vertebral) fracture groups at baseline but not in the clinical vertebral fracture group. AMCI had slightly higher predictive ability for various fracture types than NDMCI or DMCI, but this was lower than that of hip and forearm BMD. None of the SMCM indices were significantly predictive of clinical vertebral fracture risk.

6.5.1 HAND DOMINANCE AND MCI

Although MCM has been traditionally performed on the non-dominant side, there have been few papers commenting on the effect of handedness, with particular reference to fracture risk assessment. In our study, NDMCI was significantly higher than DMCI across the whole cohort. This is in contrast to a recent report of significantly higher MCI on the dominant side in right handed people (0.62 vs 0.61, P=0.02), but no significant difference in left handed people (Vehmas, Solovieva et al. 2005). However, this study included only 543 subjects, the MCI was calculated from the 2nd metacarpal alone, and the difference was small although statistically significant.

In another study comparing the structure of the 2nd metacarpal based on hand dominance, Roy et al found that overall cortical thickness did not show significant side-related differences for either handedness although

significant periosteal and endosteal expansion of the second metacarpal cortex was noted on the dominant side, in both left- and right-handers (Roy, Ruff et al. 1994). Similarly, as noted earlier, in the present study mean bone width was higher on the dominant side, but this was off-set by lower mean cortical thickness, producing a lower mean DMCI compared to NDMCI. A greater loss of metacarpal cortical thickness in women compared to men after the 5th decade has been reported previously (Plato and Purifoy 1982). However, the mechanism for a differential loss producing a lower cortical thickness in either hand compared to the other is unclear.

6.5.2 PREDICTING FUTURE FRACTURE RISK

The performance of total hip and femoral neck BMD in predicting hip fracture (OR's 2.09 and 2.47 respectively) was somewhat lower than that reported by Bouxsein and colleagues for femoral neck BMD (relative hazard 3.0), but they used a case-cohort approach using a smaller, fracture-rich study group (Bouxsein, Palermo et al. 2002). Our results were closer to those reported in a meta-analysis of prospective studies where the relative risk for hip fracture was 2.6 for measurement at the hip (Marshall, Johnell et al. 1996).

The SMCM indices performed similarly in predicting future fracture risk in our study with AMCI performing slightly better than the other indices. A fairly large intra-observer reproducibility error (CV=9.37%) was reported previously with the SMCM technique in acquiring unilateral MCI from a single (right second) metacarpal (Dey, McCloskey et al. 2000). AMCI is a composite measurement from six metacarpals rather than a single

metacarpal. This may have reduced the confounding effect of measurement error providing a more accurate skeletal strength assessment resulting in the somewhat better performance noted in fracture prediction compared to the single metacarpal measures (DCI_2 and $NDCI_2$).

SMCM indices did not predict clinical vertebral fracture risk although non-vertebral axial fracture risk was predicted. In three previous studies metacarpal indices have been shown to predict vertebral fracture risk (Dey, McCloskey et al. 2000; Bouxsein, Palermo et al. 2002; Bach-Mortensen, Hyldstrup et al. 2006). The first two of these studies used non-prospective approaches on smaller cohorts using patients known to have (and therefore essentially prevalent) vertebral fractures and comparing them to controls. The prospective study reported by Bach-Mortensen et al had a longer mean follow-up of 6.1 years (compared to mean of 4 years for the present study), and while they reported an OR of 2.0 for vertebral fracture with 1 SD decrease in DXR-BMD, DXR-MCI was not reported on for any of the fracture types studied. In the present study only clinically reported and confirmed vertebral fractures were included prospectively, and regular radiological screening of the whole cohort was not undertaken to confirm all incident vertebral deformities. However, it is known that the majority of vertebral fractures are silent (Ziegler, Scheidt-Nave et al. 1996; McKiernan 2009). The incidence of vertebral fracture has been reported as 10.7/1000 per year in European women over 50 years (EPOS 2002). In fact, in the HIPS cohort itself, at baseline the prevalence of vertebral fracture was 14.5% by vertebral fracture analysis of densitometer acquired

images (McCloskey, Vasireddy et al. 2008). The cumulative incidence of radiological vertebral fractures is therefore likely to have been higher than the clinically reported fractures (1.6%, Table 6.1) in the present study. It may be speculated that SMCM indices may have been predictive if all radiologically detectable vertebral deformities were included in the analysis, particularly, as noted in Table 6.3, there was a trend for $NDCI_2$ for predicting vertebral fractures with an OR of 1.15 for 1 SD decrease, although the confidence intervals embraced unity. Another possibility may be that perhaps, SMCM measures are more geometric, structural indices rather than density indices, and the latter may be of more value in predicting vertebral fractures. However, this explanation seems less likely, as DXR-MCI in the VOT cohort (Chapter 5), also calculated similarly, not only significantly predicted incident morphometric vertebral fractures (cumulative incidence 16.7% over a similar follow-up period) with a performance similar to lumbar spine BMD, but it was also independent of spine BMD in its predictive ability in multivariate analysis.

6.5.3 ASSOCIATIONS AMONGST THE VARIOUS SKELETAL MEASURES

Of the SMCM indices AMCI had the strongest correlations with hip and forearm BMD. In fact, AMCI also had better correlations with DXR indices than NDMCI, although the DXR indices were also measured only from the non-dominant side. This is again possibly because AMCI is a composite measurement from six metacarpals reducing the measurement error and regressing it more towards true skeletal strength. However, there was high correlation between AMCI and NDMCI (r=0.93) and this was better than

that with DXR-MCI for either (r=0.86 and 0.81 respectively). The correlation between forearm BMD and AMCI (r=0.56) was slightly better than that reported previously between forearm BMD and MCI by the Teijin Bonalyzer® (r=0.50) (Dey, McCloskey et al. 2000), but somewhat worse than that reported by Bouxsein et al between distal radius BMD and DXR-BMD (r=0.68) (Bouxsein, Palermo et al. 2002), and that reported earlier in Chapter 4 between forearm BMD and DXR-BMD, and between forearm BMD and DXR-MCI from the HIPS cohort (r=0.71 and 0.68 respectively, Table 4.7).

