THE ROLE OF PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY AT THE ULTRA-DISTAL RADIUS IN THE ASSESSMENT AND MANAGEMENT OF OSTEOPOROSIS

by

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Declaration of the Work of Others in this Thesis

All studies were designed and subjects recruited personally, except those described in chapter 10, and the hip fracture study described in chapter 8.

Most of the pQCT scans were performed, and all were analysed personally. I performed all pQCT scans on those individuals described in chapter 10, and most of those described in the hip fracture study in chapter 8. Scans not done personally, were done by radiographers trained by myself in the use of pQCT.

Many of the DXA and ultrasound scans were performed, and all analysed personally. The precision measurements for calcaneal ultrasound were performed by Dr A Stewart, of the Osteoporosis Research Unit, Aberdeen Royal NHS Trust. She also designed the study, and recruited the patients participating in the hip fracture study discussed in chapter 8. However, she was not involved in any aspect of the pQCT measurements.

Dr R Munro assisted in the assessment of patients with rheumatoid arthritis studied in chapter 11.

All data presented in this thesis were collected, recorded and analysed personally. Statistical guidance was sought from M Campbell, Senior Statistician, Health Services Research Unit, Department of Public Health, Polwarth Building, Aberdeen.

I wrote this thesis in its entirety.

For my wife

Daniela,

and daughter

Rebecca.

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SUMMARY

Osteo-densitometry has some well defined roles in the management of osteoporosis. This thesis examined the role of a new technique, peripheral quantitative computed tomography (pQCT) at the ultra-distal radius, which quantifies trabecular and cortical bone mineral density (BMD) separately through a volumetric measurement. Comparison was made with dual energy X-ray absorptiometry (DXA), and calcaneal ultrasound attenuation (BUA) and velocity (VOS) in some studies.

The precision [expressed as the co-efficient of variation (CV)] of pQCT in young females was 1.24%, 1.33%, 1.58% and 1.88% for total (Qtot), trabecular (Qtrab), subcortical (Qscort) and cortical (Qcort) BMD respectively. The precision was improved to these figures by minimising the difference in voxel numbers between repeat scans, a strategy which was thereafter utilised to aid repositioning in follow-up scans. The corresponding CV's were higher in women with vertebral fractures, or rheumatoid arthritis. There were small, and insignificant differences in BMD between dominant and non-dominant forearms. To minimise the variance in measurements, the non-dominant forearm was always scanned unless contra-indicated.

Normative pQCT data were derived from 332 normal females aged 18-90 years. Differences compared to the manufacturers reference data were noted, stressing the importance of creating a normal range from the local population. Age (all measurements), postmenopausal status (Qtot, Qscort) and height (Qtot, Qtrab) were negatively, and weight (Qtot, Qtrab, Qcort) was positively related to radial BMD. A cubic regression model best fitted all pQCT BMD's as a function of age for the whole population. pQCT BMD was effectively stable in premenopausal women. In postmenopausal women, estimated rates of change in

BMD (derived from best fit, non-linear regression models as a function of years postmenopause) were greatest for Qtot, Qscort and Qcort at 20 years postmenopause (-1.36%/yr - -1.39%/yr), which were greater than those for Qtrab throughout the postmenopausal years (-0.53%/yr - -0.76%/yr). Significant annualized rates of change in Qscort (-1.35%/yr,p=0.024) and Qtot (-1.04%/yr,p=0.027), but not Qtrab (-0.19%/yr) or Qcort (-0.95%/yr) were observed in 23 late premenopausal women studied longitudinally. Bearing in mind precision values, these results suggest a 3 year interval between scans would be necessary to detect clinically significant individual changes in BMD. Perimenopausal differences (between 79 late premenopausal and 40 early postmenopausal women) were smaller for pQCT [BMD (T-score difference, p-value): Qscort(-0.58,0.018), Qtot(-0.54,0.013), Qtrab(-0.35,0.098), Qcort(-0.29,0.174)] than for DXA lumbar spine (LS:-0.61,0.003), and femoral neck (FN:-0.76,<0.001), trochanter (FT:-0.81,0.001) and Ward's (FW:-0.77,<0.001). These observed and estimated rates of change in pQCT BMD, and the differences between late premenopausal and early postmenopausal women, are contrary to the accepted theory of accelerated trabecular bone loss immediately following the menopause, at least at the radius. Rather they suggest remodelling, with trabecularisation of endosteal cortical bone.

In 216 perimenopausal women, correlations of Qtot, Qtrab and Qscort with DXA LS and hip measurements were moderate (r:0.35-0.53), and poorer with BUA (r:0.24-0.31) and VOS (r:0.1-0.17). Corresponding figures for Qcort were even poorer. Consequently, pQCT would be of no value in pre-selecting perimenopausal women for axial DXA assessment. To detect all potential LS or FN osteopenia based upon a pQCT measurement, 98.6%-100% of the perimenopausal population would require a pQCT scan.

BMD in female vertebral and hip fracture populations, and the

power of pQCT compared to DXA and ultrasound in fracture discrimination was studied. There were significant differences in Qtrab [(Z-score difference, p-value): -1.35,<0.001], Qtot (-0.94,0.001), LS (-1.37,<0.001), FN (-1.08,0.003), FT (-1.03,0.006) and FW (-0.64,0.023), but not Qscort (-0.71,0.063) or Qcort (-0.24,0.2) between vertebral fracture (n=39) and non-fracture (n=30) groups. Qtrab was superior (numerically, but not statistically) to other pQCT and axial DXA measurements in discriminating vertebral fractures [Area under the Receiver Operator Curve (AUC): 0.853]. There were statistically significant differences in all pQCT (Z-score differences: -0.48 to -0.73), DXA hip (-0.64 to -1.04) and ultrasound (-0.64 to -0.91) measurements between hip fracture (n=165) and non-fracture (n=45) groups. FN (AUC:0.796) was superior (numerically and statistically) to all pQCT measurements and BUA, but not VOS (AUC:0.783) in discriminating hip fractures. Corresponding AUC's for pQCT measurements (except Qcort) were greater in the vertebral than hip fracture study, suggesting that pQCT may have a greater role in the prediction of vertebral fractures.

Osteo-densitometry has a recognised role in monitoring response to drug therapy. Changes in pQCT BMD were compared to DXA hip and spine BMD during treatment for 1 year with HRT (n=11) and cyclical etidronate (ETD:n=10) in postmenopausal women. In both groups, the greatest increase after 1 year was found at LS (HRT:+6.6%,p<0.001; ETD:+5.2%,p=0.013), with significant change detected after only 4 months (HRT:+3.3%,p=0.02; ETD:+3.8%, p=0.01). In both groups, pQCT BMD remained virtually unchanged, suggesting that routinely, response to HRT and ETD in best detected by monitoring LS BMD. An adverse effect of warfarin on BMD was observed in a cross-sectional study. 40 men requiring longterm warfarin for cardiovascular disease, were matched for underlying disease with 40 controls. All pQCT and axial DXA BMD

measurements were lower in the warfarin group, reaching statistical significance for LS (-10.4% difference,p=0.003) and Qtrab (-9% difference,p=0.024).

BMD is reduced in patients with rheumatoid arthritis (RA). The pathogenesis is complex, and the contribution of low dose corticosteroid therapy controversial. pQCT was compared to axial DXA and ultrasound in 75 postmenopausal women, of which 29 were controls, 21 non-steroid treated and 25 steroid treated RA patients. There was no significant steroid effect on any BMD measurement. Qtrab (p=0.001), Qscort (p=0.009) and Qtot (p=0.016), were significantly lower in the RA groups, as were both ultrasound measurements (p=0.001) and all DXA hip measurements (p=0.012-0.002). Differences in LS and Qcort were insignificant. The principle determinant of Qtot, Qtrab and ultrasound measurements was the degree of radiological damage (Larsen score). pQCT and ultrasound measurement sites are periarticular, and may be of value in assessing RA disease activity and response to therapy.

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CHAPTER 1

INTRODUCTION

This thesis examines the clinical role of peripheral quantitative computed tomography (pQCT) in the expanding field of osteoporosis. pQCT is a relatively new method of measuring bone mineral density (BMD) at appendicular sites, and when the work for this these was undertaken, there was very little published work on its use. It is a technique which offers potential advantages over existing methods by assessing trabecular and cortical bone compartments independently at an easily accessible peripheral site. This facility is important as trabecular and cortical bone behave differently depending upon the prevailing circumstances. In addition, pQCT measurements are truly volumetric, and therefore reflect true BMD, unlike many other techniques which "correct" bone mineral content for the projected area. While several peripheral sites are accessible to pQCT, work for this thesis was limited purely to the ultra-distal radial site. Osteoporosis is recognised as a huge clinical problem and a considerable drain upon NHS resources. Delivery of effective health care for those suffering from osteoporosis includes provision of facilities to measure BMD (1.1). The purpose of this thesis was to evaluate pQCT in relevant areas of clinical care for those suffering from osteoporosis, in an attempt to define a niche for its use.

Understanding the fundamentals of bone pathophysiology and biomechanics; osteoporosis - its definition and aetiologies; and osteo-densitometry - particularly present day techniques and defined roles, was essential in planning the work

presented hereafter. The remainder of the introduction sets out present day knowledge of these matters.

1.1. Bone

1.1.1 Normal Cellular Function

Bone is the living tissue that forms the skeleton, providing a mechanical framework of support. Skeletal growth occurs during childhood and adolescence, and involves bone modelling by either endochondral or intramembranous ossification. During adult life, bone undergoes the continuous process of remodelling in response to the changing needs of an individual. Remodelling comprises of a series of complex interactions between cells and the extracellular matrix. Two processes are responsible for remodelling - bone resorption where osteoclasts remove bone, and bone formation where osteoblasts lay down bone. The opposing functions of osteoclasts and osteoblasts are closely linked by a phenomenon known as "coupling", with resorption then formation occurring in discrete areas known as "basic multicellular units" - (BMU). The process of coupling within a BMU is depicted in figure 1.1. Arrival of osteoclasts on the bone surface signals the initiation of bone remodelling. Osteoclasts are derived from haematopoietic granulocyte-macrophage fibroblast colony-forming units (1.2,1.3) which also produce monocytes and macrophages. The point at which they become committed to the osteoclast lineage is not clear, but osteoclast progenitors migrate from bone marrow to bone through the circulation or by direct migration (1.3). Having arrived on the bone surface, osteoclasts remove a quantum of bone leaving a "resorption pit". This is achieved through the expression of many features of the macrophage (1.3). Bone resorpting agents are secreted

into the extracellular space and bone is broken down. Internalization of the products occurs through phagocytosis before being further processed (1.2). The process of coupling attracts osteoblasts into the resorption cavity. Osteoblasts are derived from the pluripotent mesenchymal stem cells of the bone marrow (1.2,1.3), which can differentiate into fibroblasts, chondrocytes, adipocytes, and muscle cells. The progenitors which produce these cell lineages are known as fibroblast colony-forming units (1.3). The main function of osteoblasts is secretory. Deposition of the extracellular matrix occurs within the resorption cavity that is subsequently mineralised. The synthesis, deposition and mineralization of the extracellular matrix require the orderly expression of several genes, their correct expression being prerequisite for the next (1.4). Type I collagen is the major matrix component secreted by the osteoblast and the main structural protein of bone. Its expression occurs early, during the proliferative phase of osteoblast function. Synthesis of many other non-collagenous proteins occurs. To name but a better known few, alkaline phosphatase and osteopontin are expressed later during the osteoblast matrix maturation phase. Osteocalcin is expressed even later during its mineralization phase (1.4). Filling of the resorption cavity is achieved with completion of osteoblast function. The surface is then covered with flattened cells that line the surface of all bone that is quiescent (1.2). Remodelling occurs continuously throughout the skeleton during adult life. Inspection of the surface of a section of bone reveals several resorption hollows at different stages surrounded by areas of quiescent bone. The control of osteoclast and osteoblast function and its coupling is extremely complex, involving

cellular interplay, the interaction of many cytokines and hormones, and local mechanical factors (1.2,1.3).

1.1.2. Bone Types, Skeletal Distributions and Biomechanical Properties

Division of bone is possible into two distinct types - cortical and trabecular.

Cortical bone makes up approximately 80% of the skeleton. It consists of a series of irregularly spaced, overlapping cylindrical structures known as Haversian systems, each comprising a central canal surrounded by concentric layers of bony tissue. Remodelling of cortical bone occurs at periosteal and endosteal surfaces, and within the Haversian canals. Increased Haversian system resorption will cause increased porosity of cortical bone, while increased periosteal and endosteal resorption results in increased numbers of surface BMU's (1.5). The proportion of cortical and trabecular bone varies within individual bones and according to skeletal site. Cortical bone is found primarily in the diaphyseal region of long bones in the appendicular skeleton, with metaphyseal areas containing a smaller proportion. With increasing age, endosteal exceeds periosteal resorption resulting in progressive cortical thinning, an increased intramedullary space and a small increase in the diameter of the bone (1.5,1.6). There is considerably less cortical bone in the axial skeleton, where trabecular bone predominates. However, within the clinically important vertebrae, the vertebral body has a thin envelope of cortical bone, and the posterior elements are predominantly cortical bone (1.5,1.7), contributing significantly to antero-posterior lumbar spine

bone mass assessments - 53% in women and 44% in men (1.7).

Trabecular bone comprises approximately 20% of the skeleton, and consists of a meshwork of interconnecting trabeculae. It is found predominantly in the axial skeleton within the vertebral bodies and flat bones, and within the metaphyseal region of lone bones in the appendicular skeleton (1.2,1.5). Due to the greater surface area to volume ratio of trabecular bone, it is metabolically more active and responds more quickly to stimuli than cortical bone (1.2,1.3,1.5,1.8). Consequently, about 25% of trabecular, compared to 3% of cortical bone is remodelled each year during adulthood (1.3,1.9). Of great importance is the effect of the menopause upon bone quantity and quality. Ovarian failure and reduced levels of circulating oestrogen in women results in increased activation of BMU's, with increased bone resorption and a deficit in bone formation within each BMU (1.10,1.11). The net effect is bone loss, which preferentially effects trabecular bone. Not only is the BMU activation frequency increased, but the depth of resorption cavity is also increased (1.11,1.12). This results in increased perforation of trabecular plates, decreased connectivity and disruption of the trabecular lattice structure, and subsequent reduction in load carrying capacity (1.11,1.13).

Also of importance is the presence of bone marrow, which is in close proximity to trabecular bone within the medullary cavities of bone. During childhood and adolescence, red or haemopoietic marrow is present in all bones. By the age of 20, marrow in the long bones has become inactive, being replaced by fat, which is then known as yellow marrow (1.14). This

occurs in all long bone with the exception of the upper femur and humerus. In addition to the upper humerus and femur, haemopoietic marrow persists in the axial skeleton. However, marrow fat increases by about 7% per decade in the vertebral body (1.15). Consequently, the proportion of active marrow in elderly females with vertebral fractures is as low as 25% (1.5). This age related change in the distribution and type of bone marrow may have important implications for the measurement of BMD, and the response of bone to different stimuli.

In this thesis, the radius, lumbar spine, proximal femur and os calcis are the main skeletal sites studied, and the proportion of cortical and trabecular bone varies with skeletal site. At the radius there is variation in the proportion of cortical and trabecular bone along the radial length. Four common measurement sites are encountered in the literature, these being denoted by the percentage of the total radial length, proximal to the most proximal point of the radio-carpal joint that the measurement occurs. The most distal measurement site is the 4% "ultra-distal" site where typically 50-55% of bone is trabecular (1.16,1.17). pQCT measurements occur at this site. At the 8-10% "distal" site, characteristically 25% of the bone mass is trabecular, and less than 10% at the 33% "1/3", and 50% measurement sites (1.16). The radius has been the subject of extensive study previously, mainly using single photon absorptiometry (SPA). This technique and others are discussed in greater detail later in this chapter (see section 1.3). It is worth stating at this point however, that SPA measurements occur at the distal, 1/3 and 50% measurement sites where the proportion of

trabecular bone is much lower than that found at the ultra-distal "4%" site. It is also worth noting that there are dramatic changes in the proportion of cortical and trabecular bone within the distal radius, which occur within small distances (1.16,1.17,1.18,1.19). The proportion of trabecular bone in the lumbar vertebral body is about 65% (1.2,1.5,1.20). In the proximal femur, the proportion is about 25-30% at the femoral neck (1.2,1.5,1.20), increasing to approximately 50% within the trochanteric region (1.20). The proportion at the os calcis is 90-95% (1.21).

Bone mineral density contributes about 75-85% of bone strength (1.22), with both cortical and trabecular components being important (1.22). A decline in bone mass results in a disproportionately greater decrease in bone strength (1.9,1.22). Bone mass of the spine (1.9,1.13,1.23,1.24,1.25), proximal femur (1.26,1.27,1.28) and distal radius (1.29,1.30) is strongly related to bone strength. For trabecular bone, both bone density (1.13,1.31,1.32,1.33) and structure (1.9,1.22) are important in determining its strength. Halving the cross-sectional area of a vertical trabecular column, or doubling the effective vertical length of the column through loss of horizontal support reduces its carrying capacity by 75% (1.22). Although trabecular bone is of great importance, cortical bone at the spine (1.31,1.34), femoral neck (1.26,1.35) and radius (1.36) are also important in determining the overall strength of bone. More pertinent in the context of this thesis, both cortical shell geometry and trabecular BMD at the ultra-distal radial site (1.36), and cortical BMD and thickness at the distal 1/3 site (1.37) as assessed by pQCT, is related to fracture force.

1.1.3 Normal Age Related Bone Mass Changes

A simple graphic representation of gender and age related changes in BMD is shown in figure 1.2. Skeletal growth and bone mass increases during childhood (1.38,1.39,1.40,1.41). During puberty, there is rapid skeletal growth matched by an increase in bone density (1.41,1.42,1.43,1.44,1.45). Marked accumulation occurs at the lumbar spine during puberty (1.43,1.44), while a more linear increase has been found at the radius (1.40), albeit assessed by SPA. It is possible that accretion of cortical and trabecular BMD during childhood and adolescence may differ. This issue cannot be adequately addressed using measurement techniques which measure areal BMD, such as SPA and DXA. Maximum accretion of bone mass occurs during early adulthood, and the maximum potential in an individual is known as peak bone mass (PBM).

PBM is an important concept in the pathogenesis of osteoporosis, as fracture risk in later life is considered (although not yet proven) to be dependent upon PBM, and the rate of subsequent bone loss in later life (1.46,1.47,1.48). PBM in men is generally accepted as being greater than that in women. While this is accepted at the radius (1.40,1.49,1.50,1.51,1.52), it is more controversial at the spine, some having found greater bone mass in males (1.53,1.54), others having found no gender difference (1.52,1.55,1.56). It is thought that areal BMD measurements acquired using dual energy x-ray absorptiometry (DXA) and dual photon absorptiometry (DPA), rather than volumetric BMD measurements using QCT may account for in part these discrepancies, as the greater bone size in males results in an overestimation of areal BMD gender differences (1.57).

However, even data acquired using volumetric measurements have been conflicting (1.53,1.54,1.55,1.56). PBM is predominantly influenced by genetic factors, which account for about 80% of the population variance (1.58,1.59). Other factors such as parity and lactation, oral contraceptive use, diet, physical activity and smoking have been shown to have an inconsistent and variable effect upon PBM (1.49,1.60). There is controversy regarding the timing of PBM (1.46). Based upon older, cross-sectional data, the consensus was that PBM was attained by the end of the third decade (1.46,1.51). Recent cross-sectional (1.44,1.60,1.61,1.62,1.63,1.64) and longitudinal (1.45,1.65) studies with greater numbers of subjects suggest that PBM is achieved by the end of the second decade.

After acquisition of PBM, bone mass is generally considered to be maintained until the latter part of the fifth decade, after which continuous trabecular and cortical bone loss occur at all skeletal sites, in all individuals of both sexes (1.47,1.49,1.51,1.64,1.66,1.67,1.68,1.69,1.70,1.71,1.72,1.73). Following the menopause, women experience a phase of accelerated bone loss which preferentially effects trabecular bone (1.49,1.64,1.66,1.67,1.74,1.75,1.76,1.77). This lasts approximately ten years and is caused by ovarian failure and oestrogen deficiency. There is controversy regarding the timing of bone loss at different skeletal sites. Most would agree that radial BMD is stable until the end of the fifth decade, or until the onset of the menopause (1.50,1.51,1.63,1.68,1.69,1.70,1.78,1.79), although others have shown bone loss in premenopausal women in a longitudinal study (1.80). The issue is less clear at axial sites, where some cross-sectional studies have documented reductions in BMD

at the hip (1.68,1.72,1.81) and spine (1.51,1.74) earlier than the fifth decade, as have longitudinal studies at the spine (1.70,1.82,1.83). If premenopausal bone loss does occur, it is considerably less than postmenopausal loss, and much less important (1.84).

Controversy also exists about bone loss in the elderly. Some work has suggested that bone loss may cease or actually increase at the spine, hip and radius (1.73,1.85). This assumption however, has been called into question. Several factors such as selection of a fracture free population, secular trends in BMD, mortality of fracture patients, and accuracy errors of BMD measurements due to concomitant osteoarthritis and marrow fatty changes, confound the study of the elderly. All these confounding factors (except marrow changes) will lead to an over-estimatation of BMD, and an under-estimatation of the rates of bone loss in the elderly (1.86).

1.1.4 Describing BMD Measurements: T-Score and Z-Score

It is important to describe BMD values in such a way that is easy to understand, and that gives as much information as possible without being misleading (1.87,1.88). There are several approaches to this.

1. The absolute BMD value. This alone has limitations as there are age and sex related differences in absolute BMD.
2. The percentage of the expected age and sex matched value. Although easy to understand, it has limitations and can be misleading. With ageing the mean value decreases, and

hence a decreasing denominator results in a wider range of percentage values representing the normal range. This is especially important if serial measurements are expressed as a percentage relative to the age related normal mean (not to be confused with expressing the percentage change relative to the baseline measurement).

3. The percentile of the expected age and sex matched value. This is also easily understood, does not depend upon a normal distribution of data, and is not misleading in comparison to age matched controls or serial measurements. Unfortunately, expression of BMD as a percentile make age related comparisons difficult, and at present, they are not widely used by the manufacturers of osteo-densitometer.

4. A unit of standard deviation (SD) from the normal mean. Data has to be normally distributed to allow BMD expression in this manner. Data not distributed normally require appropriate transformation. Population studies have demonstrated a Gaussian distribution of BMD values at all ages, in both sexes, at all skeletal sites when large enough numbers of subjects are studied. Comparison with other age groups is convenient and not misleading, but many clinicians are not familiar with data expression in SD units. Two different scores are commonly used. These are described below and graphically represented in figure 1.2.

Z-score this value is the number of SD's above or below the sex and age related normal mean.

T-score this value is the number of SD's above or below the mean value of young normals.

These values are now frequently used, and as discussed later in this chapter (chapter 1.2.1), the T-score is central to the definition of osteoporosis.

1.2 Osteoporosis

1.2.1 History and Definition of Osteoporosis

Only in recent years has osteoporosis received attention from the medical profession, and achieved public awareness that it warrants. The term "*osteoporosis*" was introduced to the medical literature in the 18th century (1.89). Its use implied a histological diagnosis of "porous bone" which was later refined to signify a reduced quantity of bone which was normally mineralised. This formed the basis for the first modern attempt to redefine osteoporosis using population based bone mass measurements performed by newer osteo-densitometers. Osteoporosis was thus defined as a BMD less than two standard deviations (SD) below the mean of young normal women i.e. a T-score less than -2 (1.90). This definition is solely dependent upon reduced bone mass, yet is it clear the structural deterioration in bone tissue is also of great important in determining bone strength. Moreover, few would argue that the most important end point of reduced bone mass, is fracture. This also is neglected in the above definition. Subsequently, the definition of osteoporosis was changed in 1991 to the following:

> Osteoporosis is a disease that is characterized by abnormalities in the amount and architectural arrangement of bone tissue, which lead to impaired skeletal strength and an increased susceptibility to fracture (1.91).

Although this definition encompasses all the important concepts of osteoporosis, its clinical and research application is limited by being purely qualitative. To overcome this problem, the World Health Organisation recently

devised an operational definition which is based upon BMD and fracture occurrence (1.92).