The mean DXR-MCI was significantly lower than the mean NDMCI measured from the same side despite the correlation being high. This is most likely because the difference is systematic, and similar to the systematic discrepancy noted previously with MCI by SMCM and the Teijin Bonalyzer® (mean, 0.44 and 0.36 respectively, P<0.001) (Dey, McCloskey et al. 2000). This is likely to be because the measurements are acquired somewhat differently by different methods. DXR cortical thickness and bone width measurements are averaged over much longer regions of interest (ROI). For example, the measurement ROI on the shaft of the second metacarpal is 2.0 cm long (Bouxsein, Palermo et al. 2002). Anatomically, the thickest part of the cortex of a tubular bone is in the mid-shaft or diaphysis, gradually thinning out towards the metaphysis, while the bone width is lowest at middle of the diaphysis and gradually increases towards the metaphysis. Therefore, the longer segments measured in DXR are likely to give, on averageing, lower cortical thickness and higher

bone width, compared to the midshaft measurements of SMCM, resulting in lower DXR-MCI.

6.5.4 POTENTIAL LIMITATIONS

The setting for the study was a trial of clodronate, which could have affected the fracture predictive ability of baseline measures. However, clodronate had no significant effect on hip and axial fractures. Although there was a protective effect on appendicular fracture and overall fracture incidence, DXA and SMCM measures remained significantly predictive of fracture risk after adjustment for clodronate treatment in logistic regression models.

The median follow up was relatively short (4 years). Bouxsein et al reported that metacarpal measures were predictive of fracture over a similar follow up period (Bouxsein, Palermo et al. 2002), and Bach-Mortensen et al reported predictive ability over a somewhat longer mean follow up of 6.1 years (Bach-Mortensen, Hyldstrup et al. 2006). The ability of MCM in predicting longer term fracture risk is unknown, but this is likely to be similar to that of other peripheral measures such as forearm BMD with which it correlates well. For example, forearm BMD has been shown to be predictive of fracture risk over a 25 year period (Duppe, Gardsell et al. 1997).

As mentioned previously, a fairly large intra-observer reproducibility error with SMCM has been reported previously for MCI from a single metacarpal which may compromise its utility in a clinical setting (Dey, McCloskey et al. 2000). However, AMCI, a six-metacarpal measure, seems to have

improved correlation with other established skeletal measures without compromising the fracture predictive ability.

6.6 CONCLUSIONS

In this prospective study, we found that a new, rapid, semi-automated MCM technique predicts future risk of fracture. Although forearm BMD and AMCI were similarly predictive of appendicular fractures, the fracture predictive ability of hip and forearm BMD by DXA remained superior overall for all fractures, including clinical vertebral fractures where SMCM indices were not predictive.

The results suggest good evidence for the use of AMCI by SMCM as an alternative peripheral measure of skeletal strength especially where other measures of skeletal assessment are not available. It may also have a screening role in identifying those who might be referred for axial DXA.

7 EFFECTS OF PRE-EXISTING MEDICAL CONDITIONS ON METACARPAL RADIOGRAPHIC INDICES

7.1 ABSTRACT

Introduction: Several medical conditions may affect the peripheries, but their effect on peripheral bone strength measurements has been poorly studied. In this study, the distribution of measurements with dual-energy x-ray absorptiometry (DXA), a semi-automated metacarpal morphometry (SMCM) technique, and digital x-ray radiogrammetry (DXR) were studied in elderly women with respect to medical history.

Methods: The MRC HIPS study was a community based study of risk factors for hip fractures in elderly women, combined with a placebo controlled trial of clodronate (Bonefos®). Self-reported medical history was recorded at study entry. Baseline measurements included hip and forearm DXA and hand radiographs for SMCM and DXR. 4929 participants had non-dominant hand and average-of-both-hands metacarpal cortical indices (ND-MCI & AMCI) measured using a locally developed SMCM technique. 687 randomly selected participants also had DXR bone mineral density (DXR-BMD) & DXR-MCI measured.

Results:

SMCM cohort: Compared to the whole cohort, hip & forearm DXA and AMCI & ND-MCI were lower in rheumatoid arthritis (RA), current glucocorticoid (GC) use, and RA+GC use ($P<0.05$), and were higher in type 2 diabetes ($P<0.01$). Hip & forearm DXA were slightly higher in hypothyroidism, while AMCI & ND-MCI were slightly lower with a history of stroke ($P<0.05$). When the measures were converted to standard deviation units (cohort Z scores) the largest magnitude for the measures (in either positive or negative direction) was seen with RA+GC use (hip DXA –0.53,

forearm DXA –0.82, AMCI –1.14, ND-MCI –1.09) and least with OA (+0.04, +0.04, -0.01 & -0.01 respectively).

DXR cohort: RA, CS use, and RA+GC use had lower forearm DXA and DXR indices ($P<0.05$). Trends in other conditions were similar to that in the larger cohort but did not reach significance. Cohort z-scores were similarly largest for all measures with RA+GC use, and least in OA. When changes were converted to standard deviation units with respect to peak bone mass (T scores), the whole cohort's mean T scores were hip DXA –1.64, forearm DXA –2.66 and DXR-BMD –2.97. Changes were largest with RA+GC use (-2.4, -4.15 & -5.09 respectively), and least for hip DXA with stroke (-1.49), for forearm DXA with hypothyroidism (-2.5), and for DXR-BMD with Parkinson's (-2.68).

Conclusions: In this study, there was a trend for disproportionately greater bone loss with age at the metacarpal site compared to the hip and forearm. In some medical conditions there is an even greater discrepancy in the MCM measures suggesting a disease related bone loss or gain compared to the mean at the periphery. The trends were significant with forearm and metacarpal indices in RA where, in fact, forearm BMD was the strongest predictor of all fracture risk, while hip BMD was the strongest predictor of all fracture risk in the whole cohort. These factors will need to be taken into account when reporting and interpreting MCM indices, especially when they are likely to be used as stand alone services.

7.2 INTRODUCTION

Although a significant proportion of osteoporosis in the community is post-menopausal or senile in etiology, it often occurs as a consequence of, or is accelerated by other conditions such as medical diseases or drug exposures (Johnson, Lucasey et al. 1989). Medical conditions have also been shown to be associated with fracture risk itself independent of bone mineral density (BMD). Rheumatoid arthritis (RA) has been shown to be associated with osteoporosis in early and late disease (Gough, Lilley et al. 1994; Shenstone, Mahmoud et al. 1994). Increased hip and vertebral fracture risk in RA has been reported previously, particularly when treated with glucocorticoids (Cooper, Coupland et al. 1995; Peel, Moore et al. 1995). Increased bone loss, with resulting osteoporosis and increased fracture risk, has also been documented with corticosteroid therapy independent of underlying disease (van Staa, Leufkens et al. 2002).

A significant proportion of patients with stroke have been shown to be osteoporotic at stroke-onset (Watanabe 2004). Stroke has also been shown to be associated with accelerated bone loss post-stroke with increased fracture risk (Poole, Reeve et al. 2002). Type 1 diabetes mellitus (DM) is associated with modest bone loss while type 2 DM is associated with increased BMD (Schwartz 2003). However, more recently both type 1 and type 2 DM have been shown to be associated with increased fracture risk (Nicodemus and Folsom 2001; Schwartz, Sellmeyer et al. 2001). In hyperthyroidism an increased fracture risk has been reported as a result of bone loss and osteoporosis, while in hypothyroidism an increased fracture risk has been reported despite

normal or increased bone density (Vestergaard, Weeke et al. 2000; Lakatos 2003).

Measurement of BMD by dual-energy x-ray absorptiometry (DXA) at the spine or hip has been the reference standard for the diagnosis of osteoporosis and estimation of fracture risk (Kanis 1994). However, setting up and running a full-fledged DXA service can be a significant expense, and this has been a limiting factor in the provision of osteoporosis services in many parts of the world. Therefore, technologies with cost, space and portability advantages are being developed for the assessment of osteoporosis and prediction of fracture and are becoming more widely available. Metacarpal morphometry (MCM) was one of the earliest methods described for systematically assessing bone strength from hand radiographs (Barnett and Nordin 1960). However traditional MCM was tedious and time consuming involving several measurements with callipers and manual calculation of metacarpal cortical index (MCI) and did not achieve mainstream recognition. More recently, a semiautomated MCM (SMCM) technology which was developed in-house in Sheffield at the WHO Collaborating Centre has been described previously (Dey, McCloskey et al. 2000), and its performance in fracture prediction was described in Chapter 6. A commercial digital x-ray radiogrammetry (DXR) system has also recently been available which uses fully automated MCM to derive MCI and DXR-BMD (Jorgensen, Andersen et al. 2000), and its performance in fracture prediction has been described in Chapters 4 and 5.

With greater availability, peripheral bone strength assessing technologies including those based on MCM are beginning to be used more frequently in the provision of osteoporosis services. Several medical conditions such as those discussed above may affect the peripheries, but their effect on peripheral bone strength measurements, and consequently on fracture prediction, has been poorly studied. Measurements with DXA at the hip and forearm, an in-house SMCM technique, and a commercially available DXR system in elderly women with respect to medical history were compared in this study.

7.3 METHODS

7.3.1 SUBJECTS

This analysis was carried out on the data from participants in the MRC Hip Fracture Prevention Study (HIPS). This was a Sheffield, UK, based study of risk factors for hip fracture in elderly women, combined with a double-blind placebo-controlled trial of the oral bisphosphonate, clodronate (Bonefos®). 5212 community dwelling women aged 75 years or over were recruited to the study. They received either oral clodronate 800 mg daily or identical placebo daily for 3 years and were followed for up to a further 2 years. At baseline extensive data were collected including self-reported medical history.

7.3.2 DESIGN

The current analysis was performed on 4929 women from the HIPS cohort who had SMCM measurements (described below) from hand radiographs. 687 participants from the HIPS who were pre-selected for other nested case-control analyses also had DXR measurements from the hand radiographs, and analysis of DXR indices from this subgroup also is presented.

7.3.3 MEASUREMENTS / INVESTIGATIONS

All subjects had height and weight measured, and had baseline hand radiographs taken at study entry.

7.3.3.1DXA

Total hip and distal forearm BMD was measured on the non-dominant side by Hologic QDR4500A (Hologic Inc., Bedford, USA), and Osteometer DTX 200 (Osteometer, Hawthorne, USA) respectively.

7.3.3.2Semi-automated metacarpal morphometry

An in-house technique developed in Sheffield and described previously was used (Dey, McCloskey et al. 2000). A transparent cross-hair cursor with click buttons and a back-lit digitising tablet were developed for capturing measurements automatically on to an electronic database. The hand radiograph was placed on the digitising tablet and the cursor was moved on the regions of interest. The distance between any two points was measured by clicking the cursor on the first point and dragging it over the digitising tablet to the second point and clicking a second time, the

distance between the two clicks being recorded electronically in the database. The software program algorithm allowed for a set sequence of measurements to be taken with a series of clicks without any further operator input.

Measurements of length, medial and lateral cortical thicknesses and total bone width of the second, third and fourth metacarpals were captured from both hands. The data were subsequently transferred to the SPSS version 11 statistical package for processing and analysis.

The cortical index (CI) of a tubular bone is calculated as follows: CI = $2t/W$, where 't' is the cortical thickness and 'W' is the bone width. The metacarpal cortical index is calculated as the weighted average of the cortical indices of the middle 3 metacarpals as follows: MCI= $(CI_2+CI_3+0.5CI_4)/2.5$.

The MCI's for both the dominant (DMCI) and non-dominant (NDMCI) hands were calculated and an average MCI was calculated as follows: AMCI=(DMCI+NDMCI)/2.

7.3.3.3DXR measurements

DXR measurements were obtained from the non-dominant hand in the hand radiograph using the Pronosco X-posure System® version 2.0 (Sectra-Pronosco, Denmark). This system uses a high resolution scanner for scanning the hand radiograph and the data are processed in a dedicated computer. The software automatically identifies the regions of interest for measurement and the output indices are DXR-MCI which is computed as above, and DXR-BMD which is computed as follows: DXR-BMD= $c \pi t (1 - t/W)$, where 't' is the average cortical thickness, 'W' the

average bone width and '*c*' is a constant representing the average mineral mass / unit volume of compact bone (Rosholm, Hyldstrup et al. 2001).

7.3.4 STATISTICS

The primary data from HIPS as well as the metacarpal radiographic data were collected initially on Microsoft Access based databases. The data were processed and analysed using the SPSS® version 11.x statistical package. Baseline measurements were compared using ANOVA and Chi-square tests. Measurements were also converted to standard deviation (SD) units and the magnitude of variation amongst the skeletal measures in each medical condition was studied using paired t-tests and Wilcoxon signed rank tests. Gradients of risk for future fracture with 1 SD decrease in measurement were calculated using regression models. Correlations between various measures were expressed as Pearson coefficients. A P value of <0.05 was considered significant.

7.4 RESULTS

SMCM measurements were compared to DXA measurements in various conditions in the larger cohort and are presented first. DXR measurements available in the smaller subgroup were compared with DXA and are presented separately below.

Medical conditions considered included any history of RA, OA, current glucocorticoid use (CS use) for any reason, stroke, Parkinson's disease (PD), type 1 diabetes, type 2 diabetes, hypothyroidism, and hyperthyroidism.