OSTEOPENIA

BMD more than 1 SD below the young normal mean, but less than 2.5 SD below.

i.e. **-1.0 > T-score > -2.5**

OSTEOPOROSIS

BMD more than 2.5 SD below the young normal mean, <u>without fracture</u>.

i.e. **T-score < -2.5** (no fracture)

SEVERE OSTEOPOROSIS

BMD more than 2.5 SD below the young normal mean, <u>with fracture</u>.

i.e. **T-score < -2.5** (plus fracture)

However, limitations persist even for these definitions. Structural considerations have been omitted, and the diagnoses of osteopenia and osteoporosis (without fracture) are dependent upon BMD measurement. Osteo-densitometry is therefore essential for the diagnosis of osteoporosis without fracture, a service not readily available to all at the present time in the UK. A further problem in definition is posed by intra-individual variation in BMD. Due to this, an individual can be classified as osteoporotic according to BMD at one skeletal site, yet not based upon another.

Consequently, the prevalence of osteoporosis in Caucasian women varies from 16% to 30% depending upon the number of skeletal sites assessed (1.92). Inspite of these limitations, this is the definition of osteoporosis which prevails at the present time.

Some idea of the magnitude now posed by osteoporosis has been shown by the applications of these definitions to a local American population in Rochester, with subsequent extrapolation nationwide. It has been estimated that 16.8 million (54%) postmenopausal white American women have osteopenia, and a further 9.4 million (30%) have osteoporosis from this calculation (1.93). Comparable figures from other populations (notably the UK) are not yet available, but these figures serve to illustrate the magnitude of the problem posed by osteoporosis.

1.2.2 Osteoporotic Fractures

Osteoporotic fractures are characterised by incidence rates greater in females than males, rates which increase steeply with age, and a tendency to occur in skeletal sites richer in trabecular bone (1.94). The sites which are typically affected are the hip, thoracolumbar spine and distal radius, although fractures of the proximal humerus and distal femur also have the above characteristics (1.95). There are considered to be two distinct types of osteoporosis, leading to different fracture types (1.67). Type I osteoporosis (and fracture) is caused by ovarian failure, reduced levels of circulating oestrogen and increased bone loss. Trabecular bone is preferentially effected and greater bone loss occurs at skeletal sites richer in this bone type - namely the spine and

distal radius. Ultimately, this predisposes to vertebral and Colles' fractures (1.67). Type II osteoporosis (and fractures) results from age related reduction in both cortical and trabecular bone. This affects all individuals of both sexes, and predisposes to hip fractures (1.67). Graphic representation of the age and gender related incidence of hip, vertebral and distal forearm fracture is shown in figure 1.3. Caucasian women and men have a lifetime fracture risk of 17.5% and 6% respectively for hip fracture, 15.6% and 5.6% for clinically diagnosed vertebral fracture, and 16% and 2.5% for distal forearm fractures (1.96). Determining the exact prevalence and incidence of vertebral fracture is complicated by asymptomatic events, and the application of differing fracture criteria (1.97). This is discussed in greater detail in section 1.2.2.2. However, from the age of 50 years onwards, the life-time risk for any of the three fractures is 39.7% for women and 3.1% for men (1.96). Consequently, in the UK around 50,000 hip fractures, 40,000 clinically diagnosed vertebral fractures and 50,000 distal forearm fractures will occur annually in women (1.12), costing the National Health Service an estimated £740 million (1.1). With an increasingly aged population, these figures are set to rise (1.98). Specific osteoporotic fractures are discussed briefly below.

1.2.2.1 Hip Fracture

Hip fracture is the most serious of the osteoporotic fractures. Its incidence rises exponentially with age, and above the age of 50 there is a females to male ratio of 2:1 (see figure 1.3). The lifetime age and sex related hip fracture rates are higher in Caucasian compared to Black or Asian populations (1.99), the female predilection also being

absent in the latter populations (1.95). There are also regional differences in hip fracture incidence between (1.95,1.100,1.101), and within countries (1.95). There is significant morbidity and mortality associated with hip fracture, with the relative survival rate at 5 years being 0.83 (1.94). The majority of deaths occur within 6 months of fracture, and are related to concomitant illnesses (1.102), although some are due to complications of the fracture or its surgical management (1.103). Aetiological factors in the pathogenesis of hip fracture are discussed further in chapter 8.

1.2.2.2 Vertebral Fracture

Inspite of being synonymous with the diagnosis of osteoporosis, information on the epidemiology of vertebral fracture remains scanty. This is in part due to clinically silent fractures, which necessitates clarification of the distinction between "fracture" and "deformity". "Fracture" applies to morphometric abnormalities detected as a consequence of symptoms, usually back pain or loss of height. "Deformity" refers to abnormalities detected from morphometric studies which have been performed regardless of clinical symptoms (1.95). Gathering of epidemiological information has also been hindered by the lack of universal agreement on the definition of a vertebral fracture. There are many differing definitions based upon vertebral body morphology (1.104,1.105,1.106,1.107,1.108,1.109). There are two main methods of determining deformities/fractures at the present time. Quantitative method relies solely upon vertebral height measurements. Semi-quantitative methods require inspection of the x-ray by a radiologist as well as measurement of vertebral

heights. Semi-quantitative methods have the advantage of allowing differentiation of change due to conditions other than osteoporosis (such as Schuermanns disease) from true vertebral fracture. However, it is also highly dependent upon the experience of the radiologist, and reproducibility can be a problem, especially if criteria are not laid down. As each vertebral body has characteristic dimensions (1.104), probably the most widely accepted definitions incorporate a distribution of vertebral body dimensions for each spinal level, with cut-off values defining a fracture (1.95,1.106,1.107). However, to date there is no agreement as to which of these numerous methods of defining a vertebral fracture is best.

The incidence of clinically diagnosed vertebral fractures is shown in figure 1.3. In men the incidence rate increases exponentially, whilst in women there is a more linear increase. The most common spinal level for fracture is the lower thoracic and upper lumbar spine (1.95), most occurring as a result of minimal trauma. It has long been appreciated that morbidity is associated with vertebral fracture. Now there is recognised to be significant associated mortality, with a relative survival rate of 0.82 (1.110).

1.2.2.3 Distal Fore-arm Fracture

The incidence pattern of this type of fracture differs from that of hip and vertebral fractures (see figure 1.3). In women, the incidence rate increases linearly between the ages of 40 and 65 years before stabilising. In men, there is a linear increase from the age of 20 to 80 years. The majority of fractures occur in females (females:male ratio of 4:1).

Although morbidity arises from this fracture, there is no associated mortality (1.95).

1.2.3.1 Risk Factors and Causes of Secondary Osteoporosis

The importance of ageing in type 2 osteoporosis, and the menopause, ovarian failure and hypoestrogenaemia in type 1 osteoporosis has already been eluded to in the preceding sections of the introduction. Table 1.1 lists the large numbers of lifestyle factors, concomitant diseases and drugs which adversely affect bone and predispose to osteoporosis (1.11,1.49,1.111). They are too numerous to discuss in detail in the introduction of this thesis, although some are discussed in greater detail in the relevant chapters of this thesis. Worthy of further discussion at this point however, is corticosteroid induced osteoporosis which is probably the commonest cause of secondary osteoporosis. Unfortunately, it was not possible to study its effect on bone per se, although its was studied in patients with rheumatoid arthritis, work which is presented in chapter 11. Corticosteroid induced osteoporosis is therefore discussed below.

1.2.3.2 Corticosteroid Induced Osteoporosis.

Direct Bone Effects.

Corticosteroids uncouple bone metabolism in favour of resorption, at least early in the course of therapy. Osteoblast function and precursor differentiation are directly inhibited, whilst the rate of mineral apposition is reduced resulting in inhibition of bone formation (1.112). Conversely, bone resorption is probably increased, although the evidence supporting this is less convincing and there is no convincing evidence that corticosteroids directly stimulate osteoclasts.

However, increased numbers of osteoclasts have been demonstrated histomorphometrically (1.113). It is thought that the increased osteoclast activity is a consequence of mild secondary hyperparathyroidism induced by depressed intestinal calcium absorption (1.114) and increased urinary calcium excretion (1.115). Thus the overall effect of corticosteroid is to reduce bone formation and probably increase bone resorption resulting in net bone loss (1.116).

Indirect Hormonal Effects

Adequate levels of oestrogen and testosterone are necessary for healthy bone. Corticosteroids have been shown to reduce circulating oestrogen levels by blunting the LHRH dependant pituitary release of LH (1.117), and the FSH dependant gonadal release of oestrogen (1.118,1.119) and testosterone (1.120,1.121). Likewise, there is evidence that adrenal androgens are important in maintaining bone density, with low dehydroepiandrosterone (DHEA) levels predicting reduced femoral BMD in post menopausal females (1.122,1.123). Corticosteroids cause ACTH suppression and adrenal atrophy, reducing androstenedione and oestrogen levels (1.124).

Vitamin D plays an important role in calcium homeostasis and bone metabolism, but as yet its role in corticosteroid induced osteoporosis in unclear. The inhibition of intestinal absorption would appear to be independent of Vitamin D status (1.125,1.126). The importance of mild secondary hyperparathyroidism has already been eluded to, net calcium loss through decreased intestinal absorption and increased renal excretion being the stimulus (1.114,1.115). Normocalcaemia is usual, and although conflicting levels of

PTH (normal or high) have been demonstrated, bone biopsies showing increased osteoclast activity(1.113) and increased nephrogenic cAMP measurements(1.127) support the contention that corticosteroids induce a state of mild secondary hyperparathyroidism. Thus corticosteroids have a profound effect on a variety of hormones involved in bone metabolism with changes favouring bone loss.

Effects upon Bone Mineral Density and Fracture.

High dose corticosteroid therapy can cause annual bone loss of 5-15% (1.128,1.129,1.130). However, not all patients lose bone (1.129,1.130), and recovery after cessation is possible (1.131). Although both trabecular and cortical bone are adversely effected, greater loss occurs from the former (1.128,1.132,1.133,1.134). The long term consequences of this is an increased fracture rate of femoral neck, rib and particularly thoracolumbar spine (1.116,1.135). The true incidence of fracture at this latter site has not been accurately defined, because painless fractures often escape detection.

Bone loss occurs most rapidly during the first few months of corticosteroid therapy, with subsequent slower, but continued bone loss(1.128,1.136,1.137). Low dose therapy (less than 7.5mg/ day prednisolone) may have less effect on premenopausal than postmenopausal women or men(1.138). Larger doses however, affect all population groups irrespective of age, menopausal status, sex or racial origin, with evidence suggesting that children and postmenopausal women lose bone especially quickly(1.139). The latter group are most at risk of fracture presumably due to the additive effect of oestrogen deficiency.

The cumulative dose has been found by most investigators to relate to the amount of bone loss, although a threshold value over which this becomes critical has not been established. Alternate day dosing offers no protection against bone loss(1.139), and all corticosteroids affect bone adversely although, equipotent doses of Deflazacort have been shown to have a less detrimental effect than other synthetic steroids (1.140). Corticosteroid induced bone loss occurs irrespective of the underlying condition being treated. Recent interest has focused on the effect of inhaled steroids used in the management of asthma on bone. Evidence is mounting that even this small dose may adversely affect bone(1.141,1.142). The longterm importance of this is yet to be established.

Through quantification of trabecular bone, pQCT would be ideally suited to monitor the effects of corticosteroid. Ruegsegger et al (1.139, 1.143) have studied a small numbers of asthmatics treated with corticosteroid for 1 year and found dose related reductions in trabecular BMD at the radius up to 17.5%, while cortical BMD was unaffected. Beyond these small, initial studies there is a paucity of data examining the use of pQCT in monitoring the effect of corticosteroid on bone. At the present time, axial DXA BMD assessments are indicated for the management of patients likely to be treated with corticosteroid for more than one year (1.144,1.145,1.146). Further work is necessary to establish whether pQCT has a role in the management of corticosteroid induced osteoporosis.

1.3 Techniques Used to Assess Bone Mass

Development of methods to assess bone mass has contributed immensely to the recent increased awareness of osteoporosis as a serious health issue. Clinicians and the public alike, are now informed that there are methods available to assess bone mass, albeit some more than others. These methods must satisfy several criteria before they can be utilised clinically. They must be accurate (reflect true bone mass), precise (reproducible) in the short and longterm, acceptable to the patient and safe in terms of radiation exposure. A number of methods exists to assessing bone mass, some more readily available than others. These have been reviewed extensively before (1.88,1.147-1.154). Techniques such as neutron activation analysis (1.147, 1.155),compton scattering (1.147) and proton activation (1.147) are not routinely used. A new area of interest, which is still very much a research tool is quantitative magnetic resonance imaging. This may reveal information about trabecular bone microstructure as well as density (1.147,1.152,1.153,1.154). The following section is a summary of the commonly used, present day methods of assessing bone mass.

1.3.1 Radiographs

A plain x-ray can detect fracture, but is not sensitive enough to accurately assess BMD (1.5,1.156). Structural analyses of radiographs have been developed in an attempt to improve the diagnostic ability of x-rays.

The pattern of trabeculae in the proximal femur can be graded, and is known as the Singh index (1.157). With age related trabecular thinning, the grade changes from VI to I. Although

the index is lower in women with hip, vertebral of Colles fractures, it has been criticised by some (1.155,1.156), but not others (1.159) for its subjectivity and high inter-observer variability. It has a low sensitivity but high specificity for diagnosing low bone mass, with a large overlap in BMD between grades (1.158,1.159). It may have a adjuvant role in conjunction with BMD, geometric or morphometric assessments in fracture prediction, but this requires further study.

Radiogrammetry is a technique where a high quality antero-posterior x-ray of the hand is performed under standard conditions. Less frequently the radius, humerus, clavicle, tibia and femur have been studied. In the hand, numerous measurements from the metacarpal (usually the second) are used to calculate various indices. As a technique of assessing bone mass, it is limited to peripheral site, is time consuming, requires skilled personnel, assesses only cortical bone, detects only advanced osteoporosis and is therefore not routinely used today (1.5,1.155).

Radiographic absorptiometry, which was previously known as photodensitometry, is a technique where an x-ray of a peripheral bone (usually phalanges, less commonly radius or tibia) is obtained under standard conditions together with an aluminium reference wedge. The density of bone on x-ray is then derived by comparison with the wedge using an optical densitometer. There has been some resurgence of interest in photodensitometry (1.160), with computer enhanced analysis and improved performance. Precision has improved to 1.5-2% (1.161,1.162) which is comparable with other scanning

modalities such as DXA. It is a readily available technique of low cost and low radiation dose. It correlates well with in vivo radial BMD as measured by SPA (1.161) and DXA (1.162,1.163), and moderately with axial hip and spine BMD as measured by DPA (1.161) and DXA (1.162,1.163,1.164). An age related decrease in the metacarpal index (one of the calculated parameters) has been documented (1.163), and evidence exists that it provides an estimate of vertebral and hip fracture risk (1.160,1.165). It may prove to be of value as a population screening tool, bearing in mind that DXA in not universally available.

1.3.2 Single Photon Absorptiometry (SPA)

SPA was developed in the 1960's. A highly collimated photon beam from a single energy radiation source (usually ^{125}I) is used to measure photon attenuation at the measurement site. Its use is limited to scanning peripheral sites as the scan site requires to be immersed in water to ensure uniform absorption of the single energy radiation from the surrounding tissues. The cortical rich radius is most commonly scanned, although the exact site can be varied to increase the proportion of trabecular bone. The distal femur and calcaneus can also be scanned. Precision is 1-3%, accuracy 5%, scan duration 15 mins with a radiation dose of 0.5-1.0 μSv. A recent development has been the replacement of the ^{125}I source with a mini X-ray tube, giving the advantage of a stable photon source with improved longterm precision. This variation is known as single energy x-ray absorptiometry.

1.3.3 Dual Photon Absorptiometry (DPA)

DPA overcomes the problems of soft tissue composition and

water immersion encountered by SPA, by using a double energy source which emits two different photons energies. These photon energies have different bone and soft tissue attenuation properties which can be subtracted from each other allowing the BMD of axial sites such as the proximal femur and lumbar spine to be quantified. Total body scans can also be performed. Initially two isotopes (iodine: ^{125}I, and americanium: ^{241}Am) were used, before the single isotope gadolinium (^{153}Gd), with dual emission energies of 44 and 100keV, became the standard. Typically, precision values are 2-4%, accuracy 4-10%, scan duration 20 mins (45 mins for total body scans) and the radiation dose is around 1 μSv. Decay of the radiation source requires its replacement after approximately 18 months which can become expensive and further adversely affect precision. This lead to the replacement of isotopes by an X-ray source giving dual energy X-ray absorptiometry.

1.3.4 Dual Energy X-ray Absorptiometry (DXA)

DXA is now probably the most widely used scanning technique, and was introduced commercially in 1987. The radionucleotide source used in SPA and DPA was replaced with an x-ray tube. Two distinct energy level beams are generated by one of two methods. One method (used in Hologic scanners) uses rapid switching of the x-ray generator between high and low voltage settings. The other (used by Norland and Lunar scanners) produces a beam from a constant voltage, which is then filtered into two different energy beams. Measurements using DXA are possible at almost any skeletal site. Sites most commonly scanned are the antero-posterior and lateral lumbar spine, proximal femur, whole body, radius and calcaneus. At

the hip a number of different measurements are recorded. The femoral neck and trochanter areas have differing trabecular contributions as detailed in chapter 1.1.2. Ward's area is a derived region of maximum trabecular bone content in the proximal femur. For AP scanning of the lumbar spine, precision is less than 1%, and 2-3% at the hip. Accuracy is 5-10%, scan duration is less than 10 mins (20 mins for total body scans) and the radiation dose 0.1-0.4 μSv. Recently fan beam (rather than pencil beam) DXA scanner have been developed and are now commercially available. These scanners quantify BMD in the thoracolumbar spine, and the images produced also allow vertebral body morphometric analysis. This development is known as morphometric x-ray absorptiometry (MXA).

DXA is now considered to be the benchmark method of measuring BMD. There are however limitations worthy of discussion. DXA, like DPA and SPA provide planar, two dimensional BMD measurements, which are expressed as g/cm^2. Such BMD measurements are influenced by skeletal size, and can be underestimated in small individuals (1.88). Although the lumbar spine is considered to be a trabecular rich site, antero-posterior scanning incorporates the posterior elements of the spinal column which is predominantly cortical bone (1.5, 1.7), and contribute 53% of BMD in women, and 44% in men (1.7). This can be minimised by using a lateral projection, but at the expense of poorer precision and accuracy, a smaller region of interest and a radiation dose 5 times greater. Both spinal and hip DXA measurements are influenced by marrow fat content (1.86,1.166,1.167). Increasing amounts of fatty marrow with age underestimates the actual BMD, and overestimates the rate of age related bone loss (1.86). Spinal measurements can

also be falsely elevated by aortic calcification (1.168,1.169,1.170) or degenerative changes secondary to lumbar spondylosis (1.171-1.177), both of which are common with increasing age. There is also evidence that spinal osteoarthritis is related to an increased BMD secondary to changes in bone metabolism, not merely a consequence of osteophytosis (1.174,1.178,1.179), which can have a generalised effect upon BMD (1.177). AP spine Scanning of the hip is less plagued by confounding factors, although smaller regions of interest and rotation during positioning does affect data acquisition (1.180), resulting in poorer precision compared to that of the lumbar spine.

1.3.5 Ultrasound

Ultrasound was first used to measure properties of bone in the 1960's, but was not widely employed until much more recently. Ultrasound use in the context of bone analysis is based upon the interaction of sound waves with bone tissue. Two ultrasonic properties are altered with transmission through bone: 1) wave velocity, and 2) wave amplitude. Alterations in amplitude are known as attenuation, which is highly dependent upon the frequency of ultrasound used. With low frequency ultrasound, the attenuation is almost linear, whereas with higher frequencies, it is non-linear. For this reason, low frequency ultrasound (0.2 - 0.6MHz) is used . Ultrasound measurements occur at peripheral sites, most commonly the calcaneus, less commonly at the tibia, patella or phalanges. In this thesis, only calcaneal measurements were done. This is a weight bearing, trabecular rich site with flat, parallel surfaces, at which overlying soft tissue is limited even in obese subjects, which has been extensively studied before.

Ultrasound measurements in this thesis were done using the McCue CUBA Clinical machine, the methodology of which is described in chapter 3. Two measurements are produced. Broadband ultrasonic attenuation (BUA) which is measured in dB/MHz, and velocity (VOS) which is measured in m/s. There are several slightly different variants of the velocity measurement. "True velocity" is the velocity of sound through bone tissue only. "Heel velocity" is the velocity of sound through bone and soft tissue. It is this measurement which is used throughout this thesis. Lastly, "time of flight" is the velocity of sound through coupling media, soft tissue and bone. The precision of BUA is 1-3.8%, and that for velocity 0.1-1.2%. Both BUA and velocity measurements are considered to reflect not only bone density, but bone structure (1.181-1.184), although the importance of this property has been questioned (1.185). The major advantages of ultrasound are that it is a low cost, easily portable, radiation free technique, with a rapid scan time of less than 5 minutes. There are however several troublesome features of calcaneal ultrasound worthy of further comment. Precision of BUA remains poorer than other scanning techniques such as DXA. This may be related to the inhomogeneous nature of calcaneal trabecular bone, which in turn can influence the measurement depending upon the region of interest studied (1.186). Recent concern has also been expressed that the present generation scanners are inherently inaccurate (1.187). BUA does not scale linearly with bone size (1.188) (although this would not be a problem unless very large or very small bones were being scanned), or with high BMD values (1.184).

1.3.6 Quantitative Computed Tomography (QCT)

Quantitative computed tomography was introduced in the mid 1970's, and measures true volumetric BMD, which is therefore expressed as g/cm^3. It is also the only method which allows separate quantification of cortical and trabecular BMD. Spinal QCT has been used extensively. Accuracy of single energy spinal QCT is rather poor at 5-15% due to the effects of marrow fat (which increases with age) which falsely reduces BMD, especially in elderly osteoporotic women. Dual energy QCT is now available which improves accuracy to 5% but at the expense of a higher radiation dose and poorer precision (3-5% compared to 1-3% for single energy QCT). Scan time is about 10 mins, but radiation dose is high at 20-200 μSv, which limits its use in repeat scanning.

There are several area of recent development with QCT (1.149,1.150). The use of stacked-slice and spiral CT scans allow a greater volume to be measured with improved precision. A more detailed analysis of spinal trabecular and cortical compartments is possible with respect to the regional effects of ageing and therapy, the relative contributions to bone strength, and fracture discrimination. Such a method of scanning also permits separate analysis of proximal femur trabecular and cortical bone, as well as providing detailed information on geometry. This is not possible with planar methods, such as DXA and DPA, or conventional QCT scanning due to its complex architecture, and rapid three dimensional variation in density and composition. Also being developed is high resolution QCT which allows assessment of trabecular micro-architecture at both axial and appendicular sites. This can be considered as being equivalent to a non-invasive bone biopsy. These are all areas of future study.

1.3.7 Peripheral Quantitative Computed Tomography (pQCT)

QCT applied to peripheral measurement sites was introduced in the mid 1970's (1.189). Radionucleotide sources (usually ^{125}I) were used initially, but found to be restrictive. Long scan times introduced movement artifact, and only small diameter sites could be scanned (1.190). To overcome these problems, modern pQCT scanners use an x-ray source (1.50,1.75,1.78,1.190). There are approximately 700 pQCT scanners worldwide, mostly in Europe (1.150). Most of these commercially available systems, which are manufactured by Stratec (including the one used for this thesis), perform a single axial slice of 2.5mm thickness at 4% of the ulnar length from the distal radial cortical endplate. The scanning procedure is discussed further in chapter 3. A smaller number of scanners, produced by Densiscan, perform multi-slice, high resolution scans, with improved precision (1.75,1.149). Although the ultra-distal radius is the site most commonly scanned, measurements at the tibia are also possible (1.149). pQCT performs a true volumetric measurement of BMD, results being expressed in g/cm^3.

In-vitro accuracy of pQCT has recently been determined from the study of 7 cadaveric forearms (1.19). The correlation between pQCT total bone mineral content and ashed weight at the standard measurement site was 0.87, with an accuracy error of 15.5%. The precision of pQCT is discussed further in chapter 3. It varies according to the scanner used, with in-vivo precision values for trabecular BMD using the multi-slice, high resolution scanner being about 0.35% (1.75), compared to 1-2% for its single slice counterpart (1.19,1.50,chapter 3).