7.4.1 SMCM COHORT: SMCM AND DXA INDICES

7.4.1.1Baseline characteristics

Compared to the rest of the cohort, total hip BMD, forearm BMD, and AMCI were lower in RA, CS use, and RA+GC use (all $P<0.05$), and were higher in OA and type 2 diabetes ($P<0.01$) (Table 7.1). Hip and forearm BMD were slightly higher in hypothyroidism, while AMCI was slightly lower with a history of stroke ($P<0.05$). There were also statistically significant differences in one or more extra-skeletal variables (age, height and weight) in RA, RA+GC, OA, type 2 DM and hypothyroidism when compared to the rest of the cohort.

Table 7.1. SMCM cohort: DXA & SMCM indices in various clinical conditions (mean ± SD).

	No.	Age (yrs)	Height (cm)	Weight (kg)	T. hip BMD (gcm^{-2})	Forearm BMD (gcm^{-2})	AMCI
Total cohort	4929	79.5±3.9	155.9±6.1	65.1±12.1	0.75±0.14	0.34±0.08	0.49±0.07
RA	98	79.5±4.0	155.4±6.3	62.3±11.7[a]	0.70±0.14[b]	0.32±0.08[b]	0.44±0.09[b]
Current GC use	164	78.9±3.3	155±6.0	63.8±13.2	0.72±0.14[b]	0.32±0.08[b]	0.46±0.08[b]
RA+GC	29	79.1±3.8	154±6.4	59.1±8.5[a]	0.68±0.12[a]	0.28±0.06[b]	0.41±0.09[b]
OA	3435	79.7±4.0[b]	155.7±6.1[a]	66.1±12.3[b]	0.76±0.14[b]	0.34±0.08[b]	0.49±0.07
Stroke	122	80.2±4.1[a]	155.5±6.6	66±13.1	0.73±0.16	0.33±0.08	0.48±0.07[a]
Parkinson's	43	79.6±3.7	153.6±7.1[a]	62.6±15.4	0.74±0.16	0.33±0.08	0.48±0.09
Type 1 DM	40	78.8±3.7	157.2±6.6	72.8±14.2[b]	0.77±0.18	0.36±0.09	0.48±0.08
Type 2 DM	222	79.8±4.0	155.6±6.5	68.8±12.7[b]	0.81±0.15[b]	0.37±0.08[b]	0.51±0.07[b]
Hypothyroidism	416	79.3±4.0	156.3±6.0	68.1±13.0[b]	0.77±0.14[a]	0.35±0.08[b]	0.50±0.07
Hyperthyroidism	47	80.1±4.0	156.4±6.2	62.4±10.0	0.72±0.14	0.32±0.08	0.48±0.07

[a]$P<0.05$, and [b]$P\leq0.001$ by ANOVA compared to rest of cohort.

The differences in the mean skeletal measures in these conditions were studied in linear regression to determine significance with respect to extra-skeletal variables (Table 7.2). After adjustment for significant extra-skeletal variables, Beta coefficients for hip BMD, forearm BMD and AMCI in RA, and for forearm BMD and AMCI in RA+GC remained significantly lower compared to the total cohort. Similarly, in type 2 DM, Beta coefficients remained significantly higher for all three skeletal measures compared to mean cohort values after adjustment for significant extra-skeletal variables. Beta coefficients were no longer significant in OA and hypothyroidism after adjustment for extra-skeletal variables.

Table 7.2. Differences in mean skeletal measures in selected conditions compared to mean cohort values expressed as Beta coefficients in linear regression: Unadjusted (univariate) and adjusted (multivariate) for significant extra-skeletal variables (one or more of age, height and weight as appropriate).

	Hip BMD		Forearm BMD		AMCI	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
RA	-0.056[b]	-0.041[b]	-0.026[a]	-0.017[a]	-0.055[b]	-0.052[b]
RA+GC	-0.075[a]	-0.041	-0.063[b]	-0.043[b]	-0.080[b]	-0.073[b]
OA	0.017[b]	0.001	0.01[b]	0.001	-	-
Type 2 DM	0.062[b]	0.04[b]	0.035[b]	0.023[b]	0.021[b]	0.017[b]
Hypothyroidism	0.017[a]	0.001	0.014[b]	0.003	-	-

[a]P<0.05 and [b]P<0.001.

7.4.1.2Comparison of cohort Z scores in various medical conditions

When the measurements were converted to standard deviation units (cohort Z scores) the largest magnitude (either positive or negative) in the scores was seen with RA+GC use (hip DXA –0.53, forearm DXA –0.82, & AMCI –1.14) and least with OA (+0.04, +0.04, & -0.01 respectively) (Table 7.3). AMCI Z scores were significantly lower than hip Z scores in RA and RA+GC subgroups, and significantly lower than forearm Z scores in RA, type 1 DM and type 2 DM subgroups (paired t tests, $P<0.05$). Similar findings were noted with OA, but the magnitude of the scores themselves was smallest compared to the other medical conditions as mentioned above, suggesting the statistical significance is secondary to the large numbers of patients rather than a clinically relevant difference. Although there were some trends towards lower AMCI Z scores in other medical conditions, they were not statistically significant.

Table 7.3. SMCM cohort: comparison of cohort Z scores [mean (standard error of mean)] of skeletal measures in prevalent medical conditions.

	Hip BMD	Forearm BMD	AMCI
RA	-0.39(0.10)	-0.34(0.10)	-0.77(0.13)[a,b]
Current GC	-0.26(0.08)	-0.28(0.08)	-0.41(0.09)
RA+GC	-0.53(0.16)	-0.82(0.16)	-1.14(0.23)[a]
OA	0.04(0.02)	0.04(0.02)	-0.01(0.02)[a,b]
Stroke	-0.16(0.11)	-0.1(0.10)	-0.21(0.09)
Parkinson's	-0.11(0.18)	-0.2(0.15)	-0.21(0.19)
Type 1 DM	0.11(0.21)	0.22(0.19)	-0.25(0.18)[b]
Type 2 DM	0.42(0.07)	0.44(0.07)	0.29(0.07)[b]
Hypothyroidism	0.11(0.05)	0.16(0.05)	0.07(0.05)
Hyperthyroidism	-0.24(0.14)	-0.21(0.14)	-0.21(0.15)

Paired t-tests: [a]P<0.05 compared to hip BMD; [b]P<0.05 compared to forearm BMD.

7.4.1.3Gradients of risk for incident fracture in SMCM cohort, and RA and type 2 DM subgroups (Table 7.4)

To assess whether the significant differences amongst the three skeletal measures in RA were reflected in prediction of fracture risk, gradients of risk for incident fracture for 1 SD decrease in measurement were computed for the whole SMCM cohort and for the RA subgroup of the

SMCM cohort with adjustments for age, weight and clodronate treatment status.