Rapid scan time of 10-15 minutes, forearm radiation dose of only 3 μSv and negligible whole body exposure, easy of use at readily accessible sites, and separate assessment of cortical and trabecular bone make pQCT a potentially attractive technique worthy of further study.

1.4 Clinical Indications for BMD Measurement

At the present time, measurement of BMD is the best way of defining fracture risk (1.1,1.88,1.101). There is almost an exponential rise in fracture risk with decreasing BMD. Consequently, a small change in BMD of the osteopenic/osteoporotic individual results in large changes in fracture risk. Data from many studies (1.101,1.191) have shown that the risk of fracture increases between 1.5 and 3.1 times for each standard deviation decrease in BMD. The gradient of fracture risk for each standard deviation decrease in BMD is largely similar between fracture types and between measurement sites. However, the gradient of risk is generally greater when a site specific measurement for each fracture type is performed - i.e. the optimum measurement site to determine hip fracture risk is the hip (1.192).

There are many indications for BMD assessment (1.1,1.145,1.146), and these are listed in table 1.2. Previous fragility fracture of hip, spine of forearm should result in BMD assessment. Although hip fracture is a late consequence of osteoporosis, the same is not true of Colles fracture. Modest (5-8%) reductions in hip and spinal BMD have been found in patients with Colles fracture (1.193), which should be regarded at a risk factor for future, more serious fracture. Monitoring the effect of drugs which have an adverse effect on bone (such as corticosteroids) or those which are used to prevent or treat osteoporosis [Hormone Replacement Therapy (HRT), bisphosphonates] is advisable. Radiological evidence of osteopenia is an indication for BMD assessment, because as discussed above, a standard x-ray gives only a crude measure of BMD which is easily misinterpreted. Vertebral deformity

warrants BMD assessment, as old traumatic vertebral fractures may not be associated with low BMD. Other findings, risk factors and conditions which are deserving of BMD assessment are shown in table 1.2.

1.5 Screening for Osteoporosis

At the present time there is great debate as to whether population based screening for the prevention of osteoporosis should be implemented. This issue has recently been discussed at some length by a worldwide panel of experts, from which a WHO report was produced (1.101). Another important report was published in 1992 (1.194). Although funded by the Department of Health (DOH), this report was not an official doh publication. Based upon these publications and recent papers, the important issue of screening is discussed in the following section.

If screening were found to be feasible, uptake is likely to be in the region of 70-80% (1.101,1.195,1.196). Several methods have been proposed, none of them tested, all shrouded in controversy. A single BMD measurement to assess fracture risk has been proposed. The present day scanners fulfill the requirements necessary to be applied to screening. As discussed above, they are comfortable, accurate, precise machines which scan rapidly and are capable of predicting future fracture. Importantly, they are of low radiation dose (spinal QCT less so). Prospective fracture prediction data on pQCT is not yet available, and although there is good prospective data for ultrasound in hip fracture, it is limited for other fracture types. Based upon the relationship of increasing fracture risk and decreasing BMD, the best site of measurement depends upon which osteoporotic fracture is being predicted. Hip fracture is best predicted by DXA of the hip, while any osteoporotic fracture is predicted equally well by radial SPA or axial DXA. Regarding the timing of a single measurement, there are two schools of thought. One supports

measurement during the perimenopausal years as there is profound bone loss following the menopause, and peak bone mass is considered important in determining future fracture risk. The other supports a measurement around the age of 65 years. This option seem more favoured at the present time (1.101,1.197) as bone loss (another important determinant of fracture risk) has had a substantial effect on bone mass, the incidence of hip fracture is still low, and it appears more cost effective to target intervention at this age compared to the age of 50 years.

Another propose method of screening is the use of repeat BMD measurements. Fast bone losers will more quickly reach a critical bone mass at which fracture is likely to occur. A second BMD measurement 5 years following the initial perimenopausal would be considered adequate to assess the rate of bone loss for screening purposes (although an earlier measurement is advisable to assess treatment response), but only improves the estimate of ultimate bone mass by about 50%. Peak bone mass (PBM) is considered to be of greater importance in determining fracture risk up to the age of 70, but thereafter the relative importance of rate of loss and PBM equates. It should be borne in mind however that the precision of repeat measurements worsens in older age, so that a smaller proportion of BMD variance will be related to bone loss. Allied to the concept of assessing rates of bone loss is the use of markers of bone metabolism. There is now a plethora of such tests, some indicating bone formation (bone iso-enzyme alkaline phosphatase, osteocalcin, collagen propeptides markers - P1NP, P1CP), other resorption (hydroxy-proline, pyridinoline, de-oxypyridoline, collagen degradation markers -

1-CTP, 1-NTP). Analysis of a panel of such markers is useful in characterising the rate of bone loss over many years. This in conjunction with a baseline BMD assessment is the third method of screening proposed. The development of more accurate and precise measures of BMD, and more specific markers of bone turnover may increase the predictive power of these proposed methods in the future.

Several criteria should be met before population based screening is accepted (1.101,1.194). Ideally a randomised controlled study should be performed which shows that screening reduces fracture rates - no such study yet exists. Failing this, several other criteria have to be considered. Firstly, the social burden of the disease should be great enough to warrant screening. As described above, osteoporotic fractures undoubtedly fulfil this criteria, being a major social and financial burden. Secondly, effective therapy must be available. HRT has been shown to reduce fracture incidence, but there was lack of data showing its longterm benefit in the elderly population. More recent studies shows longterm protection against vertebral and forearm fracture by HRT in the elderly (1.198,1.199). Also, conventional prescription of HRT is for a maximum of 10 years, after which bone loss resumes and fracture protection diminishes. The major benefits of HRT are to reduce cardiovascular morbidity and mortality, which weakens the case for targeting HRT treatment based upon BMD. However, BMD assessment may have a role if the result showed an individual to be at high risk, and they were willing to take HRT. BMD results have been shown to influence the prescription (1.200) and uptake (1.201,1.202) of HRT.

Conversely there is no indication to screen for low BMD if the individual is either intending to take HRT irrespective of the result, or would not consider HRT if low BMD was found. Non-HRT treatments are increasing available, and the increasing acceptance of their use should increase the justification for screening. Thirdly, the screening BMD measurement should adequately define future fracture risk. Although this has been shown to be the case, with hip fracture, the overlap in BMD between fracture and non-fracture patients is considered to be too great for screening purposes. Additionally, fracture prediction has been most extensively studied in older postmenopausal females. There is only early, preliminary data to suggest that a measurement during the perimenopausal years can predict future fracture (1.203,1.204). However, the follow up period reported is only 2 years, and the number of hip and vertebral fractures reported were small (1.203) or absent (1.204). Lastly, the result of the screening test would have to encourage longterm HRT use. Although uptake of HRT has been shown to be influenced by a BMD result (1.201,1.202), its longterm use has not.

Bearing in mind the above points, the consensus of opinion is that population based screening cannot yet be justified (1,101,1.194). However, gathering of hitherto lacking information, and advances in densitometry and available therapies will require this to be reviewed. Present day policy encourages case finding rather than population screening, whereby patient with suitable risk factors should be offered BMD measurements. There are many conditions which predispose to low bone mass, as detailed in table 1.1. However, it is only those individuals with "strong" risk factors, as detailed

in table 1.2, who should routinely undergo BMD assessment, although clinical judgement must also influence this decision. It is noteworthy however, that clinical risk factors do not adequately predict BMD (1.205,1.206,1.207) and perform even worse in predicting fractures (1.207,1.208,1.209). As such they cannot be considered as a replacement for BMD measurement and fracture risk prediction, only a rough guide for further assessment.

1.6 Rational behind Thesis Work

The central issue regarding pQCT is independent quantification of trabecular and cortical bone, the behaviour of which differs depending upon the prevailing conditions. Ultrasound is the other newly developed technique of assessing BMD which has received alot of attention in recent years. Ultrasound measurements are therefore compared to pQCT in a number of chapters. The preceding sections of chapter 1 lay the foundation of the thesis. Chapter 2 largely describes the methodology of the different densitometry techniques used, concentrating on pQCT. The precision of an osteo-densitometer is of great importance. Chapter 3 describes the measures taken during scanning to ensure the best possible precision for pQCT. More especially, the hypothesis that the difference in scan voxel numbers between repeat scans influences the precision of pQCT is investigated. Chapter 4 examines the effect of dominance upon pQCT BMD measurements. It is important to document this effect and develop a policy regarding scanning, as even small differences could assume greater clinical importance when changes related to treatment, or differences between groups are being sought. Lack of such a scanning policy may increase the variance of measurements and reduce the chance of finding significance. Osteo-densitometers usually have pre-loaded normative data which is used to create T and Z scores. In the case of the pQCT scanner used in this thesis, the normative data was based upon a German population. Differences in normal ranges are known to exist between countries, hence it is important to develop a normal range derived from the local population. Chapter 5 describes the creation of a normal female range from the local population. The relationships of important anthropometric

variables to different pQCT BMD measurements within this population are also investigated in this chapter. It is recognised that BMD at one site may not reflect that of another. Chapter 6 examines the relationship between pQCT BMD measurements, and measurements at other sites using different scanning modalities. It also touches on the potential use of pQCT should a screening program ever be implemented. In chapter 7, cross-sectional age related changes in pQCT BMD's are determined from the population described in chapter 5. Perimenopausal change in BMD is considered to be profound, and preferentially affect trabecular bone. Differences in pQCT BMD between late premenopausal and early postmenopausal women are therefore examined, and compared to axial DXA differences in a cross-sectional study. Also in chapter 7, observed annual rates of change in pQCT BMD are compared to axial DXA changes in longitudinal studies of late premenopausal, and postmenopausal women. Of immense importance in the field of osteo-densitometry is the role of fracture prediction, and no work would be complete without addressing this issue. Prospective, fracture prediction studies require many years, which is outwith the timescale of this thesis. Discriminatory studies have demonstrated almost the same relationship between specific sites of BMD assessment and fracture risk as subsequent prospective studies, and are within a feasible timescale. The discriminatory power of pQCT in hip and vertebral fracture, was therefore compared to modalities known to discriminate and predict both these types of fracture respectively, the results of which are presented in chapter 8. There are now effective treatments for osteoporosis, although not all individuals respond adequately. Another very important role for osteo-densitometry is monitoring the response to

therapies such as HRT and bisphosphonates. Both these therapies preferentially increase trabecular BMD, and one could hypothesise that the pQCT trabecular BMD measurement may be particularly valuable in monitoring therapeutic response. The potential role of pQCT in monitoring response to HRT and etidronate is therefore examined in chapter 9, and compared to axial DXA measurements. The effect of warfarin on adult bone has received little attention. Chapter 10 describes the effect of longterm warfarinisation upon axial DXA BMD and appendicular pQCT BMD. The relative contribution of the inflammatory aspects of rheumatoid arthritis (RA), its inevitable effect on mobility and the use of low dose corticosteroid on appendicular and axial BMD remains controversial. Also, peripheral BMD measurements are being cited as potentially useful tools in monitoring disease progression and treatment response in RA. In chapter 11, these issues are addressed using pQCT, with comparison with axial DXA, and ultrasound measurements. The concluding chapter draws together the important findings from the previous investigative chapters, highlights potential areas of clinical use, and proposes potential explanations for the apparent difference in behaviour of axial and appendicular bone.

Table 1.1. Risk factors for low bone mass.

Genetic	Race (Caucasian, Oriental), gender (female), family history of osteoporosis. Osteogenesis imperfecta, Turner's syndrome, Klinefelter's syndrome
Life style	Physical inactivity, immobilization, exercise induced amenorrhoea, cigarette consumption, excess alcohol and alcoholism.
Nutritional	Low body weight, anorexia nervosa, calcium insufficiency. Excess salt[a], caffeine[a], protein[a], phosphate[a]
Endocrine	Hypogonadism, early menopause, Cushing's syndrome, thyrotoxicosis, hyperparathyroidism, hypopituitarism, hyperprolactinaemia, diabetes mellitis[a]
Post Operation	Hysterectomy (whilst premenopausal), post transplantation, gastrectomy, bowel resection
Rheumatological	Rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosis
Drugs	Corticosteroid, excess thyroxine replacement therapy, heparin
Gastrointestinal	Crohn's disease, ulcerative colitis, malabsorption
Haematological	Sickle cell haemoglobinaemia, homozygous β thalassaemia, pernicious anaemia, multiple myeloma, marrow accumulation of iron and aluminium
Storage disorders	Gauchers disease, haemochromatosis
Others	Mastocytosis

[a] controversial

Table 1.2 Indications for assessment of bone mineral density

Radiological evidence of osteopenia, or vertebral deformity
Previous fragility fracture of forearm, spine or hip
Significant loss of height or thoracic kyphosis
Monitoring therapy for osteoporosis
Strong risk factors
Early menopause (<45 years)
Prolonged secondary amenorrhoea
Primary hypogonadism
Corticosteroid therapy
Conditions associated with osteoporosis
Anorexia nervosa
Malabsorption
Primary hyperparathyroidism
Hyperthyroidism
Cushings syndrome
Transplantation
Chronic renal failure
Multiple myeloma
Prolonged immobility
Osteogenesis imperfecta

Figure 1.1. Schematic representation of the bone multicellar unit (BMU). Stage 0 - "Resting" - where the bone is quiescent and lined by flattened cells. Stage 1 - "Activation" - where osteoclast progenitors are atracted to the bone surface. Stage 2 - "Resorption" - where osteoclasts remove a quantum of bone. Stage 3 - "Coupling" - where osteoclastic resorption is completed, and osteoblasts are attracted into the resorption cavity. Stage 4 - "Formation" - where osteoblasts synthesise and secrete the extracellar bone matrix. Stage 5 - "Mineralisation" - where the bone matrix undergoes mineralisation through further osteoblast processing, and the resorption cavity is completely filling in. The bone is then quiescent, the surface being covered by flattened cells - Stage 0 - "Resting".

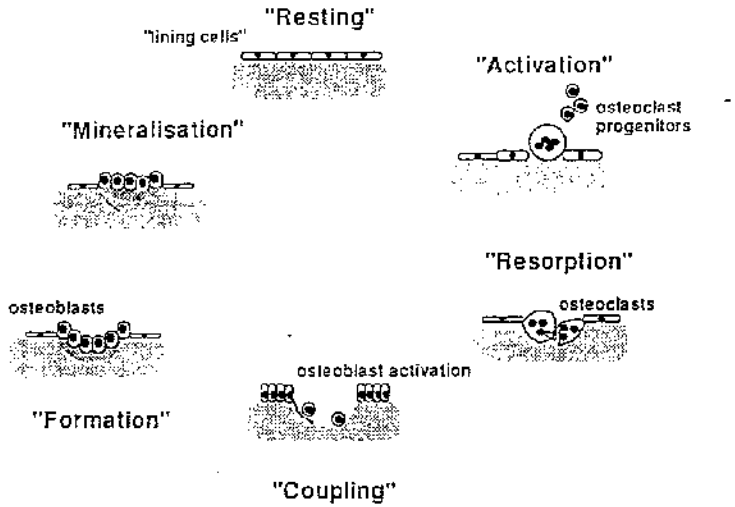


Figure 1.2: Gender related differences in bone mass (left graph), and graphic representation of T-scores and Z-scores (right graph)

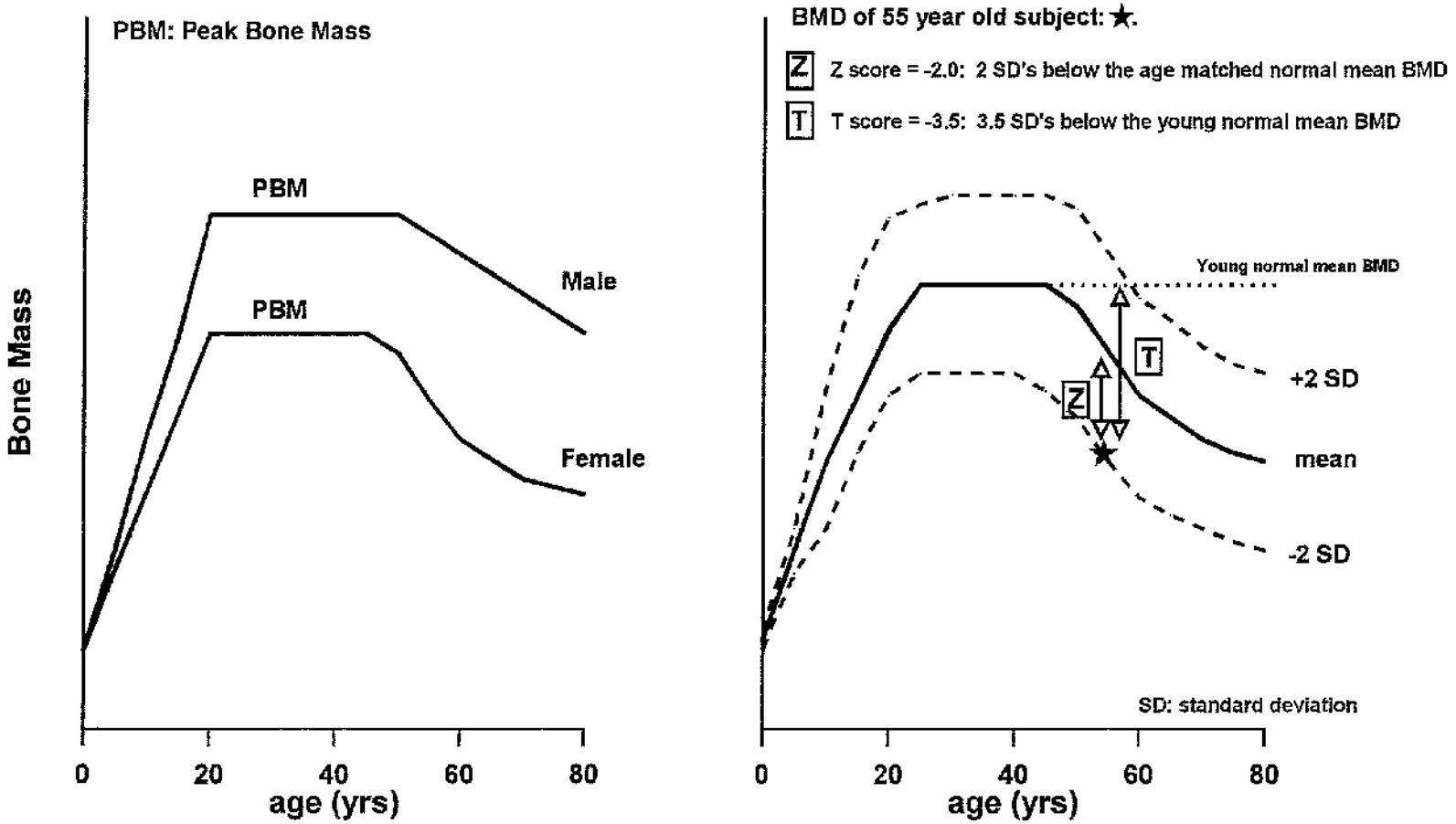
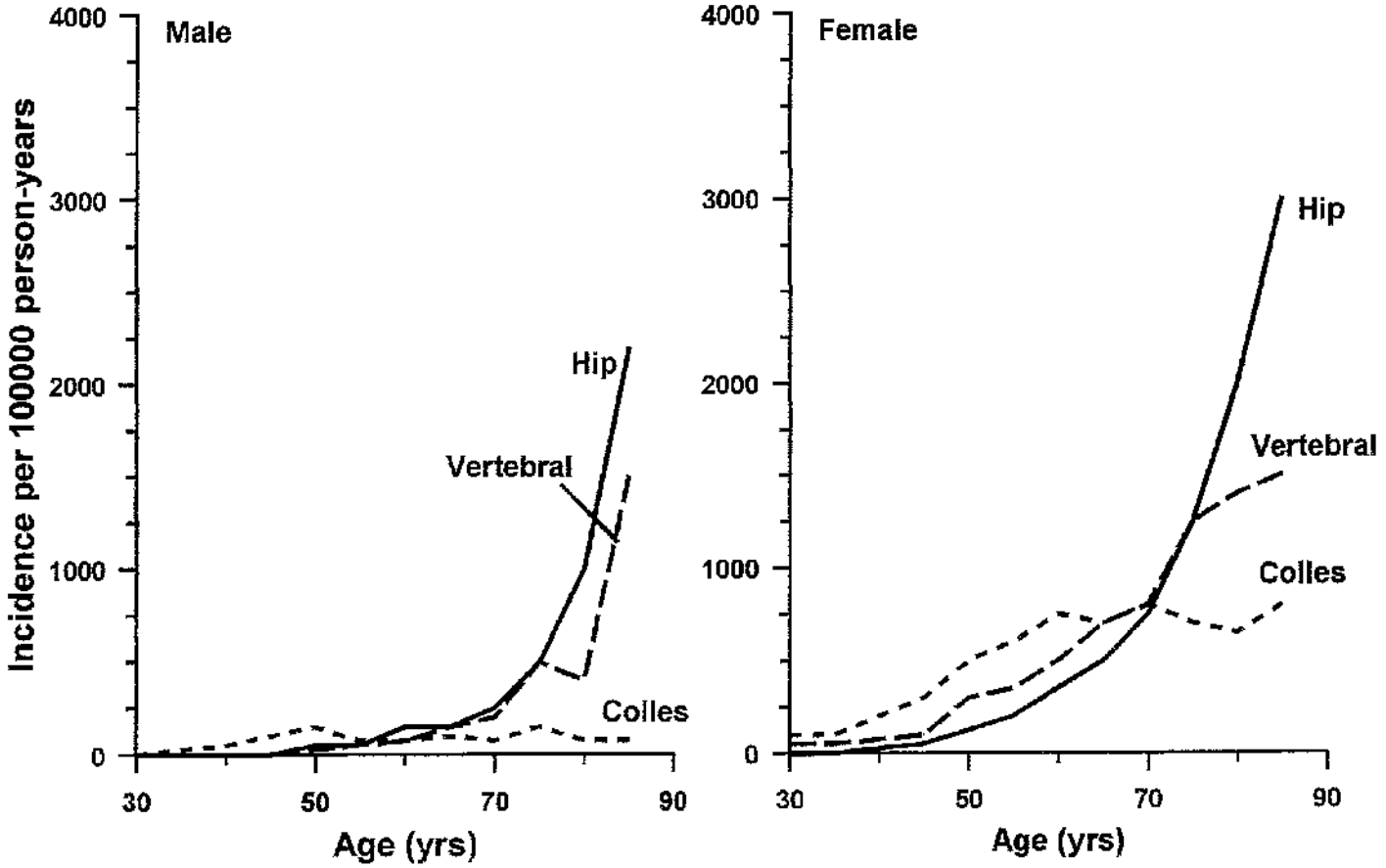


Figure 1.3: Age specific incidence rates of hip, vertebral and Colles fractures



CHAPTER 2

METHODOLOGY

2.1 Introduction

Osteo-densitometry has many roles in the management of metabolic bone disease. In the investigation of a new bone scanner, it would be impossible to address such a multitude of important issues in one study. Therefore, for the purposes of this thesis, a number of studies were designed to examine the role of pQCT in areas of clinical importance. The study designs, the numbers of patients recruited, the methods of recruitment and the statistical analyses are discussed in the appropriate chapters. The remainder of this chapter deals largely with the different methods used to quantify BMD, with the emphasis being placed on the description of pQCT.

2.2 Peripheral Quantitative Computed Tomography (pQCT)

2.2.1 The Osteo-densitometer

pQCT measurements were made of the ultra-distal radius using the Stratec XCT-960 scanner (Stratec Medizintechnik, Birkenfeld, Germany). It produces a narrow fan beam by means of a single energy X-ray tube with heavy filtering (45 kilovolts). The detector unit comprises 6 semiconductor detectors with amplifiers. Movement of the source-detector unit occurs in 3 different directions (longitudinal, transverse and rotational) and is controlled by microcontrollers. Patient forearm radiation dose is 0.3 μSv for each of the scout and measurement scans (see below). Leakage and scatter results in total body exposure of less than 0.1 μSv/hr to patient and operator. The operator radiation exposure can be reduced at least by a factor of 4 by simply standing 1m from the x-ray source, such that external radiation protection is unnecessary for both patient and operator. The total time for scanning and data acquisition is approximately 12 minutes. An individual being scanned using

the Stratec XCT-960 is shown in figure 2.1.

2.2.2 Scanning Method

The patient's forearm length is measured with a millimetre ruler from the ulnar styloid process to the point of the olecranon before the arm is positioned for scanning. This measurement is used to set an elbow support in front of the scanning aperture to ensure the distal forearm and carpus is in the scanning field. The upper limb is then positioned with the elbow in its support, the fingers resting on a finger rest at the back of the scanner with the thumb dangling comfortably below.

Scanning then takes place in two stages. Firstly a coronal scan provides an image of the distal forearm and carpus, and is known as the "scout scan". This allows accurate repositioning of the scanner for the "measurement scan", by positioning a cross-sectional cursor at the distal end of the radius. The measurement scan then occurs at 4% of the previously documented length of forearm, proximal to the cross-sectional cursor (see Fig 2.2). From the measurement scan, 15 tomograms are merged to create an axial slice of 2.5mm thickness, which is depicted on a monitor screen (see figure 2.2). The reconstructed image is comprised of thousands of cubes of uniform dimension but differing density, which are known as "voxels". The density is colour coded on the screen, with high density areas depicted as white/yellow, medium density areas as red, and low density areas as blue/black. This allows visual identification of the radius and ulna within the image. A thresholding algorithm between 0 and 100 is then applied to the image. Bone with a linear attenuation co-efficient (and density) lower than the threshold is defined as trabecular bone, and that above as cortical bone. The default threshold setting is 50, which was not changed in standard scanning. Subsequently the radius is

isolated as the region of interest (ROI), from which several BMD measurements are obtained as described below (chapter 2.2.3). The number of voxels within the ROI is also automatically calculated (typically 900-1000 for a female). As the voxel dimensions and measurement slice width remain constant, the number of voxels in any given ROI is directly proportional to its size.

2.2.3 Bone Mineral Density (BMD) measurements acquired by pQCT

4 different BMD measurements are recorded and shown in Fig 2.2. These are truly volumetric measurements so the resultant BMD values are expressed in g/cm^3.

1) **TOTAL BMD (Qtot)** is the overall measurement of radial BMD at the measurement site.

2) **TRABECULAR BMD (Qtrab).** From the cross-sectional image, the outer 55% of the radial area is concentrically removed by the computer software. This leaves a central core of purely trabecular bone which is then quantified giving trabecular BMD. The default setting for the peeling process is 55%, but this can be altered if, in the rare occurrence, cortical bone (white colour) persists after peeling of the outer area.

3) **SUBCORTICAL BMD (Qscort)** is the density of bone in the outer 55% of voxels which are removed. It is mainly cortical bone with a small rim of trabecular bone.

4) **CORTICAL BMD (Qcort)** is calculated from the outer 55% area which has been removed. The computer software defines bone with a high density, eliminating less dense bone through the further use of thresholding algorithms. This process occurs automatically for any chosen threshold used

(50 by default) in the overall analysis.

The precision of pQCT measurements is discussed in Chapter 3. The non-dominant forearm was scanned in all individuals to excluded any potential effect of mechanical loading on BMD measurements. The effects of dominance is discussed further in Chapter 4. In the rare occurrence of a previous Colles fracture of the non-dominant arm, the dominant arm was scanned, as previous fracture distorts the anatomy at the scan site, and post-fracture radial BMD is known to be reduced (2.1).

2.3 Dual Energy X-ray Absorptiometry (DXA)

The technique of scanning using DXA has been described in chapter 1.3.4, and in detail elsewhere (1.153,1.154). DXA scanning was mainly performed using a single Norland XR26-Mark II bone densitometer (Norland Corporation, Fort Atkinson, USA). Figure 2.3 shows a woman undergoing DXA scanning of the lumbar spine and proximal femur. The following measurements were made using an antero-posterior projection, with representative scans being shown in figures 2.4-2.6.

1. Lumbar spine [L2-4: (**LS**)]
2. Left hip [femoral neck (**FN**), trochanter (**FT**) and Ward's area (**FW**)]
3. Whole body [bone mineral density (**WB-BMD**)].

The in-vivo short-term precision expressed as the coefficient of variation is 0.9%, 2.8%, 1.3%, 4.9% and 1.5% for lumbar spine, femoral neck, trochanter and Ward's area, and whole body BMD measurements respectively (2.2,2.3). To prevent unnecessary repetition throughout the thesis, use of the term "DXA hip" measurements will encompass femoral neck, trochanter and Ward's BMD measurements.

A small proportion of patients with vertebral fractures

described in chapter 8, were scanned using a Lunar DPX-α densitometer. The scanning procedure is the same as that for the Norland XR26-Mark II, with the subject lying comfortably on the scanner base which is padded. Data acquisition differs between Norland and Lunar scanners with slight disparity of BMD results. This is dealt with further in chapter 8.

2.4 Ultrasound (CUBA)

The technique of scanning using ultrasound has been described previously (1.154). Ultrasound was performed using the McCue CUBA Clinical (McCue Ultrasound, Winchester, UK), which is shown in figure 2.7. The non-dominant foot is placed in the foot recess of the ultrasound machine, and two silicone rubber faced transducers applied to either side of the heel. K-Y jelly is applied to eliminate air from between the contact surfaces. Two measurements are recorded: broadband ultrasound attenuation (**BUA**), and velocity of sound (**VOS**), results being expressed in dB/MHz and m/s respectively. The in-vivo shorterm precision for these measurements is 3.8% and 1.4% respectively (based upon paired measurements in 16 healthy premenopausal individuals with the foot removed from the machine between measurements). To prevent unnecessary repetition of information throughout the thesis, "calcaneal ultrasound" measurements will refer to both BUA and VOS.

Although pQCT was performed in all studies, DXA and ultrasound measurement were not. The measurements performed in specific studies are detailed in each of the appropriate chapters.

2.5 Statistical Analyses

The statistical analyses used in the various studies differ and are discussed in each of the chapters. The normality of data distribution was verified using normality plots and Shapiro-Wilks statistics. Data which violated normality criteria were compared using non-parametric tests.

2.6 Ethics and Consent

All patients participated in studies approved by the local Ethical Committee, and gave informed, written consent.

Figure 2.1. The Statec XCT-960 pQCT osteo-densitometer is shown in this figure. A volunteer sits comfortably with her left forearm in the machine aperture during scanning.

Figure 2.2. The top image is a graphic representation of the "scout scan" showing the distal forearm and proximal carpus. The cross-sectional cursor (solid line) is placed at the distal end of the radius and the measuement scan takes place at the "4% measurement site", across the dotted line. The 2nd from top image is a graphic representation of the cross-sectional image of the distal forearm produced by the measurement scan. The radius is identified as the region of interest (within the hatched area) and the voxel number indicates the number of packets of bone in the cross-sectional radial image (voxel number). The total BMD (Qtot) is derived from this image. The bottom two images indicate how the remaining trabecular BMD (Qtrab), subcortical BMD (Qscort) and cortical BMD (Qcort) measurements are derived from the region of interest.

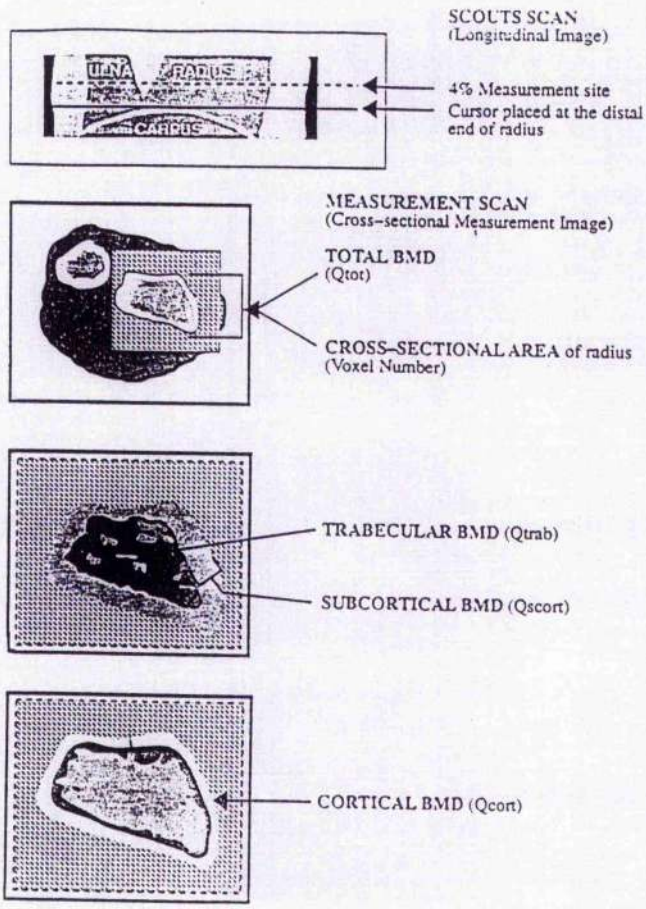
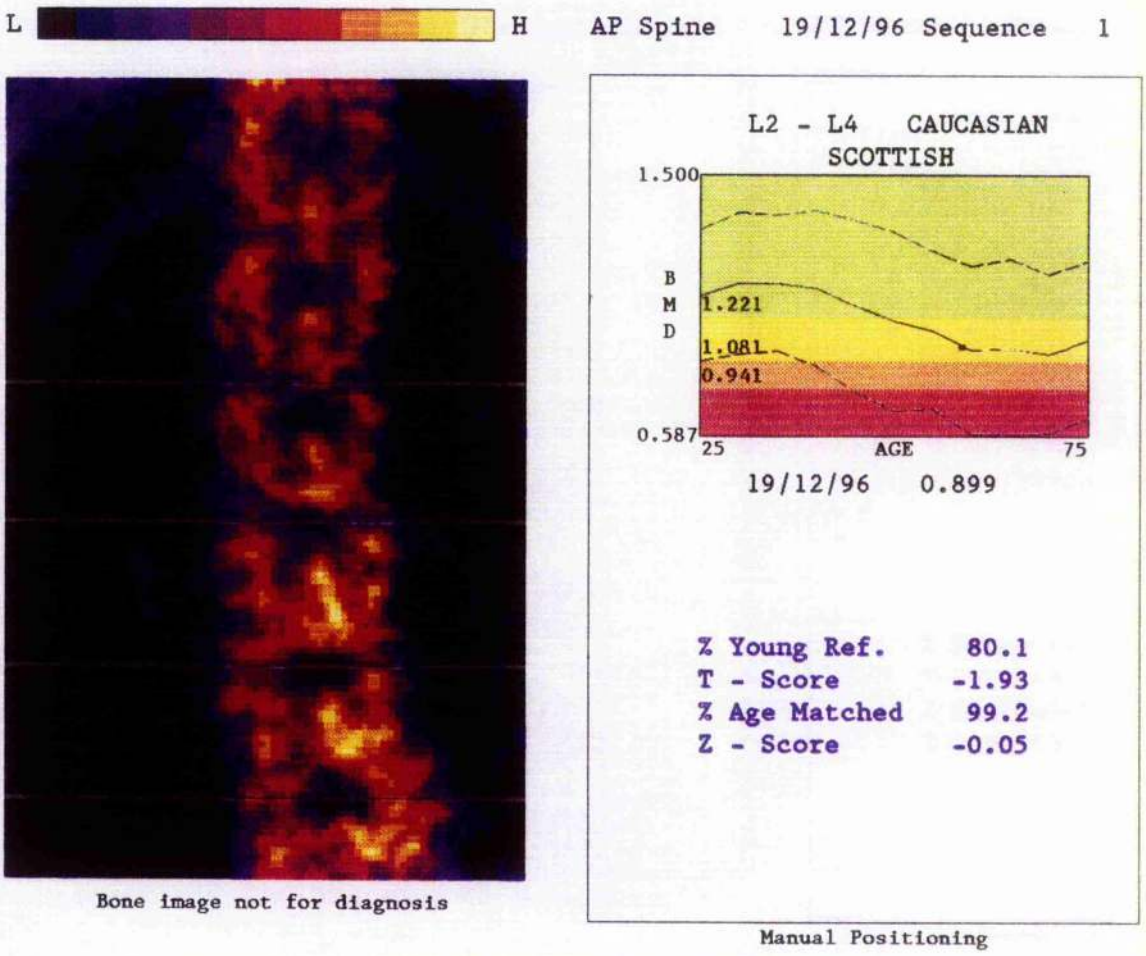


Figure 2.3. A woman undergoing DXA scanning of the lumbar spine (above) and proximal femur (below) using the Norland XR26-Mark II.

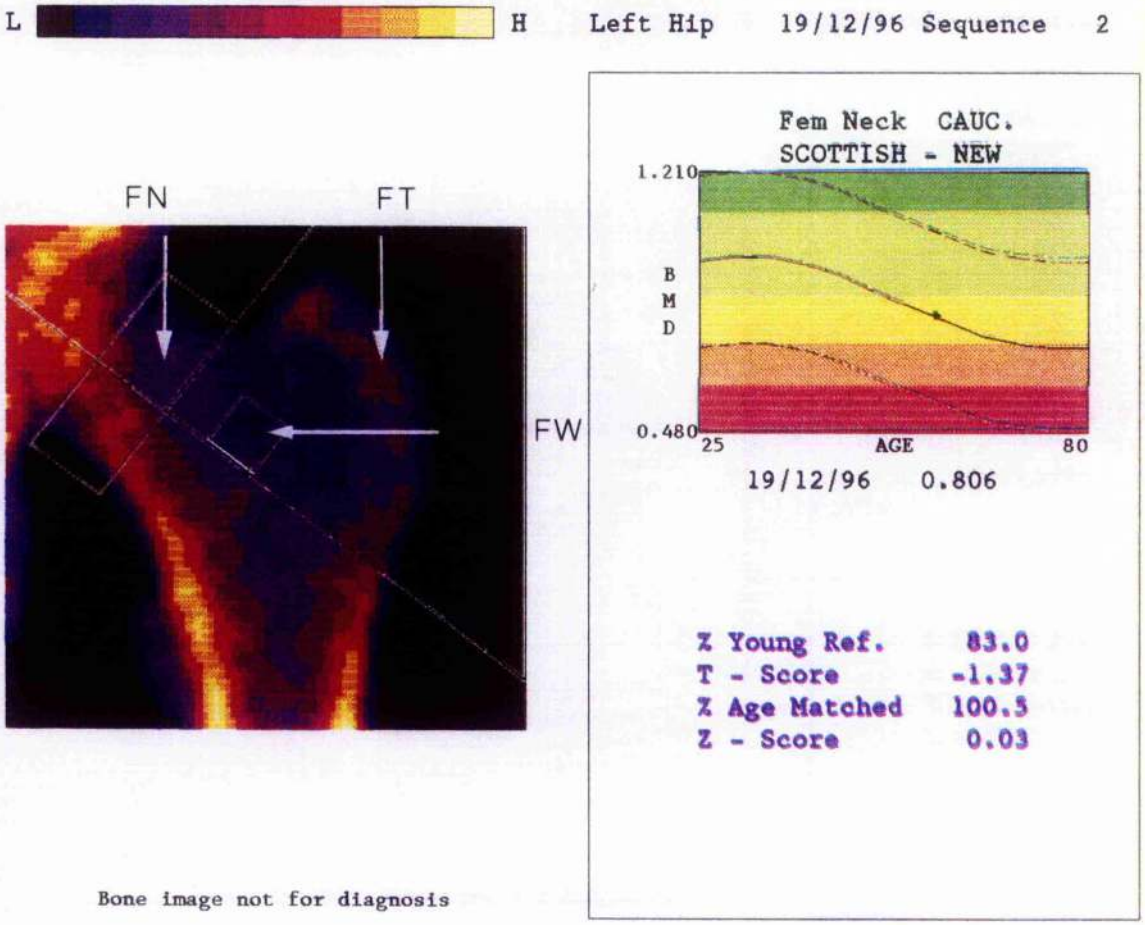
Figure 2.4. DXA scan of the lumbar spine using the Norland XR26-Mark II. The region of interest (L2-4) is selected for analysis. The BMD is shown in the box below the spinal image, with associated T and Z scores in the box on the right.



	BMD g/cm²	BMC g	LENGTH cm	AREA cm²
L2	0.782	10.92	3.30	13.96
L3	0.952	15.02	3.45	15.78
L4	0.950	14.85	3.15	15.63
L2 - L4	**0.899**	**40.79**	**9.90**	**45.37**

STD CVs for L2-L4 BMD: 1.0 BMC: 1.5 See Guide for other CVs.
1.5 x 1.5 mm, 60 mm/s, 12.00 cm Rev. 2.5.2 / 1.3.1 Calib. 19/12/96

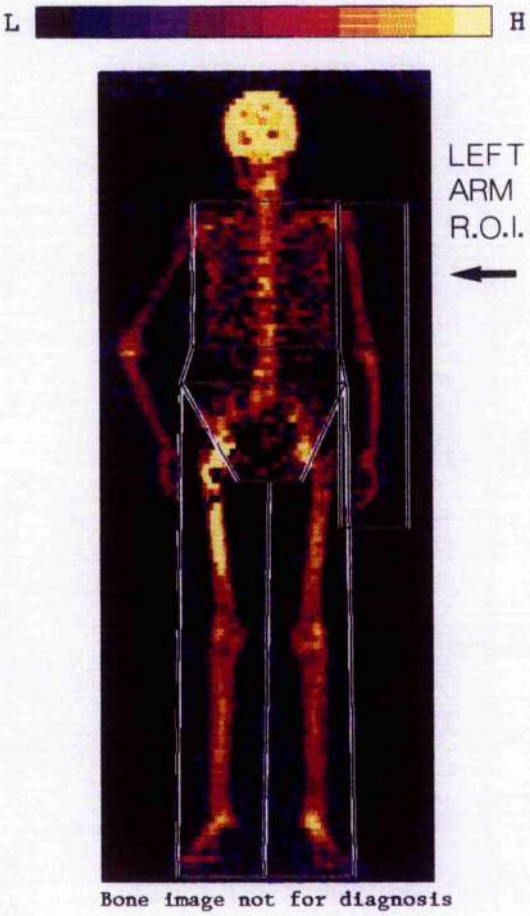
Figure 2.5. DXA scan of the left proximal femur using the Norland XR26-Mark II. The regions of interest are shown: femoral neck (FN), femoral trochanter (FT) and femoral Ward's area (FW). The BMD values are shown in the box below, with associated T and Z scores for FN in the box on the right.



	BMD g/cm²	BMC g	LENGTH cm	AREA cm²
Fem Neck	**0.806**	**3.903**	**1.50**	**4.85**
Troch	0.618	8.923		14.44
Wards Tri	0.553	0.553	1.00	1.00

STD CVs for Neck BMD: 1.2 BMC: 1.7 See Guide for other CVs.
1.0 x 1.0 mm, 45 mm/s, 9.00 cm Rev. 2.5.2 / 1.3.1 Calib. 19/12/96

Figure 2.6. A whole body DXA scan using the Norland XR26-Mark II. In this instance, the left upper limb has also been selected as an additional region of interest (ROI) . The medial border of the selected ROI passes through the glenohumeral joint and excludes all other bony area. The associated BMD values are shown in the boxes below, and to the right of the whole body image.



Total BMD (g/cm) :	0.827
Total BMC (g) :	1498
Total Lean Mass(g):	29520
Total Fat Mass (g):	13092
Total Fat % :	29.7
Siri UWE Fat % :	25.4
Brozek UWE Fat % :	24.7
Soft Tissue Fat % :	30.7
% TBMC/FFM :	4.8

DETAILED RESULTS

	BMD	BMC	AREA	LENGTH	WIDTH	LEAN MASS	FAT MASS
	g/cm^2	g	cm^2	cm	cm	g	g
Head	1.370	346.7	253.1			2889	628.4
Trunk	0.818	462.2	564.9			14365	5082
Abdomen	0.924	183.7	198.7			7459	2213
Arms	0.477	131.7	276.1			3125	1548
Legs	0.777	557.2	717.4			9141	5834
Total	0.827	1498	1811			29520	13092
Left Arm	0.670	99.97	149.2	63.70	13.00	1162	1622

Figure 2.7. A volunteer undergoing a calcaneal ultrasound measurement using the McCue CUBA Clinical scanner.

CHAPTER 3

THE PRECISION OF pQCT AND HOW IT IS IMPROVED USING SCAN VOXEL NUMBERS

3.1. Introduction

3.1.1 Precision

Precision, which is the reproducibility of measurement results, is an important concept in osteo-densitometry. The standard value quoted in the literature is the coefficient of variation (CV). The better the precision of a scanner (ie the lower the CV), then the greater its potential for detecting small but significant age, drug or disease related BMD changes. It is also important to evaluate precision in different age groups, as factors in the elderly, such as low BMD and movement artifact, may influence precision.

3.1.2 Voxel Numbers and "Trending".

With repeat measurements of the ultra-distal radius, it is vitally important to scan at the same anatomical site, as the cross-sectional area and proportion of trabecular and cortical bone changes dramatically over short distances (1.17,1.19). Ensuring standardised scanning technique will minimise inter and intra-operator variability, and improve precision.

If the cross-sectional area of a repeat scan in an individual is similar to the original, this should ensure a comparable measurement site, and improved precision. The cross-sectional area of the radius in the ROI is quantified by a "voxel number: (VN)" (Fig 2.2). This could be a useful surrogate measure of area, and therefore a marker of anatomical site in any given individual, assuming there is no real change in the cross-sectional area of the radius.

The Stratec 960 has a "trending" function which allows an

additional measurement scan to be performed if the site of the first follow up measurement scan is too far removed from the original. "Trending" utilises the difference in voxel numbers to make small adjustments to the scanner position for a further measurement scan. We were advised by the manufacturer to accept a difference in voxel numbers of 50 or less between repeat measurements. Typically there are approximately 900-1000 voxels per measurement slice in a female subject. Our initial experience suggested that the precision of the scanner using this cut off value was poorer than we would have expected. The effect upon the CV of reducing this value to 30 was therefore examined, then applied to a group of postmenopausal females with vertebral fractures, and another group of postmenopausal females with rheumatoid arthritis.

3.2 Methods

Each individual underwent two consecutive scans at one visit, the arm being removed from the scanner between scans. In addition to BMD data, the VN in each ROI was recorded as was the difference in voxel numbers between scans (vox-diff).

3.3 Statistical Analysis

Continuous variables are expressed as median with ranges. Mean BMD values are also shown as the CV is dependent upon the mean and the SD of measurements. The CV was calculated for each BMD measurement.

3.4 Study Populations

Group A comprised 14 men and 12 women. All women were young healthy volunteers. 13 of the men were volunteers with various cardiovascular diseases participating in a study examining the effects of warfarin on BMD (see chapter 10), whilst the remaining man was young and healthy. None were known to have suffered an osteoporotic fractures. Group A was subdivided according to vox-diff: (Group A-S1: vox-diff $\leq$ 30; Group A-S2:

vox-diff > 30). Group B comprised 6 postmenopausal females with at least 1 osteoporotic vertebral fracture documented on x-ray (see chapter 8). Group C comprised 8 postmenopausal females who had suffered from rheumatoid arthritis for at least 1 year (see chapter 11). The vox-diff in groups B and C was ≤ 30 for all females.

3.5 Results

Demographic, BMD, VN and vox-diff data for each of the groups are shown in table 3.1. The age, gender mix and BMD data for the subgroups of group A were comparable. The VN was greatest in group A-S2, and smallest in group C. By design, the vox-diff is less in subgroup A-S1 than in A-S2. The vox-diff in groups B and C is comparable to group A-S1, although they are all females and older. All BMD values are lower in groups B and C. The CV's for each group for each BMD measurement are shown in table 3.2. By reducing the vox-diff to 30 of less, and comparing group A-S1 with A-S2, the CV is lowered for all BMD measurements. When the vox-diff is comparable (≤ 30), the CV is higher in groups B and C than in group A-S1 for each of the BMD measurements with the exception of Qscort in group B.