In the whole cohort, total hip BMD was the strongest predictor of all (any) fractures with the odds ratios (OR's) for t. hip BMD, forearm BMD and AMCI being 1.61, 1.47 and 1.26 respectively (all $P<0.05$). In the RA subgroup, forearm BMD was the strongest predictor of all fractures with the OR's for the three measures for all fractures being 1.63, 1.85 and 1.17 respectively ($P<0.05$ for forearm BMD only). In type 2 DM, hip BMD was the strongest predictor with the OR's for the three measures being 1.99, 1.81 and 1.29 respectively ($P<0.05$ for hip and forearm BMD only).

Similar trends were noted for prediction of appendicular fracture. The OR's for appendicular fracture in the whole cohort were 1.47, 1.38 and 1.29 for total hip BMD, forearm BMD and AMCI respectively (all $P<0.05$). The OR's for appendicular fracture in the RA subgroup were 1.35, 1.84 and 1.15 respectively (none significant). In type 2 DM, hip BMD remained the strongest predictor of appendicular fracture as well, with the OR's for the three measures being 1.82, 1.0 and 1.15 respectively ($P<0.05$ for hip BMD only).

Table 7.4. SMCM cohort: Gradients of risk for incident fracture for 1SD decrease in skeletal measurement in whole cohort, and RA and type 2 DM subgroups (adjusted for age, weight and clodronate treatment; n=number of fractures).

	All fractures			Appendicular fracture		
	SMCM cohort (n=792)	RA subgroup (n=21)	Type 2 DM (n=32)	SMCM cohort (n=449)	RA subgroup (n=14)	Type 2 DM (n=15)
T. hip BMD	1.61, 1.48-1.74[a]	1.63, 0.92-2.90	1.99, 1.35-2.92[a]	1.47, 1.33-1.63[a]	1.35, 0.71-2.59	1.82, 1.10-3.02[a]
Forearm BMD	1.47, 1.35-1.59[a]	1.85, 1.04-3.29[a]	1.81, 1.20-2.72[a]	1.38, 1.24-1.53[a]	1.84, 0.86-3.91	1.0, 0.51-1.96
AMCI	1.26, 1.16-1.36[a]	1.17, 0.76-1.78	1.29, 0.88-1.90	1.29, 1.17-1.44[a]	1.15, 0.70-1.86	1.15, 0.68-1.95

[a]Forward-conditional regression, P<0.05.

7.4.1.4Correlations amongst the skeletal measures in SMCM cohort and RA subgroup

AMCI had similar correlations with hip BMD in the whole SMCM cohort and in RA and type 2 DM subgroups (Pearson coefficients, r= 0.41, 0.44 and 0.40 respectively, all P<0.001). AMCI had similar correlations with forearm BMD also in the SMCM cohort and RA and type 2 DM subgroups (r=0.56, 0.57, and 0.60 respectively, all P<0.001). However, the correlation between hip and forearm BMD was better in the whole SMCM cohort than in the RA subgroup, but was similar to that in type 2 DM subgroup (r=0.65, 0.51 and 0.66 respectively, all P<0.001).

7.4.2 DXR COHORT: DXR AND DXA INDICES

7.4.2.1Baseline Characteristics

Compared to the rest of the cohort mean forearm BMD, DXR-BMD and DXR-MCI were lower with RA, CS use and RA+GC use ($P<0.05$ for all) (Table 7.5). Although total hip BMD was also somewhat lower with RA, CS use, RA+GC use and type 1 DM, this did not reach significance. There were no significant trends with the other disorders. Although there were some differences in extra-skeletal variables (age, height and weight) in the various conditions compared to the rest of the cohort, none were statistically significant.

Table 7.5. DXR cohort: DXA measures and DXR indices in various clinical conditions (mean ± SD).

	No.	Age	Height	Weight	T. hip BMD	Forearm BMD	DXR-BMD	DXR-MCI
Total cohort	687	79.7±4.0	156±6.4	64.4±12.3	0.74±0.15	0.34±0.08	0.43±0.06	0.32±0.05
RA	14	79.1±3.8	157.7±7.3	64.8±10.7	0.71±0.15	0.28±0.08[b]	0.40±0.07[a]	0.27±0.05[b]
Current GC use	21	79±2.4	155.7±5.6	64.8±12.9	0.70±0.12	0.30±0.05[a]	0.40±0.06[b]	0.29±0.06[b]
RA+GC	4	76±0.8	158.2±7.1	66.7±3.0	0.65±0.04	0.25±0.02[a]	0.33±0.04[b]	0.23±0.04[b]
OA	479	79.8±4.0	155.8±6.5	64.9±11.9	0.75±0.15	0.34±0.08[a]	0.43±0.05	0.32±0.05
Stroke	15	79.7±2.8	155.6±4.8	63.7±9.9	0.76±0.16	0.33±0.07	0.42±0.04	0.30±0.04
Parkinson's	7	80±3.6	155.6±5.0	60.9±7.4	0.76±0.10	0.33±0.07	0.45±0.06	0.32±0.05
Type 1 DM	4	80.8±4.8	155.6±5.5	69.2±24.0	0.66±0.20	0.37±0.14	0.44±0.07	0.31±0.09
Type 2 DM	25	80.8±4.2	155±6.5	68.3±13.9	0.75±0.12	0.34±0.07	0.42±0.05	0.31±0.05
Hypothyroidism	61	80.1±4.7	156±7.1	66.7±13.4	0.75±0.16	0.35±0.08	0.44±0.05	0.32±0.05
Hyperthyroidism	8	77.4±2.3	157.3±6.7	65.3±10.2	0.75±0.06	0.35±0.05	0.44±0.05	0.32±0.05

[a]$P<0.05$, and [b]$P<0.01$ by ANOVA compared to rest of cohort.

7.4.2.2Comparison of cohort Z scores in various medical conditions

Like in the SMCM group, cohort Z scores in the DXR group were of the largest magnitude for all measures with RA+GC use (total hip -0.64, forearm -1.13, DXR-BMD -1.79 and DXR-MCI -1.64); and least in OA (0.04, 0.05, 0.01, and 0.03 respectively) (Table 7.6). When Z scores for all 4 indices were compared within each medical condition subgroup, forearm and DXR-MCI Z scores were significantly lower than total hip Z score in the RA subgroup (paired t-test $P<0.05$). Differences within other conditions were not significant.