3.6 Discussion

The precision of an osteo-densitometer is of great importance and care should be taken to ensure high reproducibility of BMD measurements. The following technical aspects of pQCT scanning must be standardised to improve reproducibility. The ulnar length should be measured in an identical manner by all operators. This determines the scanner position for the "4% measurement site". The forearm, hand, fingers and thumb must be positioned in the scanner in a similar manner as forearm rotation influences localisation of the region of interest (radius) from the measurement scan. Localisation of the distal end of the radius on the scout scan has to be defined to ensure uniform positioning of the cross-sectional cursor. To aid

relocation of the same measurement site in repeat measurements, the scout scan from previous measurements (eg the baseline scan in a longitudinal study) can be recalled. This permits the baseline cross-sectional cursor and measurement site to be referred to during subsequent scanning. Standardising the above procedural elements will minimise operator variation in scanning technique.

Voxel numbers can be used to further improve precision. If the number of voxels between consecutive measurement scans is greater than a predetermined threshold, fine-tuning of the scan site is possible though the "trending" function on the Stratec 960-XCT pQCT. Repositioning then occurs, the scanner moving a tiny distance towards the original scan site. An additional measurement scan (without scoutscan) then takes place at the new site within close proximity of the original scan. This is of vital importance in repeat radial measurements as there are marked changes in the proportion of cortical and trabecular bone over short distances (1.17, 1.18,1.19).

By reducing the difference in voxel number between repeat scans to 30 rather than 50, an improvement in precision was achieved as seen by comparing the CV's of subgroups 1 and 2 of group with CV's of 1.24%, 1.33%, 1.58% and 1.88% for Qtot, Qtrab, Qscort and Qcort respectively in subgroup 1 of group A. This compares well with the precision of other osteo-densitometers in our centre (see chapter 2), and other centres (1.153,1.154). They are also comparable to in-vivo precision values published for the same pQCT scanner at other centres (1.50,3.1).

The precision of pQCT is poorer in the groups with vertebral osteoporotic fractures (group B) and RA (group C), even when the vox-diff was 30 or less. These results can be explained by the fact that the median (and mean) BMD values are lower in these two groups compared to Group A. As the CV is determined

by dividing the standard deviation of the difference between measurements by the mean of the measurements, even if the errors between groups are similar, the lower mean value will ensure a higher CV (3.2). Another contributory factor could be movement artifact in the scan images of the older individuals in groups B and C, which falsely elevates the scan voxel number. Older individuals find it more difficult to prevent forearm movement during scanning, particularly when the "trending" function is needed and the scan time increases. Consequently, the repeat measurement site may not be so close to the original as the voxel number suggests, resulting in greater between scan BMD differences. There were however no gross movement artifacts in any of the scans analysed. Also, the median voxel numbers in groups B and C were lower than in subgroup 1 of group A. A difference of 30 is therefore relatively greater in these groups (B & C), resulting in poorer proximity of the follow-up scans. Although the precision in the RA group is poorer, the use of voxel numbers is probably more useful for repeat measurements in this population. The destructive change which occurs at the radio-carpal joint in RA can make it indistinct during the pQCT scout scan. This anatomical landmark is essential for the correct positioning of the scanner for any measurement scan. When this is less well defined, scan voxel numbers are invaluable in repositioning the follow up scan ensuring proximity to the original measurement site.

Whilst the improvements in the precision values between the subgroups of group A are obvious, there are some confounding factors. The mean BMD values of subgroup 1 were slightly greater than the corresponding values in subgroup 2, with the exception of Qscort. This could result in a bias towards better results in subgroup 1. Also the median voxel number of the scans in subgroup 1 was slightly lower than that in subgroup 2. This work could be repeated using a cadaveric radius and ulna

mounted in resin, obtained from a normal individual, an osteoporotic individual, and an individual who suffered from rheumatoid arthritis. This would eliminate in-vivo movement artifact and fatigue factors. The effect of reducing the difference in voxel numbers upon the CV could be studied, and a threshold determined below which there is no further improvement in the CV.

It became our policy to do a further measurement scan using the "trending" function when the difference in voxel numbers exceeded 30 in repeat measurements. This ensured close anatomical proximity of follow up and baseline measurement sites which is reflected in the improved CV figures. However, there is a large difference in the cross-sectional area, and therefore voxel numbers, of the radius between individuals. It would therefore be better to specify the threshold for a further scan using the trending function, as a percentage of the original scan voxel number rather than an absolute value. A percentage difference of 3% would appear to be appropriate. This figure could be validated or adjusted using the cadaveric radius studies as suggested above.

Table 3.1. Demographic and pQCT BMD data, first scan voxel number (VN) and voxel difference (vox-diff) for Group A-S1 (vox-diff ≤ 30), Group A-S2 (vox-diff > 30), Group B (postmenopausal females with vertebral fracture: vox-diff ≤ 30), and Group C (postmenopausal females with rheumatoid arthritis: vox-diff ≤ 30).

	Group A-S1	Group A-S2	Group B	Group C
Number	20	6	6	8
Age (yrs)	52 (23-73)	53 (26-68)	81 (72-85)	67 (53-73)
F/M ratio	9:11	3:3	6:0	8:0
VN	990 (769-1471)	1066 (932-1463)	936 (496-1131)	791(557-1205)
Vox-diff	14 (1-30)	46 (34-66)	11 (1-25)	15 (9-29)
Qtot median (range)	373 (271-578)	370 (311-478)	273 (166-321)	291 (158-381)
[mean BMD]	[382]	[379]	[264]	[289]
Qtrab median (range)	187 (110-277)	179 (141-216)	163 (49-210)	119 (54-271)
[mean BMD]	[190]	[178]	[149]	[136]
Qscort median (range)	506 (356-719)	535 (431-704)	368 (262-419)	384 (227-502)
[mean BMD]	[526]	[538]	[357]	[389]
Qcort median (range)	534 (441-689)	544 (478-667)	430 (348-514)	478 (321-539)
[mean BMD]	[551]	[550]	[425]	[468]

Table 3.2 Co-efficients of variation (CV) for pQCT BMD measurements in group A-S1 (vox-diff ≤ 30), group A-S2(vox-diff > 30), group B (postmenopausal females with vertebral fracture: vox-diff ≤ 30), and group C (postmenopausal females with rheumatoid arthritis: vox-diff ≤ 30)

	Group A		Group B	Group C
	S1	S2		
Qtot	1.24	3.43	1.73	1.64
Qtrab	1.33	1.78	2.96	4.03
Qscort	1.58	4.05	1.57	1.84
Qcort	1.88	3.31	5.18	2.82

CHAPTER 4

THE EFFECT OF DOMINANCE ON RADIAL pQCT BMD MEASUREMENTS

4.1 Introduction

The effect of mechanical stimulation and exercise upon BMD at appendicular and axial sites is controversial (4.1). This is due to differing exercise and loading regimes being studied in varying population groups, at different skeletal sites where bone composition varies. With regard to the radius, upper limb exercise and mechanical loading has been shown to have a beneficial effect upon radial bone mass in both cross-sectional (4.2,4.3,4.4,4.5) and longitudinal studies (4.6,4.7,4.8,4.9,4.10). When the issue of dominance was addressed in some of these studies, bone mass in the dominant forearm was uniformly found to be greater than its non-dominant counterpart (4.2,4.3,4.4,4.9). However these studies examined the effects of regularly playing tennis or specific upper limb exercises, neither of which typically prevail in the normal population. They do however suggest that at the radius, mechanical loading and dominance is of some importance, although the magnitude of this in the general population is poorly defined. The influence of dominance upon radial BMD in the general population was therefore investigated.

4.2 Patient Recruitment and Methods

Dominant and non-dominant forearms were scanned using pQCT on the same day in 31 individuals. 10 individuals (5 males: 5 females) were volunteers participating in a study comparing the precision of DXA scanners in 3 different Scottish centres (2.3). In addition there were 12 men participating in the study discussed in chapter 10, and 9 females participating in the study discussed in chapter 8. 2 of the 31 individuals were left handed.

4.3 Statistical Analyses

Continuous variables are expressed as the mean and standard deviation. Comparison between the dominant and non-dominant BMD values was performed by the paired t-test, and differences expressed as percentages.

4.4 Results

The BMD measurements of dominant and non-dominant forearms with percentage differences are shown in table 4.1. Considering all individuals as a single group, there was a trend for all BMD measurements to be greater in the dominant radius, although this failed to reach significance: percentage differences of 1.6%, 1.1%, 1.2%and 0.6% for Qtot, Qtrab, Qscort and Qcort respectively. BMD values of the dominant forearm were slightly higher than the non-dominant forearm with the exception of Qtrab in the male subgroup, and Qscort and Qcort in the female subgroup. None of the differences were statistically significant. BMD values in the male subgroup were higher than the corresponding values in the female subgroup, although they were not age matched.

4.5 Discussion

These data suggest that there is no statistically significant effect of dominance upon any radial BMD measurement in either males of females, although there was a trend for BMD to be slightly higher in the dominant arm. Although not statistically significant, the differences may be clinically important. The differences were largely in the region of 1-2%, which is similar to the precision error for the different BMD measurements. Introducing a further 1-2% variation in BMD measurements would limit the ability of pQCT to differentiate osteopenic/osteoporotic populations from normals, to detect rates of change and to monitor response to drugs.

A previous study examining the effect of dominance upon radial BMD using pQCT in normal sedentary individuals found cortical and total, but not trabecular BMD to be significantly greater in the dominant forearm, the differences being 11%, 10% and 6% respectively (4.11). The disparity with our findings is difficult to explain as the study populations seemed comparable in their level of physical activity (no elite athletes), and the same pQCT scanner was used.

Small, and statistically insignificant differences between DXA BMD of opposing proximal femora have also been documented (4.12,4.13). Infrequently however, considerable individual variations have also been noted (4.12,4.13), and thought to be due largely to local factors such as previous fracture or hip osteoarthritis (4.12). 7-8% variation in ultrasound attenuation (BUA) measurements between opposing os calces have previously been found which was unrelated to stated handedness. The conclusion of the authors was that the same site should always be measured, particularly in longitudinal studies (4.14).

In summary, dominance and local mechanical stimulation do appear to have a mild influence on radial BMD, which may be of clinical importance without achieving statistical significance. Although only small and insignificant differences were found between radii in this work, the numbers studied were relatively small. Greater differences have been recorded previously in the general population (4.11), and in those undertaking specific upper limb exercises (4.2,4.3,4.4,4.9). Bearing in mind that even small percentage differences would be clinically important, it is important to remove the influence of dominance as a confounding factor in pQCT BMD measurements. Consequently it was our policy to always scan the non-dominant forearm, unless an individual had suffered a previous Colles fracture, when the contralateral forearm was scanned. In longitudinal

studies the same forearm was always scanned.

Table 4.1. pQCT BMD measurements for the dominant (DOM) and non-dominant (NON-DOM) forearms in the whole study population (whole pop), and the male and female subgroups.

	DOM	NON-DOM	p	% diff
Whole pop. (n=31)				
Qtot	363.4 (85.1)	357.6 (77.4)	0.23	1.6
Qtrab	181.6 (53.4)	179.6 (54.0)	0.60	1.1
Qscort	500.2 (113.2)	494.0 (96.7)	0.41	1.2
Qcort	528.6 (82.7)	525.4 (79.9)	0.67	0.6
Males (n=17)				
Qtot	409.5 (76.9)	400.5 (67.5)	0.23	2.3
Qtrab	210.6 (43.9)	212.7 (39.1)	0.68	-1.0
Qscort	556.6 (96.7)	541.1 (82.6)	0.16	2.7
Qcort	558.7 (65.0)	545.9 (65.7)	0.19	2.3
Females (n=14)				
Qtot	307.4 (57.4)	305.6 (54.0)	0.77	0.6
Qtrab	146.4 (42.3)	139.4 (40.9)	0.22	4.8
Qscort	431.7 (94.1)	436.9 (82.3)	0.61	-1.2
Qcort	491.9 (89.1)	500.4 (90.5)	0.49	-1.7

Values are mean (SD). p value is for the paired t-test.
% difference is that between the mean dominant and non-dominant BMD.

CHAPTER 5

CREATION OF A NORMAL RANGE AND DETERMINATION OF IMPORTANT ANTHROPOMETRIC FACTORS ON RADIAL pQCT BMD MEASUREMENTS IN FEMALES AGED 18-90.

5.1 Introduction

The Stratec XCT-960 pQCT bone scanner was developed in Germany. The manufacturers did provide a normal range for trabecular and total BMD values, although this was based on a German population aged 20-79 scanned using a precursor to the Stratec XCT-960 - the Stratec SCT-900 - which used a ^{125}I rather than X-ray source. There had been concern that the normal range provided was inaccurate, a worry which has recently been confirmed in a German population (1.50). Therefore, it was felt prudent to investigate whether the manufacturers reference range was representative of the population of Grampian region, Scotland. The best method of determining a normal range from a reference population would be to randomly select females from a population or GP register. Financial and time restraints meant that this was not possible, but all normal females who had been scanned with pQCT were analysed. Since age, height, weight and menopausal status are known to be important factors in determining BMD (1.50,5.1,5.2,5.3), their influence on pQCT radial BMD measurements was examined in this population.

5.2 Study Population

332 normal females who had been scanned with pQCT were studied. All females completed a health questionnaire. None were known to suffer from any condition or were taking medication known to influence bone mass or metabolism and none had previously undergone hysterectomy. They were recruited in the following way:

1. 61 volunteers who worked in the Osteoporosis Research Unit

and the hospital at which the Unit was based.

2. 197 females who attended an osteoporosis screening programme which has been described previously (1.196). These females were aged 45-55 years old, lived in the Grampian region of Scotland and were randomly selected from a community register. Primary screening involved DXA scanning of the lumbar spine and hip. pQCT was performed within 2 months at an additional visit .

3. 31 volunteers selected from a previously studied random population who took part in an epidemiological study (European Vertebral Osteoporosis Study - EVOS) (5.4). They were known to fulfill criteria for normality 2 years previously, and agreed to return for further assessment. 30 again fulfilled normality criteria and were included in this study population, but one had suffered a vertebral fracture, and was excluded. They formed part of the control group for the studies discussed in chapters 8 and 11.

4. 45 volunteers who were recruited through advertising as normal controls for a study examining the power of different scanning modalities (DXA, CUBA and pQCT) to discriminate patients with previous hip fracture from a control population. This study is discussed further in chapter 8. One female self reported a history of rheumatoid arthritis and was therefore excluded, leaving 44 females to be included in this normal population

5.3 Statistical Analyses

BMD was stratified by age into consecutive decades, and by menopausal status (premenopausal: regular menses still occurring; postmenopausal: no menses for at least 12 months). Age specified mean and SD BMD values were compared to those provided by the manufacturer, and also a recently published German normal range. The effect of the independent variables

age, weight, height and menopausal status was examined by stepwise multiple regression analyses in the whole population. Analyses of premenopausal and postmenopausal subgroups were undertaken, with years since the menopause being substituted for menopausal status in the postmenopausal group.

5.4 Results

119 of the population were postmenopausal. Total and trabecular BMD data for our normal population and that provided by the manufacturer are shown in table 5.1. Cortical and subcortical BMD data for our population are shown in table 5.2 (there were no corresponding manufacturers values). Our normal range differed from that of the manufacturer and also that recently published for a German population (1.50). There are data on only 6 females in the 30-39 age band, which unfortunately cannot be considered a truly representative sample of the normal population. This could explain why Qtot, Qtrab and Qscort BMD values are lower than expected in this age band. Mean Qtot and Qtrab BMD values were generally higher in our population, compared to the manufacturers and recently reported German population (1.50). Compared to the manufacturer's figures, the difference tended to be greater for Qtot (+9.5% - +31.1%) than for Qtrab (-1.2% - +10.6%: excluding those aged 30-39).

The age related changes in Qtot, Qtrab, Qscort and Qcort are shown in figures 5.1-5.4 respectively. Multiple regression equations examining the influence of the independent factors age, height, weight and menopausal status (years postmenopause in postmenopausal females) upon BMD measurements in the whole population, and premenopausal and postmenopausal subgroups are also shown in the corresponding figures.

There was an age related decrease in all BMD values. Examining

the whole population by decades, this was not apparent until the 6th decade for Qtot, Qscort and Qcort and the 7th decade for Qtrab. Age related changes in BMD are discussed further in chapter 7. Important anthropometric determinants in the whole population were as follows: weight which was positively correlated with Qtot, Qtrab and Qcort; age which was negatively correlated to all measurements; height which was negatively correlated to Qtot and Qtrab; menopausal status which was negatively correlated to Qtot and Qscort.

For premenopausal females, weight was positively correlated to Qtrab, and height negatively correlated to Qtot and Qtrab. The amount of variance explained in the premenopausal group was small with only 5% of the variance in Qtot, and 8% of Qtrab being explained. The amount of variance in Qscort and Qcort explained by these independent variables (age, height and weight) was so low that no equation was formed.

For postmenopausal females, weight was positively correlated to Qtot, Qscort and Qcort, whilst age was negatively correlated to all BMD measurements. Years since the menopause was not an important determinant for any pQCT BMD measurement. The degree of variance in BMD explained in the postmenopausal group was much greater than in the premenopausal group: 35% for Qcort, 34% for Qscort, 33% for Qtot, but only 8% for Qtrab.

5.5 Discussion

These results highlight the importance of obtaining a locally derived normal reference range. Values supplied by the manufacturer were consistently lower across the decades than those of the local Grampian population. There were also differences in BMD values between the female population of Grampian, and the German population reported recently by Butz et al (1,50). These differences are probably real, but the

following factors could also be important. Firstly, the recruitment methods for the study populations were different. The entire German population reported by Butz et al (1.50) was randomly selected, whilst about 100 of the 332 females in our population were volunteers, the remainder being randomly selected from the population. Secondly, our pQCT scanner (Stratec XCT-960) was the upgraded model from that used to scan the German population (Stratec XCT-900). Differences in performance of the scanners are not known, but are unlikely to result in the large BMD differences reported here. The finding of population differences does however support the findings of a recent study, which reported that normative female pQCT BMD data vary between a number of different European centres (5.5). Mean trabecular BMD of females aged 60 years at the different centres varied between 101-117 mg/cm^3, although this was statistically insignificant. Similar findings have also been shown for normative DXA spinal (5.6,5.7) and hip (5.7,5.8) data. Differences between a locally derived normal range and that provided by the manufacturer have also been found for axial DXA (5.7,5.9,5.10) and pQCT measurements (1.50). Such difference are important as they can lead to the misclassification of patients as osteoporotic or not (5.7,5.10). If must be concluded that, if possible, normative data should be derived from the local population.

For the purposes of this thesis, the population studied in this chapter is referred to as a "normal" population. However there are several limitations of this population. Firstly, approximately 30% of females were not randomly selected. Secondly, there is a paucity of females aged 30-39 years, with BMD values in this age group generally being lower than their counterparts aged 18-29 years and 40-49 years. This suggest that the females in this age band are not representative of the population. Unfortunately, it is this age group which is used

most often to create T-scores. Hence, during the remainder of the thesis, T and Z scores are quoted for DXA femoral neck and lumbar spine measurements, but not for pQCT measurements.

Examining the BMD values across the decades, pQCT values do not appear to alter greatly until the 6th decade for Qtot, Qscort and Qcort, and the 7th decade for Qtrab. This is a similar pattern to that observed previously for pQCT measurements (1.50,1.78). Bearing in mind the limitations of trying to determine peak bone mass with a small number of females aged 30-39 years, maximum mean BMD is achieved in the age group 40-49 years for Qtot, 18-29 years for Qtrab and Qscort, and 30-39 years for Qcort (40-49 years if the 30-39 age group is excluded). It is surprising that there does not appear to be a dramatic reduction in Qtrab during the 6th decade, bearing in mind that the accelerated phase of bone loss during the 5-10 years following the menopause preferentially affects trabecular bone. Rates of radial bone loss are examined further in chapter 7.

Weight and height are generally positively related to axial hip and spine BMD, whilst age and postmenopausal status are negatively related (1.51,4.2,5.1,5.2,5.11,5.12). The results presented here suggest that in premenopausal females, the above independent variables explain only a small amount of the variance in the various pQCT BMD values, although other local and environmental factors were been examined. This is in keeping with the previous finding that peak bone mass at the radius (1.58), and hip and spine (1.59) is largely genetically determined, with up to 80% of variance being explained by genetic and familial factors.

The variance in pQCT BMD explained by age, weight, height and menopausal status for the normative data presented here, was

much greater in the postmenopausal, compared to the premenopausal subgroup. Age was an important determinant of all BMD measurements, being negatively related in the whole population and the postmenopausal subgroup. It was surprising that years since the menopause was not related to any measurement in postmenopausal females, particularly as trabecular bone is preferentially affected during the earlier postmenopausal years, and is independently quantified by pQCT. However, postmenopausal status was negatively related to total and subcortical BMD measurements. Weight was also positively related to BMD measurements in the whole population, but seemed to have a greater influence upon BMD of postmenopausal females. Conversely, height was negatively related to total and trabecular BMD in the whole population, and more important in premenopausal females. This relationship of height with radial BMD is an unexpected and unusual finding which is difficult to explain, but has been noted before for trabecular BMD (1.64). It is possible that taller women have thinner radii.

Considering the two menopausal groups together, these results are similar to previously published studies. Age, has been shown to be negatively related (1.50,1.51,1.63,1.68,1.69,1.70,1.78,1.79,5.3,5.13), and weight unrelated (1.50,1.64,5.13) or weakly positively related (1.51) to radial BMD. Height has been variably shown to be unrelated (5.13), weakly positively (1.50,1.51,5.14) or weakly negatively (1.64) related. Postmenopausal status (1.51) and years postmenopause (5.13) have been found to be negatively related to radial BMD. The effect of the menopause upon radial pQCT BMD measurements is discussed further in chapter 7. Disparity with the some of the results of others could be explained by differing method of analysing the relationship between anthropometric and BMD variables, as some have used linear regression, others multiple regression and others a combination

of both. Additionally, although pQCT was used in some of the work quoted above (1.50,1.64), SPA was used by others (1.51,5.13). Accordingly, the scan site and therefore proportion of trabecular bone differs, as do the reported BMD measurements.

Table 5.1. pQCT BMD values for our normal population compared with the manufacturers reference data (Qtot and Qtrab only).

	Age (yrs)	Our Normal data			Reference data		Difference	
		n	Mean	SD	Mean	SD	mg/cm^3	% age
Qtot	18-29	33	387.4	54.6	267.0	40.0	+120.4	+31.1
	30-39	6	348.4	57.7	269.2	40.0	+79.2	+22.7
	40-49	173	392.2	48.6	270.8	40.0	+121.4	+31.0
	50-59	55	370.0	70.0	268.0	40.0	+102.0	+27.6
	60-69	22	331.0	63.7	264.3	40.0	+66.7	+20.2
	70-79	29	286.8	59.4	259.6	40.0	+27.2	+9.5
	80-90	14	257.6	54.2	-	-	-	-
Qtrab	18-29	33	191.2	27.9	170.9	35.5	+20.3	+10.6
	30-39	6	137.3	25.0	174.1	35.5	-36.8	-26.8
	40-49	173	186.7	36.5	176.1	35.5	+10.6	+5.7
	50-59	55	180.4	45.5	168.2	35.5	+12.2	+6.8
	60-69	22	165.7	41.7	159.3	35.5	+6.4	+3.9
	70-79	29	154.4	51.2	156.3	35.5	-1.9	-1.2
	80-90	14	130.6	48.0	-	-	-	-

Table 5.2. Subcortical (Qscort) and cortical (Qcort) BMD values for our normal population. There were no corresponding reference data from the manufacturer.

	Age (yrs)	Our Normal data				Age (yrs)	Our Normal data		
		n	mean	SD			n	mean	SD
Qscort	18-29	33	542.3	86.9	Qcort	18-29	33	562.3	78.5
	30-39	6	518.5	91.7		30-39	6	588.7	61.0
	40-49	173	538.2	57.9		40-49	173	563.9	54.3
	50-59	55	508.1	86.0		50-59	55	544.0	65.1
	60-69	22	454.8	88.3		60-69	22	501.2	87.1
	70-79	29	392.1	82.6		70-79	29	447.5	76.0
	80-90	14	359.4	74.8		80-90	14	427.7	79.1

%age is the percentage difference between our normal population and the reference data. n=number of measurements in each age range.

Fig 5.1: Age dependent distribution of Qtot BMD for normal females

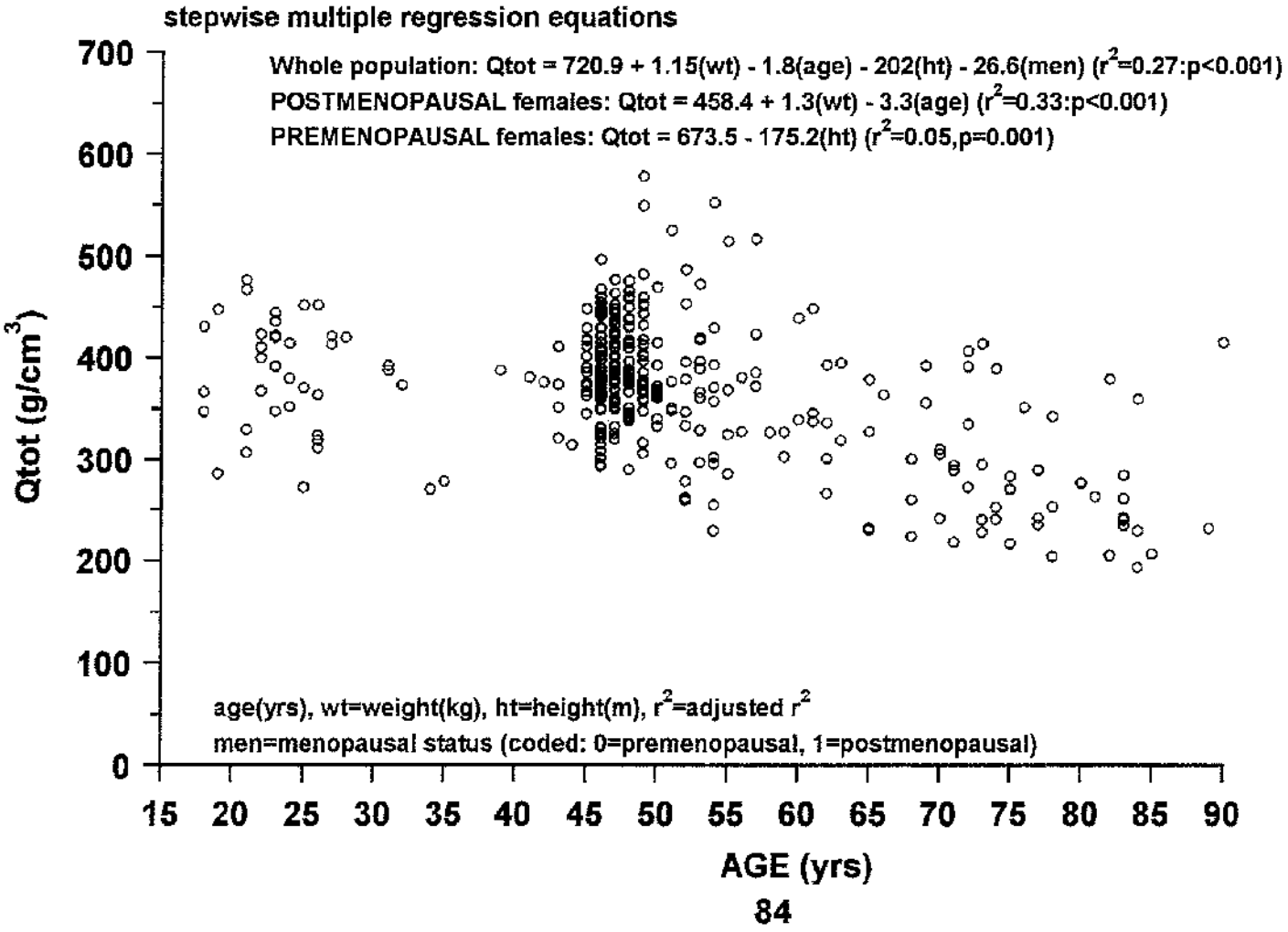


Fig 5.2: Age dependent distribution of Qtrab for normal females

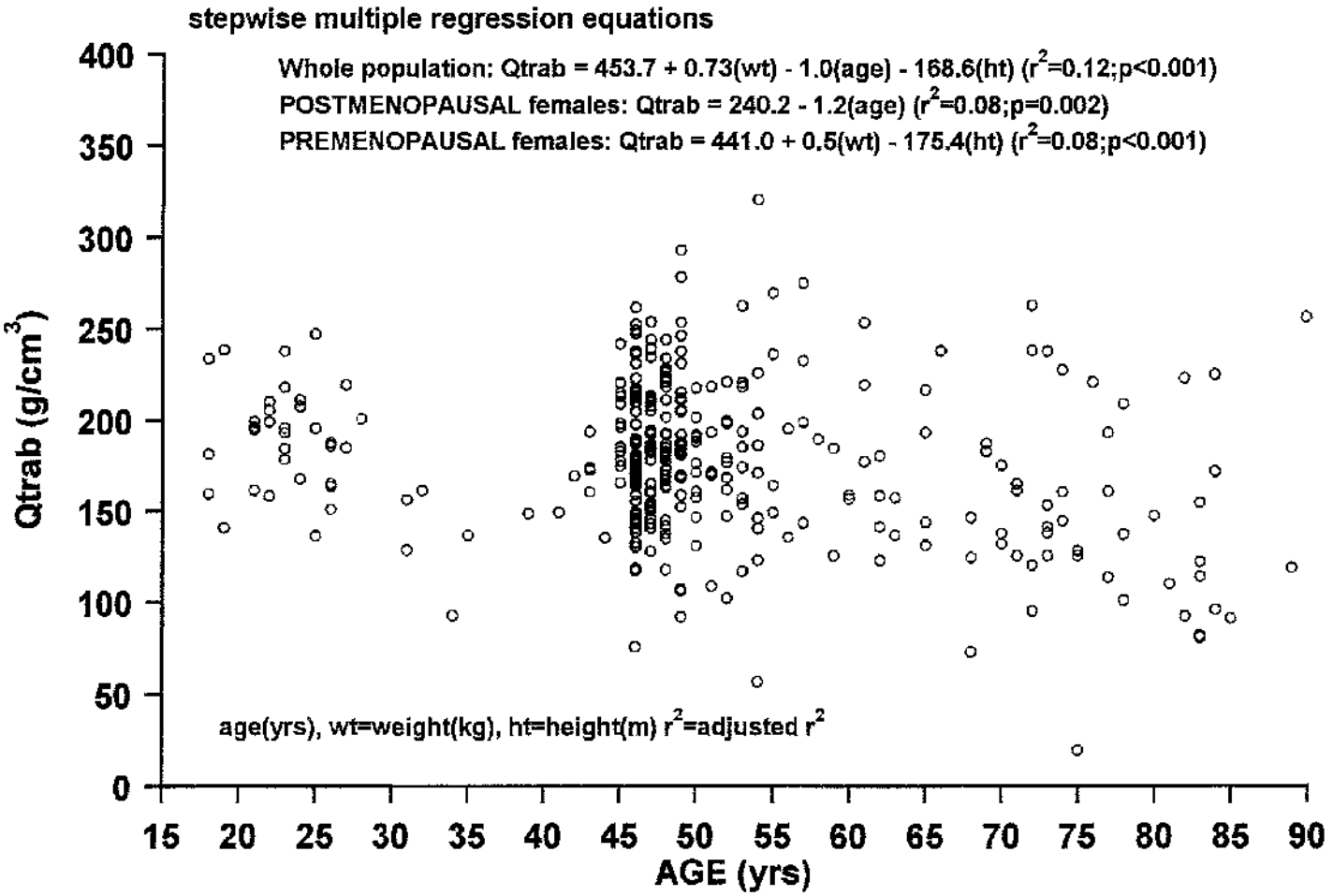


Fig 5.3: Age dependent distribution of Qscort BMD for normal females

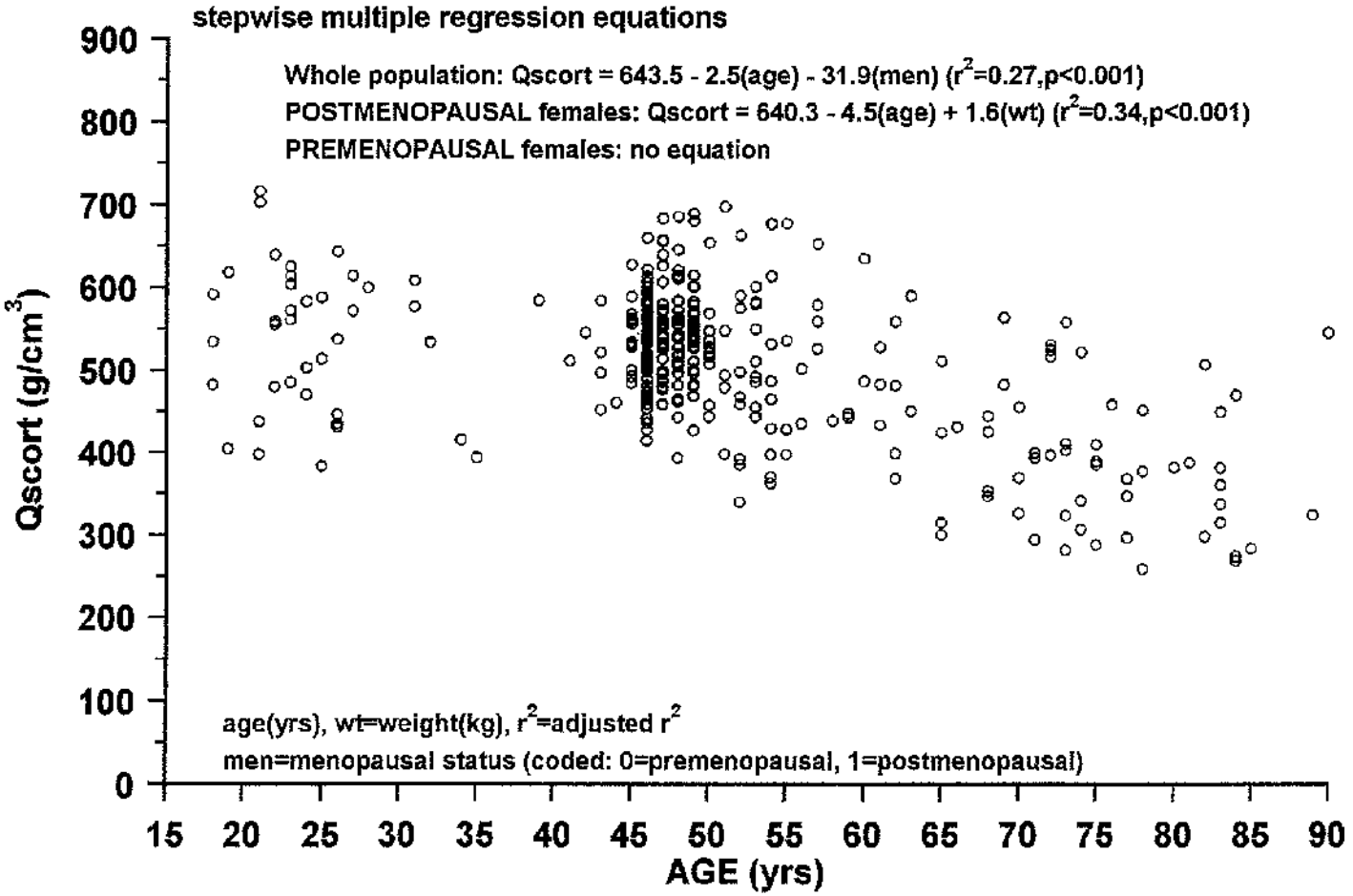
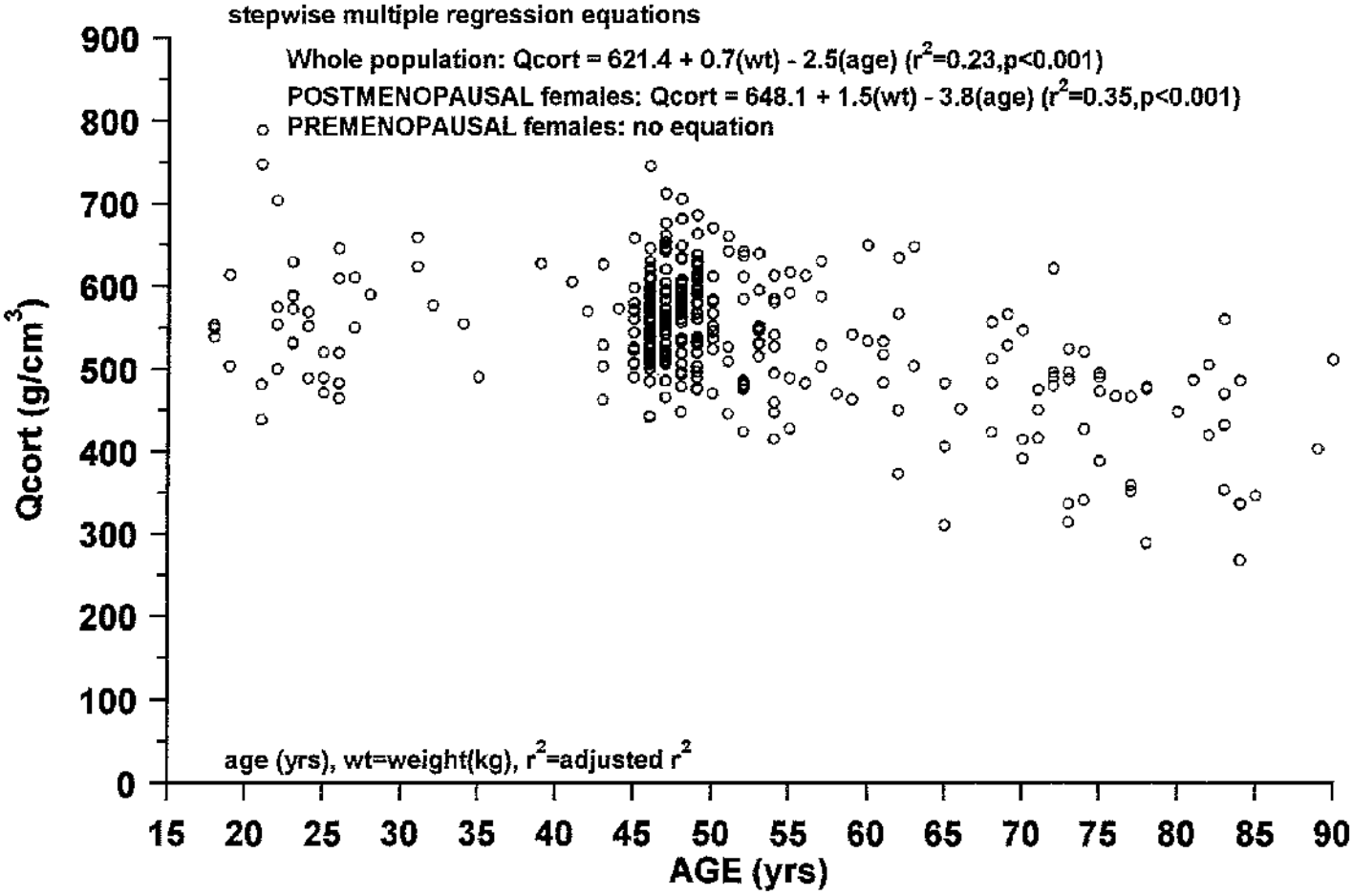


Fig 5.4: Age dependent distribution of Qcort BMD for normal females



CHAPTER 6

COMPARISON OF RADIAL pQCT BMD MEASUREMENTS WITH MEASUREMENTS AT OTHER SKELETAL SITES: IMPLICATIONS FOR THE USE OF pQCT IN SCREENING FOR LOW AXIAL BMD.

6.1 Introduction

Bone density measurements are now possible at a variety of skeletal sites using different techniques. At the present time DXA is considered the "benchmark" method of assessment. Therefore, in the development of pQCT, it would be important to document the relationship between DXA and pQCT BMD measurements. Similarly, it would be useful to know the relationship between pQCT and other emerging scanning techniques such as ultrasound. This is particularly important as regional variation in bone mass status exists within individuals (6.1,6.2,6.3).

Osteo-densitometry has some well defined roles in the management of bone disease (1.145,1.146). However, the issue of screening and prevention for the general population remains contentious (1.101,1.194). Screening for osteoporosis has been discussed in more detail in the introduction (chapter 1.5). It has been suggested that DXA may be of value in screening perimenopausal women, targeting those considered to be "at risk" for life style and therapeutic intervention. Selection of individuals in the lowest quartile (1.88) or quintile (1.101) of aged-matched DXA hip and lumbar spine measurements is one method proposed for identifying individuals for intervention, while another is to target prevention in those with osteoporosis (T-score of ≤ -2.5), or osteopenia (T-score of ≤ -1.0 but > -2.5) (6.4). An ideal bone density screening tool will accurately predict subjects at risk of future osteoporotic fracture. As discussed in the introduction (chapter 1.4 & 1.5),

BMD assessment is the best method of defining fracture risk (1.101,1.194). The best predictive power is achieved by measuring BMD at the site of future fracture, ie at hip and spine (1.88). pQCT is probably cheaper and more portable than DXA, so could be used either to predict fractures or to select subjects for measurement with the more expensive DXA technique. The predictive capacity of pQCT can only be determined by long-term prospective studies, as already done for radial SPA measurements in spine (6.5) and hip (1.192) fractures. Pending publication of such studies with pQCT, it could be used in an attempt to select individuals with a high risk of low hip and spine BMD.

The relationships between BMD measurements using different techniques at various sites were therefore examined by comparing pQCT BMD measurements with DXA (hip and spine) and calcaneal ultrasound measurements in a perimenopausal female population, and whole body DXA measurements in a postmenopausal female population. The potential for pQCT to be used as a community based screening tool preliminary to axial DXA measurement was examined in the perimenopausal population - that is, could it pre-select a group from the community who could be offered an axial DXA BMD measurement.

6.2 Study Populations and Bone Mass Measurements

The relationship of pQCT BMD measurements and those at other skeletal sites was examined in two groups:

Group 1. The relationships between the four pQCT BMD measurements were examined in 216 perimenopausal females who attended an osteoporosis screening programme. The method of recruitment has been described previously (Chapter 5.5.2-point 2). The relationships between pQCT and DXA hip and lumbar

spine BMD measurements, and calcaneal ultrasound measurements were also studied in this population. DXA measurements were performed on the initial screening visit, whilst pQCT and ultrasound measurements were performed on the same day at an additional visit within 2 months.

Group 2. Comparison of pQCT measurements with DXA whole body BMD (WB-BMD)was made in 45 postmenopausal females who were acting as controls in a study examining the power of different scanning modalities (DXA, CUBA and pQCT) in discriminating patients with hip fracture from a control population. This study is discussed further in chapter 8. Women within this group who had undergone hysterectomy had done so more than 2 years after cessation of their menses, and were considered to be postmenopausal. Further analysis of the whole body scan identified the non-dominant arm (ipsilateral to that scanned using pQCT) as an additional region of interest (ROI). The medial border of this ROI passed through the gleno-humeral joint and excluded all other bony areas. This is depicted in figure 2.5. The BMD of the whole arm was then derived (WB-ARM). All measurements were all done on the same day.

6.3 Statistical Analyses

Results for continuous variables are expressed as mean with standard deviation when normally distributed, median with range otherwise. Maximum and minimum values are shown for all bone density variables. The relationships between the various BMD measurements were examined by linear regression and Pearson correlation co-efficients. In the perimenopausal population (group 1), quartiles of the DXA, CUBA and pQCT measurements

were calculated with comparison of the proportion of individuals in the lowest quartiles of the different measurements. In view of the recently agreed WHO criteria for the diagnosis of osteoporosis and osteopenia based on bone density measurements (6.4), the proportional cut off value for each pQCT measurement which would be required to detect all women with osteopenia (T-score of ≤ -1.0) at either the hip (femoral neck) or spine site was determined, and compared to ultrasound measurements.

6.4 Results

6.4.1 Demographic and Bone Mass Data

Details of age, height and weight for all individuals (groups 1 & 2) are shown in Table 6.1. In group 1, 101 (46.8%) of the study population were premenopausal, 46 (21.3%) had previously undergone hysterectomy and 69 (31.9%) were postmenopausal. All females in groups 2 were postmenopausal. Bone mass data for groups 1 and 2 are shown in tables 6.2 and 6.3 respectively. Due to scanner malfunction, it was not possible to record BUA and VOS results in 5 and 7 subjects respectively in group 1, and it proved impossible to isolate the arm as a ROI from the whole body scan in 1 female in group 2. Only the DXA hip and spine measurements have a locally acquired normal range based on 300 women known not to have osteoporosis. Locally derived T-scores are given for the group 1 study population compared to this normal range.

6.4.2 Intra-Technique BMD Correlations for pQCT

The relationships between the different pQCT measurements are shown in figures 6.1-6.3. Qtot and Qscort correlated best (r=0.917). Qtot correlated less strongly with Qtrab and Qcort (r=0.687, r=0.551 respectively). Qscort was highly correlated with Qcort (r=0.739) but only moderately with Qtrab (r=0.457). Qtrab and Qcort were very poorly and negatively correlated (r=-

0.152).

6.4.3 Correlations of PQCT BMD Measurements with Bone Mass Measurements at Other Skeletal Sites

The relationships of Qtot with hip, spine, arm and whole body BMD measured by DXA, and calcaneal ultrasound BUA and VOS measurements are shown in figures 6.4-6.7. The correlation with hip measurements were all of a similar magnitude (FN: r=0.459, FT: r=0.443, FW: r=0.441), and slightly lower with LS (r=0.389). Correlation were comparable with WB-ARM (r=0.456), and slightly higher with WB-BMD (r=0.545). The relationship with calcaneal ultrasound measurements were generally poor (BUA: r=0.272; VOS: r=0.159).

The relationships of Qtrab with the above measurements are shown in figures 6.8-6.11. The relationships were similar to those found for Qtot, with slightly higher correlation with LS (r=0.41), FT (r=0.462), FT (r=0.525), WB-BMD (r=0.573) and BUA (r=0.306), and slightly lower correlation with FW (r=0.438), WBA-ARM (r=0.435) and VOS (r=0.097).

The relationships of Qscort with the above measurements are shown in figures 6.12-6.15. The correlations with LS (r=0.345), hip (r=0.406, 0.363, 0.403 for FN, FT and FW respectively), WB-BMD (r=0.416), WB-ARM (r=0.371)and BUA (r=0.242) were slightly poorer, and VOS (r=0.165) slightly greater than those found for Qtot.

The correlations of Qcort with other measurements (figures 6.16-6.19) were found to be extremely poor: (r: 0.047-0.207), and was best with WB-ARM.

6.4.4 Comparison of the Proportion of Females in the Lowest Quartiles of the Different Measurements for the

Perimenopausal Population (Group 1)

All women were placed in a quartile for each of the DXA (hip and spine), pQCT and ultrasound measurements. The percentage of females falling into the lowest quartiles (QU_4) of pQCT and DXA measurements also in the lowest quartile of other mutually exclusive hip and spine measurements are shown in Figure 6.20. Around 50% of women in QU_4 of LS, FT and FW and around 25% in QU_4 of FN were also in QU_4 of Qtot, Qtrab and Qscort. The corresponding figures for Qcort were around 30%. However, only about 60% of women in QU_4 of the hip measurements were also in QU_4 of LS, and about 70% when comparing intra-hip measurements. Figure 6.21 shows a similar analysis comparing women in QU_4 of the pQCT and ultrasound measurements. Generally, less than 50% of women in QU_4 of all pQCT measurements were also in QU_4 of BUA, with the corresponding figures for VOS being lower.

6.4.5 Proportional Cut-Off Figures for pQCT Measurements in Detecting Low Axial BMD in the Perimenopausal Population :Comparison with Ultrasound Measurements (Group 1).

In group 1, 97 (44.9%) women had a T-score $\leq$ -1.0 at LS, and 108 (50%) at FN. The proportional cut off values to detect all women with T scores $\leq$ -1.0 at LS and FN and the percentage of women below this value for each of the other bone density measurements are shown in Table 6.4. The proportional cut-off values for all pQCT measurements were such that almost the whole population would have to be scanned to detect all women with hip and spine osteopenia. However, the findings were similar for ultrasound measurements. Also, to detect all women with spinal osteopenia based upon a FN measurement, 96.3% of the population would have to be scanned, and 88.4% to detect hip osteopenia based upon a lumbar spine measurement.