Table 7.6. DXR cohort: comparison of cohort Z scores [mean (standard error of mean)] of different skeletal measures in prevalent medical conditions.

	T. hip	Forearm	DXR-BMD	DXR-MCI
RA	-0.21(0.28)	-0.7(0.26)[a]	-0.64(0.33)	-0.8(0.28)[a]
Current GC	-0.31(0.18)	-0.45(0.13)	-0.62(0.22)	-0.56(0.25)
RA+GC*	-0.64(0.15)	-1.13(0.15)	-1.79(0.36)	-1.64(0.36)
OA	0.04(0.05)	0.05(0.04)	0.01(0.04)	0.03(0.04)
Stroke	0.12(0.28)	-0.07(0.24)	-0.28(0.18)	-0.34(0.20)
Parkinson's*	0.13(0.26)	-0.14(0.33)	0.25(0.40)	0.11(0.36)
Type 1 diabetes*	-0.55(0.70)	0.41(0.91)	0.11(0.63)	-0.12(0.83)
Type 2 diabetes	0.04(0.16)	0.1(0.19)	-0.14(0.18)	-0.11(0.18)
Hypothyroidism	0.03(0.14)	0.12(0.14)	0.17(0.12)	0.08(0.13)
Hyperthyroidism*	0.09(0.15)	0.24(0.25)	0.14(0.28)	0.13(0.32)

[a]$P<0.05$ compared to t. hip Z score by paired t-tests. *Wilcoxon signed rank test.

7.4.2.3Comparison of T scores in various medical conditions

T scores (standard deviation units compared to peak bone mass in young adult) were computed from manufacturer's normative databases for hip and forearm BMD, and from previously determined normative data with peak measurements for DXR-BMD (peak value for DXR-BMD occurred at age 38, mean = 0.598 g/cm2, standard deviation = 0.034 g/cm2) (Black, Palermo et al. 2001). The magnitude of the scores was largest for all three measures (hip BMD, forearm BMD and DXR-BMD) with RA+GC use (-2.4, -4.15 and -5.09 respectively); and least for hip DXA with stroke (-1.49); for forearm DXA with hypothyroidism (-2.5); and for DXR-BMD with Parkinson's (-2.68) (Table 7.7). For the whole group, forearm and DXR-BMD T scores were significantly lower compared to hip T score ($P<0.05$), and this trend was repeated significantly with each medical condition except type 1 DM. Overall, DXR-BMD T score was also significantly lower than forearm T score for the whole cohort (-2.97 vs -2.66 respectively, $P<0.05$); similar trends were noted in most of the medical conditions but were significant only in OA, stroke, type 2 DM and hypothyroidism (all $P<0.05$). The RA subgroup within the DXR cohort was too small (n=14) with small fracture numbers (n=4) to meaningfully compare the performance of the various measures in fracture prediction.

Table 7.7. DXR cohort: comparison of mean T scores of skeletal measures (deviation from mean peak bone mass in SD units, paired t-tests).

	Hip BMD	Forearm BMD	DXR-BMD
Whole cohort	-1.64	-2.66[a]	-2.97[a, b]
RA	-1.9	-3.58[a]	-3.73[a]
Current GC	-2.01	-3.26[a]	-3.7[a]
RA+GC	-2.4	-4.15[a]	-5.09[a]
OA	-1.6	-2.59[a]	-2.95[a, b]
Stroke	-1.49	-2.75[a]	-3.3[a, b]
Parkinson's	-1.49	-2.84[a]	-2.68[a]
Type 1 DM	-2.3	-2.11	-2.84
Type 2 DM	-1.59	-2.52[a]	-3.13[a, b]
Hypothyroidism	-1.61	-2.5[a]	-2.77[a, b]
Hyperthyroidism	-1.53	-2.34[a]	-2.8[a]

[a] $P<0.05$ compared to t.hip T score; [b] $P<0.05$ compared to forearm T score.

7.4.2.4Correlations amongst the skeletal measures in the DXR cohort and RA subgroup

There were significant correlations amongst the various measures. DXR-BMD and DXR-MCI had somewhat poorer correlation with hip BMD in the whole DXR cohort compared to the RA subgroup ($r=0.57$ and 0.69 respectively for DXR-BMD, both $P<0.01$; $r=0.54$ and 0.61 respectively for

DXR-MCI, both P<0.001). Similarly, DXR-BMD and DXR-MCI had somewhat poorer correlation with forearm BMD in the whole cohort than in the RA subgroup (r=0.71 and 0.81 respectively for DXR-BMD; r=0.68 and 0.78 respectively for DXR-MCI, all P<0.001). The difference was more marked in the correlations between forearm BMD and hip BMD in the whole DXR cohort and the RA subgroup (r=0.67 and 0.86 respectively, both P<0.001). Correlations between DXR-BMD and DXR-MCI however were similar in the whole cohort and the RA subgroup (r=0.90 and 0.96 respectively, both P<0.001).

7.5 DISCUSSION

In this study the effect of medical history on peripheral bone strength measurements was studied and compared with the effect on hip BMD. Compared to the whole cohort, the deviations of bone strength measurements (Z scores) in the studied disorders were largely in the same direction irrespective of the skeletal measure used. However, there was a trend for the magnitude of the Z scores to be greater with peripheral (forearm and metacarpal) measures than with central (hip) measures. The trends were statistically significant with RA where in fact, forearm BMD was the strongest predictor of fracture risk while hip BMD was the strongest predictor of fracture risk in the whole cohort.

7.5.1 MEDICAL HISTORY

Women with a history of RA (especially RA+GC) weighed significantly less at baseline and had lower bone strength measures than the rest in the SMCM cohort. However, even after adjusting for weight in linear regression, RA remained significantly associated with lower skeletal measures. BMD loss at the spine and at the hip in RA was reported previously as being related to the disease activity (Gough, Lilley et al. 1994). More recently, DXR-BMD has been reported as being significantly correlated with markers of inflammation in RA (Jensen, Klarlund et al. 2004). Bottcher et al also reported a significant reduction of DXR-BMD as well as DXR-MCI dependent on the severity of RA and found that DXR "surpassed multisite quantitative ultrasound as a promising diagnostic tool" for peripheral bone status in RA (Bottcher, Pfeil et al. 2006). Our finding that RA has a detrimental effect on skeletal measures independent of weight is in keeping with these previous findings. Women with a history of OA and hypothyroidism had one or more skeletal measures significantly greater than the rest of the SMCM cohort, but this was no longer significant after adjustment for body weight in linear regression. This suggests that the differences in skeletal measures were a reflection of associated overall body habitus rather than any independent direct effect of OA or hypothyroidism on bone strength. This is in contrast to the small study reported by Kemper et al, where young women with cogenital hypothyroidsm treated with thyroxine were found to have somewhat lower spine BMD than controls (but comparable femoral neck BMD) (Kempers, Vulsma et al. 2006). However, higher skeletal measures noted in type 2

DM remained significant after adjustment for weight suggesting a direct effect on bone. This is consistent with the previous report that hyperinsulinemia of type 2 DM in women may be associated with raised BMD independent of obesity (Barrett-Connor and Holbrook 1992).