6.5 Discussion

Intra-technique correlations of pQCT BMD measurements were variable. The highest correlation was found between total and subcortical BMD values, which can be explained by subcortical measurements incorporating the cortical shell and a small rim of trabecular bone, thus both cortical and trabecular components are represented in this measurement, as they are in the total BMD measurement. The correlations between other pQCT BMD measurements were only moderately high, with the relationship between trabecular and cortical measurements being negative. This suggests that radial bone at this site is inhomogeneous, as previously suggested (1.153). Also, rapid and dramatic changes in the proportion of cortical and trabecular bone occurs within the distal 3cm of the radius (1.17). The measurement site for ultra-distal pQCT measurements falls within this area so small differences in the relative scan position between individuals will result in a large scatter of results, and poorer correlation between BMD values. These correlation coefficients are similar to previously reported results for the same scanner (3.1,6.6). It is worth noting that the relationship between trabecular and cortical BMD measurements at the ultra-distal radial site is very poor, a feature which has also been noted previously (3.1). This is probably related to the thinness of the measurement slice introducing sampling errors (3.1), an age related diminution in both cortical bone thickness and density (6.6), and an age related increase in the proportion of trabecular bone at the measurement site (6.6). However, the age range of the population studied (group 1) to determine the correlations of pQCT BMD measurements was narrow (45-55 years), suggesting that a dramatic change in the proportion of trabecular and cortical bone over small distances at the ultra-distal site, and thinness of the measurement slice were the main reasons for the lack of correlation between pQCT cortical and trabecular BMD.

There was also only moderate correlation between pQCT BMD measurements and the total BMD of the ipsilateral arm, as identified from the DXA whole body scan. As the radius, ulna and humerus are long bones consisting predominantly of cortical bone, it is surprising that the correlation between the pQCT cortical BMD and DXA arm BMD was not higher, whilst the best correlation was found with the pQCT total BMD measurement. Once again though, this is likely to be related in part to the size of the measurement sample, relative to the size of the upper limb.

The correlations between total, trabecular and subcortical pQCT radial BMD measurements and DXA BMD measurements of the lumbar spine, proximal femur and whole body are all of a similar magnitude and at best only moderate, whilst those for cortical BMD are even poorer. Similar relationships between pQCT and DXA hip and spine BMD measurements have been reported previously using similar pQCT scanners with an single energy x-ray source (1.50,3.1), and a predecessor using a ^{125}-I energy source (6.7). To my knowledge there no reports comparing pQCT measurements to whole body BMD.

Similarly, correlations were poor between all pQCT measurements and both calcaneal ultrasound measurements, confirming previous findings (1.50). The best correlation was between BUA and radial trabecular BMD, which is perhaps not surprising as the os calcis consists of 90-95% trabecular bone (1.21). This differs from the results of a previous study where BUA correlated better with radial mid-shaft BMD (predominantly cortical bone), rather than with trabecular BMD measured at a distal site. The pQCT scanner which was specially built, was

different to the Stratec 960, and the study population was much smaller, with only 24 females being studied (6.8).

These results suggest that the relationship between ultra-distal radial pQCT BMD measurements and those at other skeletal sites (ipsilateral arm, lumbar spine, proximal femur, whole body and calcaneus) are at best only moderate. As such, they do not reflect, and could not be used to predict with any accuracy, BMD at other skeletal sites. Whilst these results could be explained in part by our heterogeneous population, differences in the proportion of cortical and trabecular bone between skeletal sites, scanner precision, and thinness of pQCT measurement slice, it is much more likely that they further illustrate regional variation of bone density within individuals, which has been observed previously (6.1,6.2,6.3).

For females considered "at risk" in the lowest quartile of lumbar spine measurements, about 50% would be missed based upon pQCT (other than cortical BMD) measurements, and 70% missed based upon pQCT cortical BMD. For women "at risk" in the lowest quartile of femoral neck measurements, 70% - 80% would be missed based upon pQCT measurements. Vice versa, basing risk upon quartiles of pQCT measurements would result in many women being wrongly categorised as "at risk" at the hip and spine. To detect all women with either hip or spinal osteopenia (T score $\leq$ -1.0) based upon pQCT measurements, almost the whole perimenopausal population would have to be scanned to ensure all cases were detected. The results for calcaneal ultrasound measurements were comparable to pQCT. It is also worth noting that to detect all women with femoral neck osteopenia based upon a lumbar spine scan, 88.4% of the study population would have to be scanned, and vice versa, 96.3% scanned. These data suggest that due to the poor correlation between BMD assessment at various sites irrespective of scanning modality, site

specific or at least two-site assessment of risk is preferable in those requiring fracture risk assessment. Two-site assessment has previously been shown to improve the predictive value for subsequent vertebral fracture (1.191,6.9,6.10).

These results show that pQCT would be of no value in pre-selecting individuals for further axial DXA measurements should a screening program for osteopenia become reality. However, calcaneal ultrasound measurements have been shown to predict future hip fracture (see chapter 8) and there is convincing evidence that peripheral bone density measurements are useful in determining fracture risk. Although hip fracture risk is best determined by a site specific measurement (1.192), prospective studies have shown that radial BMD measurements, using osteo-densitometers other than pQCT, can predict fracture risk at the hip (1.192) and spine (6.5). Prospective studies are required before similar claims can be made for pQCT.

Table 6.1. Details of groups 1 and 2. Group 1 is divided into premenopausal (PRE), postmenopausal (POST) and hysterectomized (HYST) subgroups. Unless otherwise stated, values are mean(SD). § is median(range).

	Group 1			Group 2
	PRE	POST	HYST	ALL POST
Number	101	67	48	45
Age (yrs)	47.2 (1.3)	50.6 (2.6)	48.9 (2.2)	75.1 (7.7)
Height (m)	1.62 (0.06)	1.59 (0.06)	1.61 (0.07)	1.57 (0.06)
Weight (kg)	67.6 (12.5)	65.6 (11.5)	63.6 (11.2)	61.4 (9.6)
Number on HRT	8	20	14	0
Number on tamoxifen	1	2	0	0
Number on oral corticosteroid	1	0	1	0
Number on thyroxine	3	2	5	3
Number with Rheumatoid Arthritis	0	0	1	1
Number with asthma	9	4	4	2
Number with diabetes	2	0	0	3
Years postmenopause §	-	3 (0.5 - 15)	-	30.4 (9.7)
Years since hysterectomy §	-	-	9 (0.5 - 24)	-

Table 6.2. pQCT, DXA hip and spine BMD, and calcaneal ultrasound measurements of the perimenopausal population (Group 1).

	Mean	SD	Min.	Max.
pQCT (BMD, g/cm³: n=216)				
Qtot	380.1	58.5	205.9	578.1
Qtrab	182.3	41.0	56.8	341.7
Qscort	521.8	69.0	306.6	697.1
Qcort	554.4	61.2	380.4	705.3
DXA (BMD, g/cm²: n=216)				
Lumbar spine (LS)	1.030	0.170	0.701	1.736
T-score	-0.81	1.46	-3.64	5.28
Femoral neck (FN)	0.860	0.130	0.580	1.222
T-score	-0.90	1.08	-3.25	2.85
Trochanter (FT)	0.690	0.120	0.411	1.037
Ward's area (FW)	0.670	0.140	0.409	1.135
Ultrasound				
Attenuation (BUA) (dB/MHz: n=211)	77.8	17.6	39.0	144.0
Velocity (VOS) (m/s: n=209)	1405	54	1151	1575

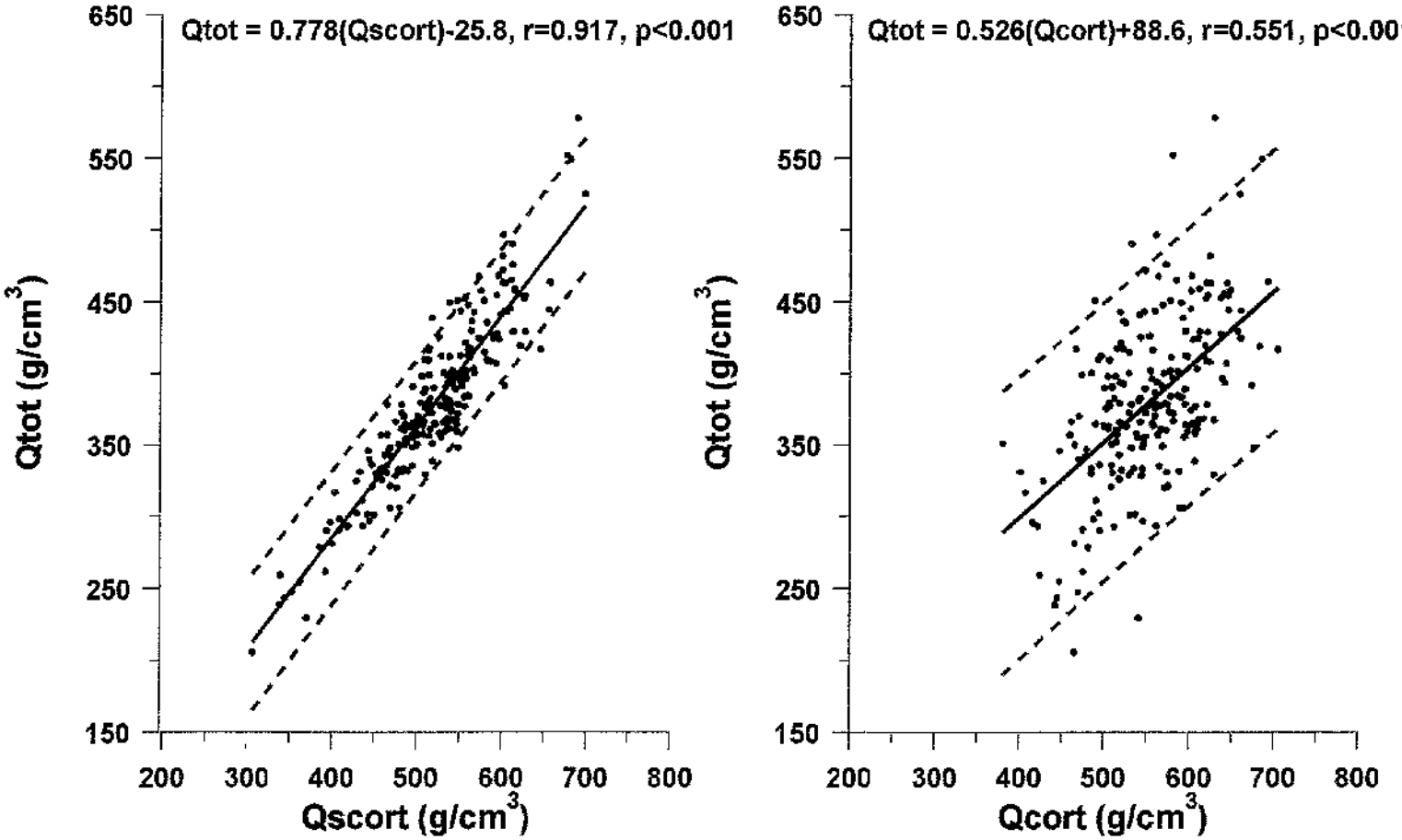
Table 6.3. pQCT total (Qtot), trabecular (Qtrab), subcortical (Qscort) and cortical (Qcort) BMD and DXA whole body (WB-BMD) and arm (WB-ARM) BMD of Group 2.

	Mean	SD	Min.	Max.
pQCT (BMD, g/cm³: n=45)				
Qtot	288.8	66.1	193.5	448.1
Qtrab	151.6	54.5	19.5	262.7
Qscort	397.6	86.1	258.4	557.4
Qcort	455.2	77.7	267.9	621.9
DXA (BMD, g/cm²)				
WB-BMD (n=45)	0.871	0.110	0.656	1.157
WB-ARM (n=44)	0.723	0.112	0.473	0.982

Table 6.4. Cut-off value and proportion of population below this value for each of the DXA, pQCT and ultrasound measurements to detect all women with T scores ≤ -1 at lumbar spine (n=97) and femoral neck (n=108). Values are: bone density cut-off value (percentage of population)

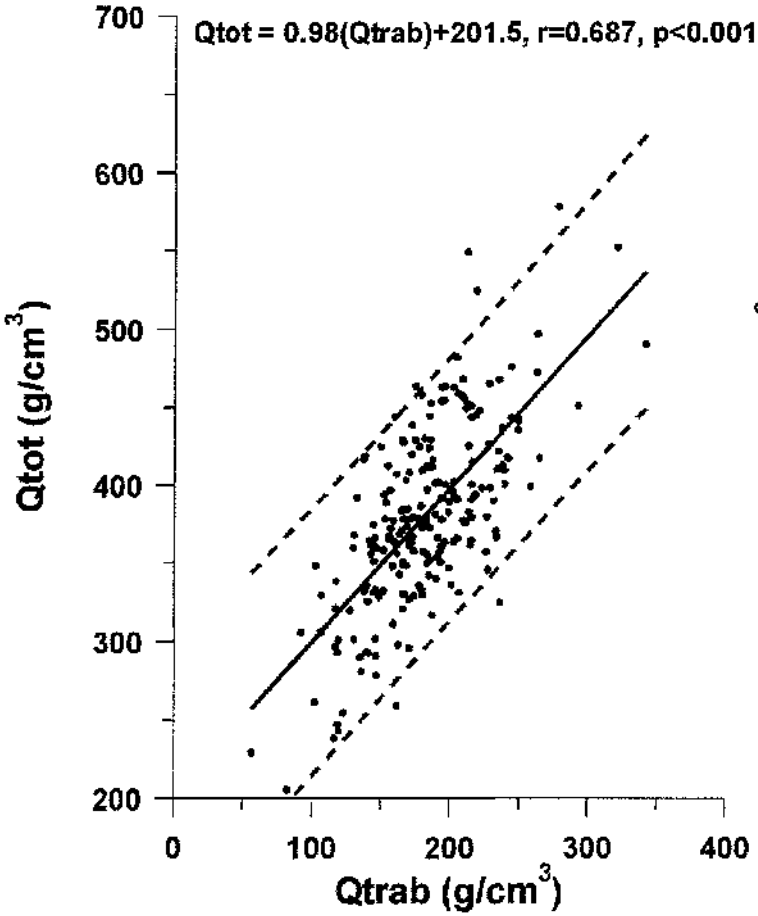
	Lumbar spine	Femoral neck
DXA (BMD, g/cm²)		
LS	-	1.236 (88.4)
FN	1.104 (96.3)	-
FT	0.835 (89.4)	0.751 (71.3)
FW	1.023 (98.6)	0.812 (85.6)
pQCT (BMD, g/cm³)		
Qtot	578.1 (100)	578.1 (100)
Qtrab	278.1 (98.6)	278.1 (98.6)
Qscort	688.6 (99.1)	688.6 (100)
Qcort	693.8 (99.5)	705.3 (100)
Ultrasound		
BUA (dB/MHz)	144 (100)	122 (98.6)
VOS (m/s)	1496 (97.1)	1514 (99.0)

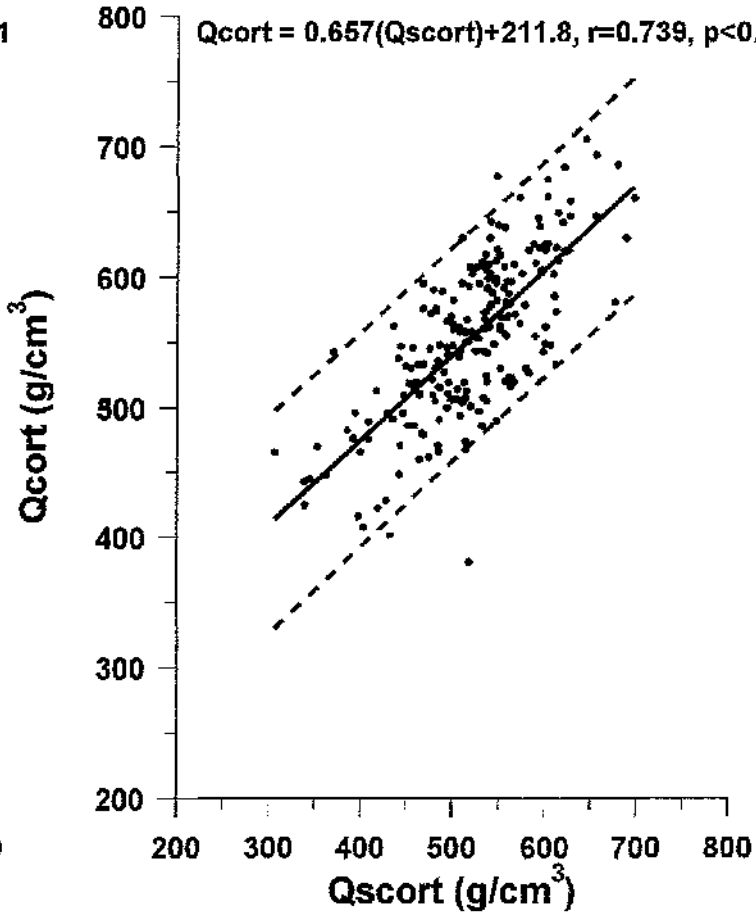
Fig 6.1: Relationship of Qtot with Qscort and Qcort



95% confidence limits for regression equations shown

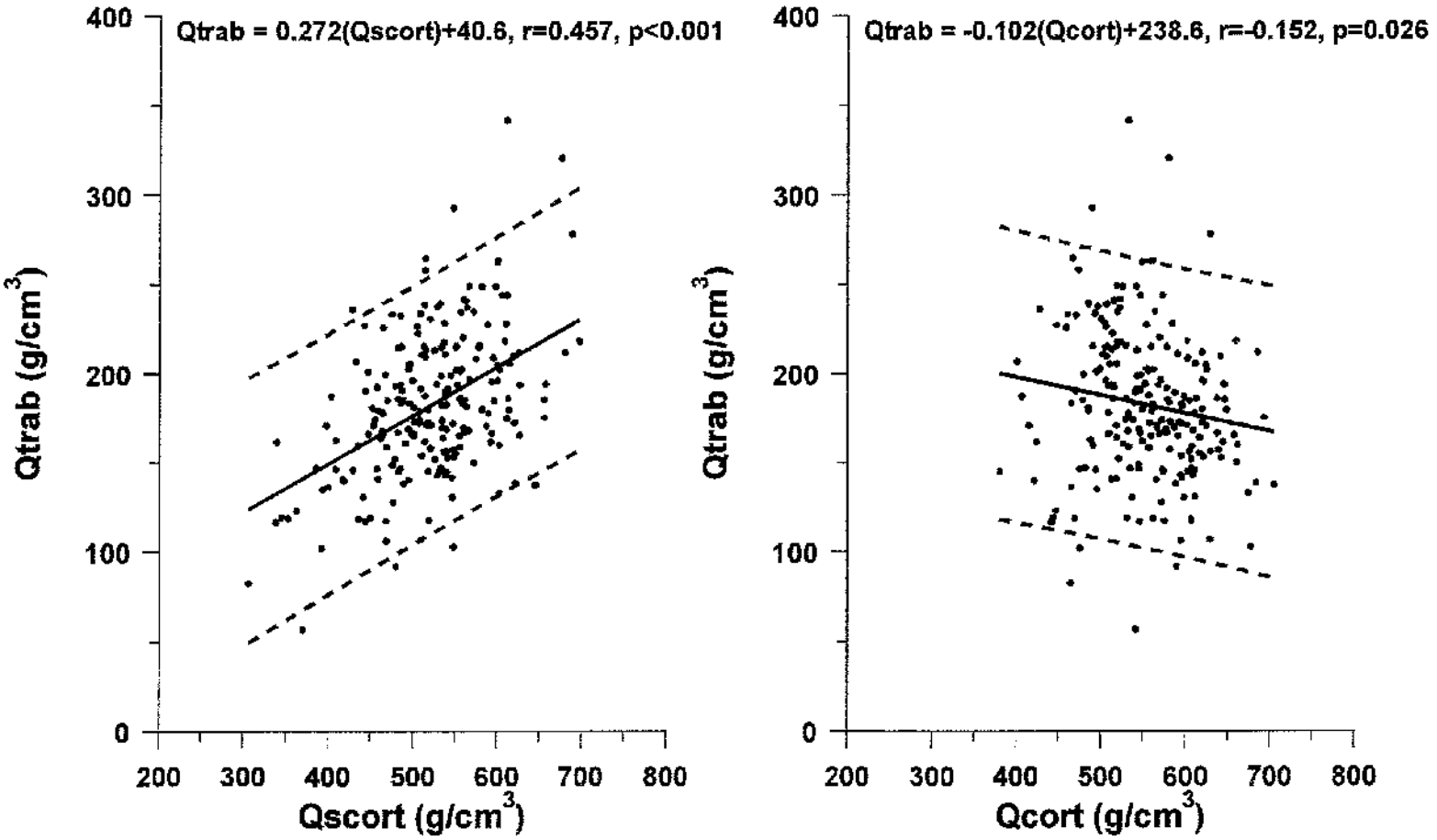
Fig 6.2: Relationships of Qtot with Qtrab, and of Qcort with Qscort





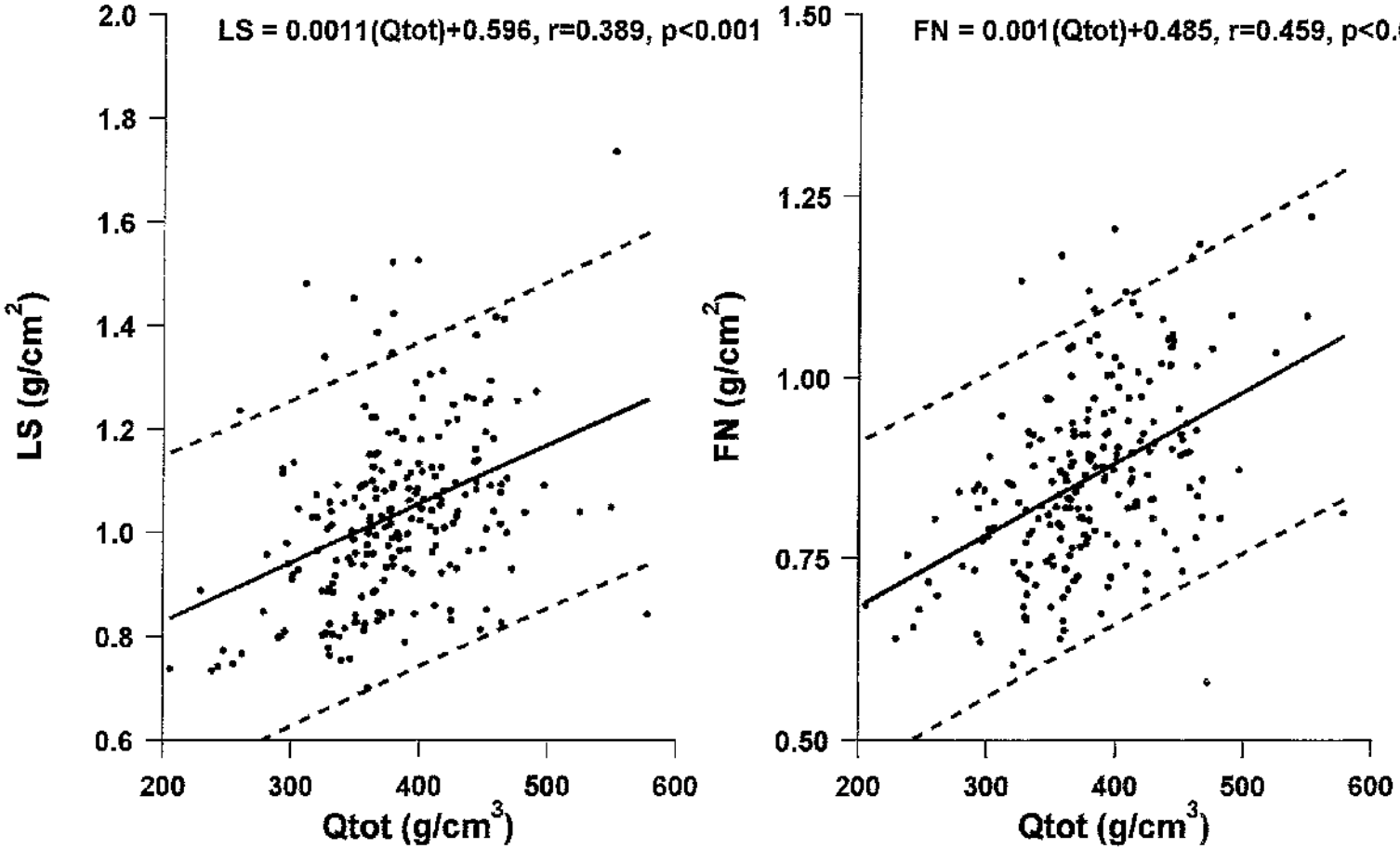
95% confidence limits for regression equations shown