7.5.2 T SCORES, COHORT Z SCORES AND FRACTURE RISK PREDICTION WITH VARIOUS SKELETAL MEASURES

T scores in the DXR cohort suggest a trend for greater loss of bone mass from the forearm and metacarpal sites than at the hip with age irrespective of any associated medical condition. The concept of disproportionate bone loss at different skeletal sites has been reported previously, with the finding of a preferential reduction in bone mineral content at long bone ends compared to diaphyseal sites (femur and radius) with age (Sievanen, Uusi-Rasi et al. 1999). Disproportionate bone loss would also explain the lower mean cohort Z scores at the forearm and possibly metacarpal sites compared to the hip in both the cohorts. The greater loss at the peripheral sites is reflected in their lower fracture predictive ability with both forearm and metacarpal indices faring less well than hip BMD in the SMCM cohort as a whole. This is in keeping with a previous report that the sites with the strongest relationship to hip fracture (hip and the heel) showed the least age-related T score decline (Faulkner, von Stetten et al. 1999).

In the RA subgroup there was an even greater statistically significant loss at the metacarpal site, which is probably directly related to the disease process itself as well as to reduced physical use of the hands. Similar findings have been reported previously (Jensen, Klarlund et al. 2004). This disproportionate loss is reflected in the lower fracture predictive ability of

AMCI in the RA subgroup. The higher fracture predictive ability of forearm BMD compared to hip BMD in RA may partly be explained by the fact that a somewhat greater proportion of the sustained fractures were appendicular fracture than that in the whole cohort.

In type 2 DM, hip and forearm BMD had somewhat higher point estimates of OR's for all fractures, which is probably in keeping with their higher mean values compared to the rest of the cohort. AMCI on the other hand had a similar point estimate to the rest of the cohort despite a somewhat higher mean value. A greater rate of bone loss despite initial higher BMD in older adults with type 2 DM has been suggested as a possible mechanism in fracture risk (Schwartz, Sellmeyer et al. 2001). This may be a mechanism whereby all three skeletal measures provide similar or higher point estimates of risk for 1 SD decreases in measurement despite higher BMD at baseline compared to the rest of the cohort.

7.5.3 POTENTIAL LIMITATIONS

The medical history was self-reported in this study, and was not independently corroborated from medical records. However, a previous study suggested good to moderate correlation in self-reported history and medical records, except in some areas such as prior thyroid disease, and corticosteroid and anti-convulsant use (Beard, Melton et al. 1990). Although prior glucocorticoid use history was also available, this analysis included current glucocorticoid use only where reportage is likely to have been of higher accuracy. The rest of the medical conditions studied were chronic conditions, where the accuracy of history is likely to have been high in simply indicating the presence or absence of the condition.

The relatively small number of fractures studied meant that where the point estimates of the various OR's reached statistical significance, the confidence intervals were relatively wide. Although the DXR cohort had a similar proportion of the medical conditions as the SMCM cohort, numbers of subjects with the various conditions in the DXR cohort were probably too small to provide adequate statistical power for the current analysis. Some trends seen in the DXR cohort may have reached significance with a larger number of subjects. The setting for this analysis was a controlled trial of clodronate which has a bone protective effect affecting fracture incidence. However, this effect was minimised by adjusting for clodronate treatment in regression models used.

7.6 CONCLUSIONS

There is a trend for disproportionate bone loss at the metacarpal site compared to the hip as well as forearm with age. This is irrespective of any associated medical conditions, and this is reflected in general in the lower fracture predictive ability of MCM measures compared to DXA measures. In some medical conditions there is an even greater discrepancy in the MCM measures suggesting a disease related bone loss or gain at the periphery. However, this trend was significant only in RA demonstrating lower mean scores, and in type 2 DM demonstrating higher mean scores compared to the rest of the cohort, and this is reflected in the differences in fracture predictive abilities of the measures when compared to the whole cohort. These factors will need to be taken into account when reporting and interpreting MCM indices, especially when they are likely to be used as stand alone services.

8 SUMMARY & OVERALL CONCLUSIONS

The findings from the various projects are summarised below, with reference to the objectives for the study stated in Chapter 3. The final conclusions are included based on these findings, and address the hypothesis for the study stated in Chapter 3.

8.1 DXR IN FRACTURE PREDICTION

8.1.1 HIP FRACTURES

- In univariate analyses from the HIPS study (Chapter 4), the odds ratios (ORs) for hip fracture per 1SD decrease in DXR-BMD and DXR-MCI were 1.79, 1.47-2.19 and 1.72, 1.41-2.11 respectively.
- Both were similar to the OR calculated for forearm BMD of 1.90, 1.55-2.34 but less than the OR calculated for total hip BMD of 2.33, 1.87-2.90.
- Following adjustment for clinical predictors (age and body weight), DXR indices remained significant predictors of hip fracture (1.46, 1.17-1.81, and 1.43, 1.15-1.76, respectively). They were comparable to that of forearm BMD (1.51, 1.19-1.91) but were lower than that for total hip BMD (1.98, 1.56-2.50).
- The point values of the OR's for both DXR indices and DXA measures were somewhat higher for the trochanteric fracture subgroup compared to the femoral neck fracture subgroup.
- In multivariate analyses, DXR indices were not independent of forearm BMD or hip BMD in predicting hip fracture.

8.1.2 VERTEBRAL FRACTURES

- In univariate analysis from the Vertebral Osteoporosis Trial (Chapter 5), the gradients of risk per 1SD decrease (ORs, 95%CI) for incident vertebral fractures were similar for lumbar spine BMD and DXR-MCI (1.82, 1.37-2.43 and 1.81, 1.37-2.39 respectively).
- These were somewhat higher than that for DXR-BMD and total hip BMD (1.56, 1.23-1.96, and 1.46, 1.16-1.96 respectively).
- In multivariate analysis, the baseline presence of vertebral fracture, lumbar spine BMD and DXR-MCI were all significant independent predictors of future vertebral fracture with ORs of 6.84, 3.66-12.78 for prevalent vertebral fracture; 1.56, 1.17-2.07 for lumbar spine BMD; and 1.47, 1.04-2.07 for DXR-MCI.

8.2 SMCM IN FRACTURE PREDICTION

8.2.1 ALL (ANY) OSTEOPOROTIC FRACTURES

- In univariate analysis from the HIPS study (Chapter 6), the gradient of risk for all (any) fractures (odds ratio, 95% CI) for 1 SD decrease in AMCI (6 metacarpal index) was 1.30, 1.20-1.40.
- The corresponding OR for total hip BMD was 1.61, 1.49-1.74, and for forearm BMD was 1.47, 1.35-1.59, both being higher than that with AMCI.
- The gradients of risk with AMCI were either similar or higher than with unilateral MCI.

- After adjusting for significant extra-skeletal variables, AMCI remained significantly associated all fractures.
- SMCM indices were not significantly predictive of incident clinical vertebral fractures.
- After adjusting for total hip BMD, AMCI or the other SMCM indices were not significantly predictive of all fracture risk.

8.2.2 HIP FRACTURES

- In univariate analysis from the HIPS study (Chapter 6), the gradient of risk for hip fracture for 1 SD decrease in AMCI was 1.42, 1.22-1.65.
- The corresponding OR for total hip BMD was 2.09, 1.80-2.43, and for forearm BMD was 1.79, 1.52-2.11, both somewhat higher than that with AMCI.
- After adjusting for significant extra-skeletal variables, AMCI remained significantly associated with hip fracture risk.
- After adjusting for total hip BMD, AMCI or the other SMCM indices were not significantly predictive of hip fracture risk.

8.3 CORRELATIONS BETWEEN VARIOUS SKELETAL MEASURES

8.3.1 DXR INDICES

- In the hip fracture analysis from the HIPS cohort (Chapter 4), DXR-BMD had significant correlations with total hip BMD and forearm BMD (r=0.57 and 0.71 respectively). DXR-MCI also had similar correlations with total hip and forearm BMD (r=0.54 and 0.68 respectively).

- In the vertebral fracture analysis from the VOT cohort (Chapter 5), DXR-BMD had significant correlations with total hip BMD and lumbar spine BMD (r=0.53 and 0.37 respectively). DXR-MCI also had similar correlations with total hip and lumbar spine BMD (r=0.51 and 0.34 respectively).
- The correlations between DXR-BMD and DXR-MCI were very similar in the HIPS and VOT studies (r=0.90 and 0.89 respectively).

8.3.2 SMCM INDICES

- In the analysis from the HIPS cohort (Chapter 6), AMCI had significant correlations with total hip BMD and forearm BMD (r=0.41 and 0.56 respectively).
- AMCI also had significant correlations with DXR-BMD and DXR-MCI (r=0.73 and 0.86 respectively).

8.4 PRE-EXISTING MEDICAL CONDITIONS AND MCM

8.4.1 RHEUMATOID ARTHRITIS

- In multivariate analyses of the SMCM cohort of HIPS (Chapter 7), in the RA subgroup forearm BMD was found to be significant independent predictor of all fractures (1.85, 1.04-3.29), but total hip BMD and AMCI were not independent predictors (1.63, 0.92-2.90 and 1.17, 0.76-1.78 respectively).
- In the SMCM cohort, compared to other medical conditions, the RA+current glucocorticoid (RA+GC) subgroup had the lowest mean

cohort Z scores for hip BMD (-0.53), forearm BMD (-0.82) and AMCI (-1.14, P<0.05 compared to mean hip BMD Z score).

- In the DXR cohort, compared to other medical conditions, the RA+current glucocorticoid (RA+GC) subgroup had the lowest mean T scores for hip BMD (-2.3), forearm BMD (-4.15, P<0.05 compared to mean hip BMD T score) and DXR-BMD (-5.09, P<0.05 compared to mean hip BMD T score).

8.4.2 TYPE 2 DIABETES MELLITUS

- In multivariate analyses of the SMCM cohort of HIPS (Chapter 7), in the type 2 DM subgroup total hip BMD and forearm BMD were found to be significant independent predictor of all fractures (1.99, 1.35-2.92, and 1.81, 1.20-2.72 respectively), but AMCI was not an independent predictor (1.29, 0.88-1.90).
- In the SMCM cohort, compared to other medical conditions, the Type 2 DM subgroup had the highest mean cohort Z scores for hip BMD (+0.42), forearm BMD (+0.44) and AMCI (+0.29, P<0.05 compared to mean forearm BMD Z score).
- In the DXR cohort, the type 2 DM subgroup's mean T scores showed a disproportionate bone loss in the peripheral measures, with the mean scores being, for hip BMD -1.59, forearm BMD -2.52 (P<0.05 compared to mean hip BMD T score) and DXR-BMD -3.13 (P<0.05 compared to mean hip and forearm BMD T scores).

8.4.3 OTHER MEDICAL CONDITIONS

- In the analyses from the HIPS cohort (Chapter 7), in the other medical conditions studied there was a general trend for disproportionately greater bone loss with age at the metacarpals (by MCM measures) compared to the hip or forearm by DXA.

8.5 OVERALL CONCLUSIONS

In the described projects, both DXR and SMCM indices were found to be predictive of future osteoporotic fracture risk in general, even after adjusting for extra-skeletal risk factors, and had moderate to good correlation with DXA measures. Specifically, DXR indices were shown to be predictive of incident hip and vertebral fractures, with DXR-MCI being an independent predictor of vertebral fracture. However, overall, *metacarpal radiographic (MCM) indices* were not superior to DXA measures in fracture prediction, and the gradients of risk for all fractures, and hip and vertebral fractures were higher for the DXA measures compared to the MCM indices.

Although DXA has largely replaced other bone strength assessing technologies in health systems of developed countries, it is still relatively expensive. The MCM technologies studied here are compact, easy to set up and run, and are also relatively inexpensive compared to a full-fledged DXA scanner. A role for these systems could be justified: 1) in epidemiological studies of osteoporosis; 2) as a clinical service where DXA services are unavailable, and 3) in some clinical conditions affecting the

spine and pelvis where spine and hip DXA measurements might be uninformative or less informative such as ochronosis, Paget's disease, previous orthopaedic surgery etc.

However, when interpreting and reporting measurements from these MCM technologies, the trend found in this study for disproportionately greater bone loss at the metacarpals compared to hip and even forearm DXA will need to be taken into account, especially when there are also medical risk factors associated such as rheumatoid arthritis etc.

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