Fig 6.3: Relationships of Qtrab with Qscort and Qcort



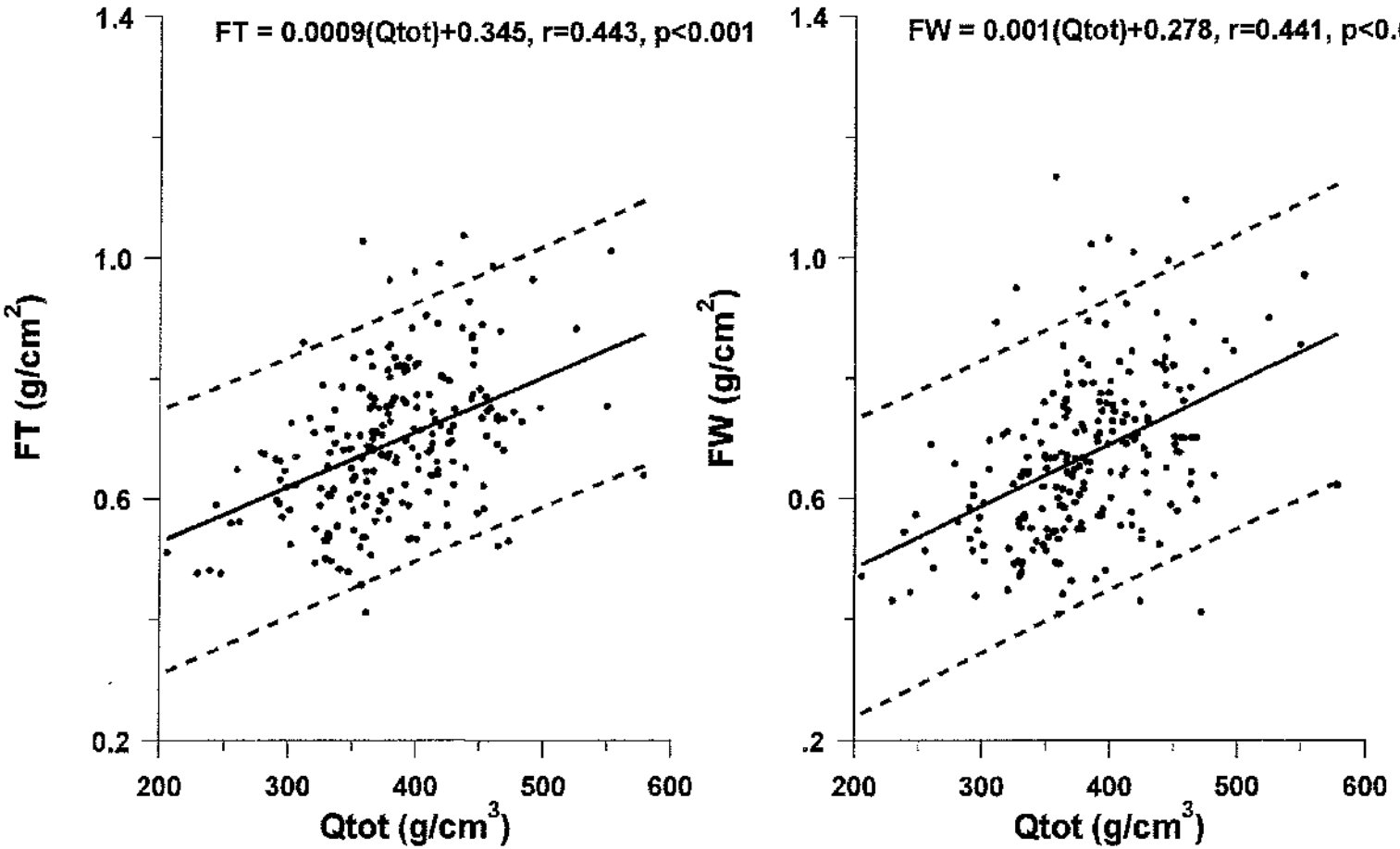
95% confidence limits for regression equations shown

Fig 6.4: Relationships of pQCT Qtot with DXA LS and FN



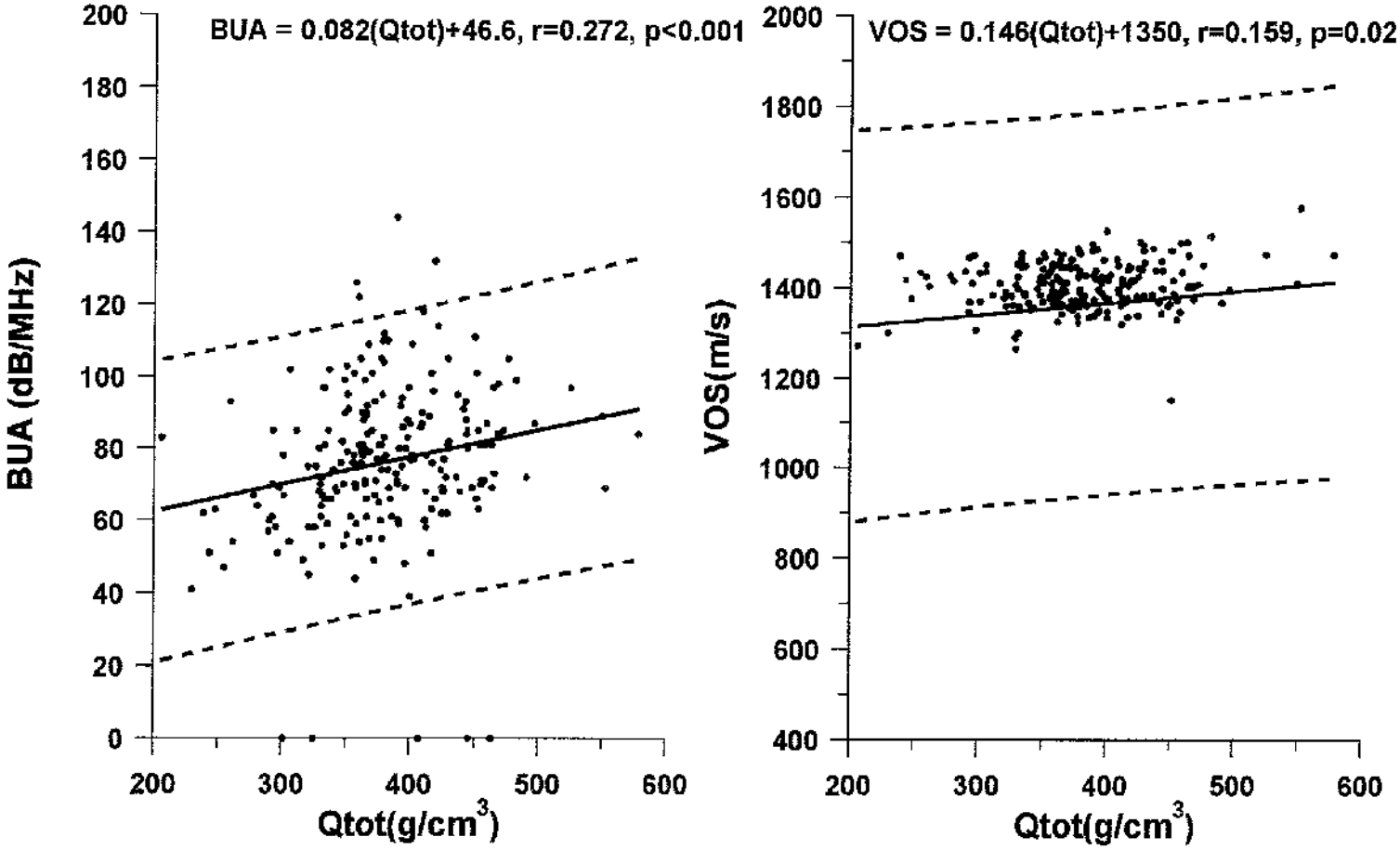
95% confidence limits for regression equations shown

Fig 6.5: Relationships of pQCT Qtot with DXA FT and FW



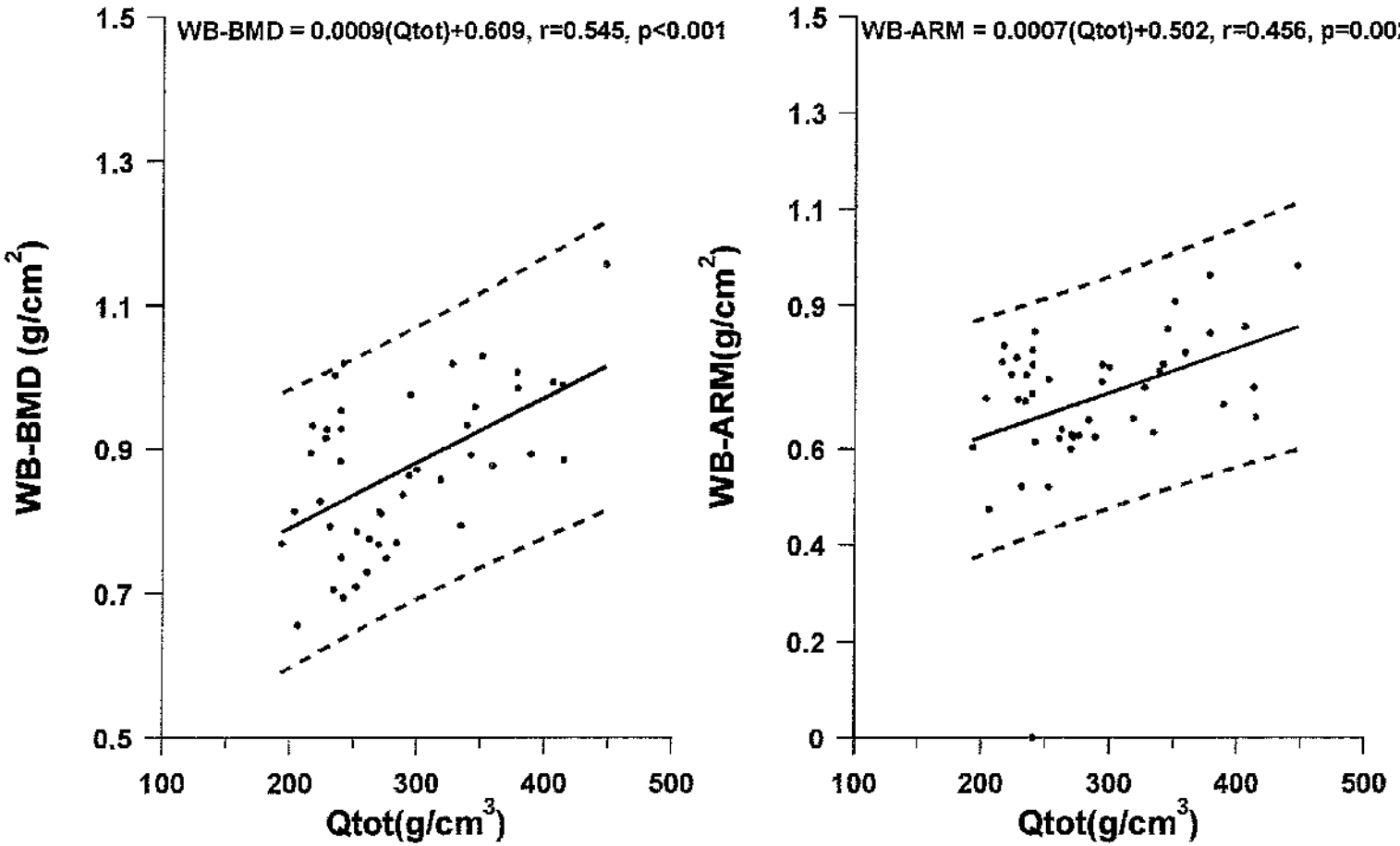
95% confidence limits for regression equations shown

Fig 6.6: Relationships of pQCT Qtot with ultrasound BUA and VOS



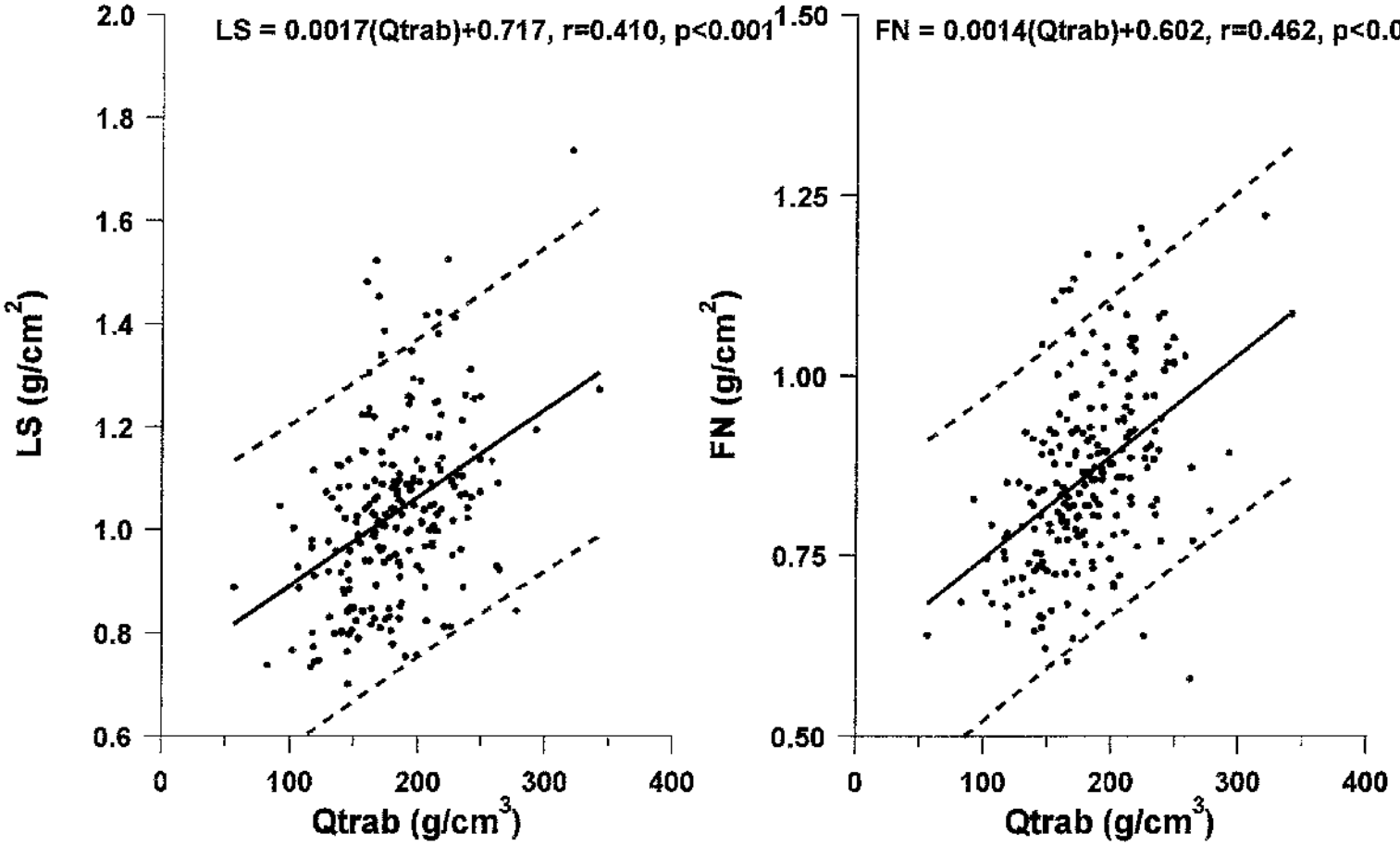
95% confidence limits for regression equations shown

Fig 6.7: Relationships of pQCT Qtot with DXA WB-BMD and WB-ARM



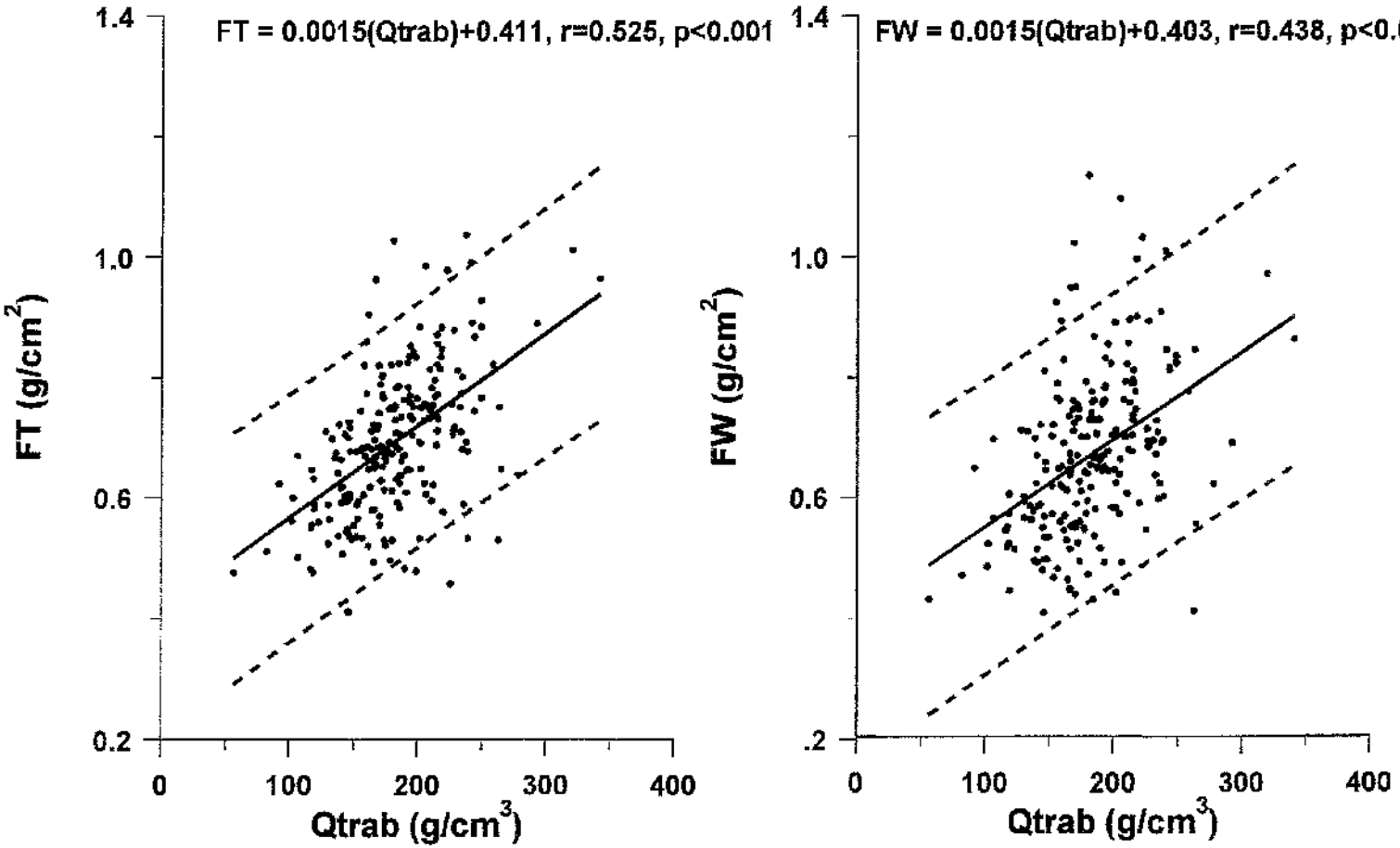
95% confidence limits for the regression equations shown

Fig 6.8: Relationships of pQCT Qtrab with DXA LS and FN



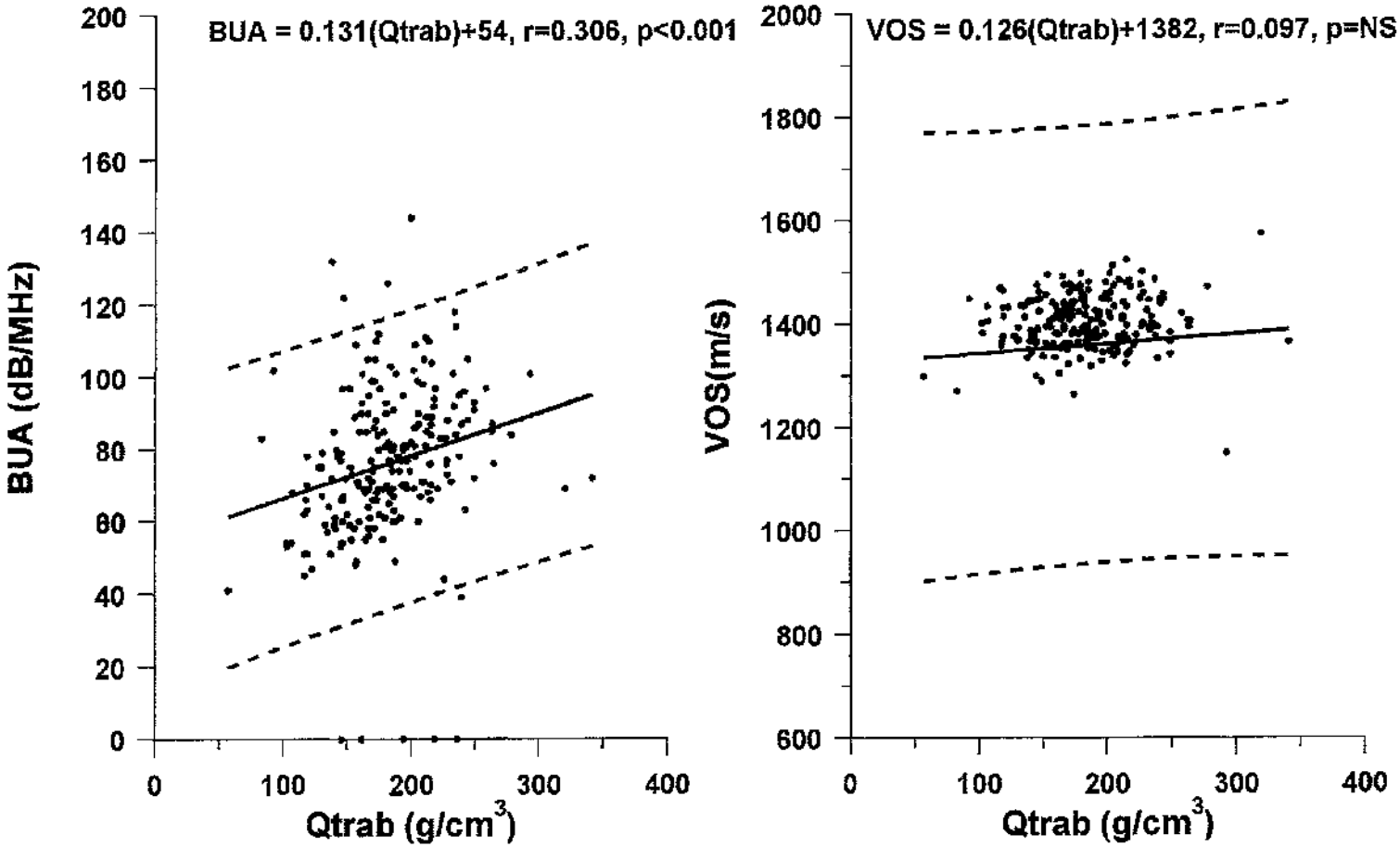
95% confidence limits for regression equations shown

Fig 6.9: Relationships of pQCT Qtrab with DXA FT and FW



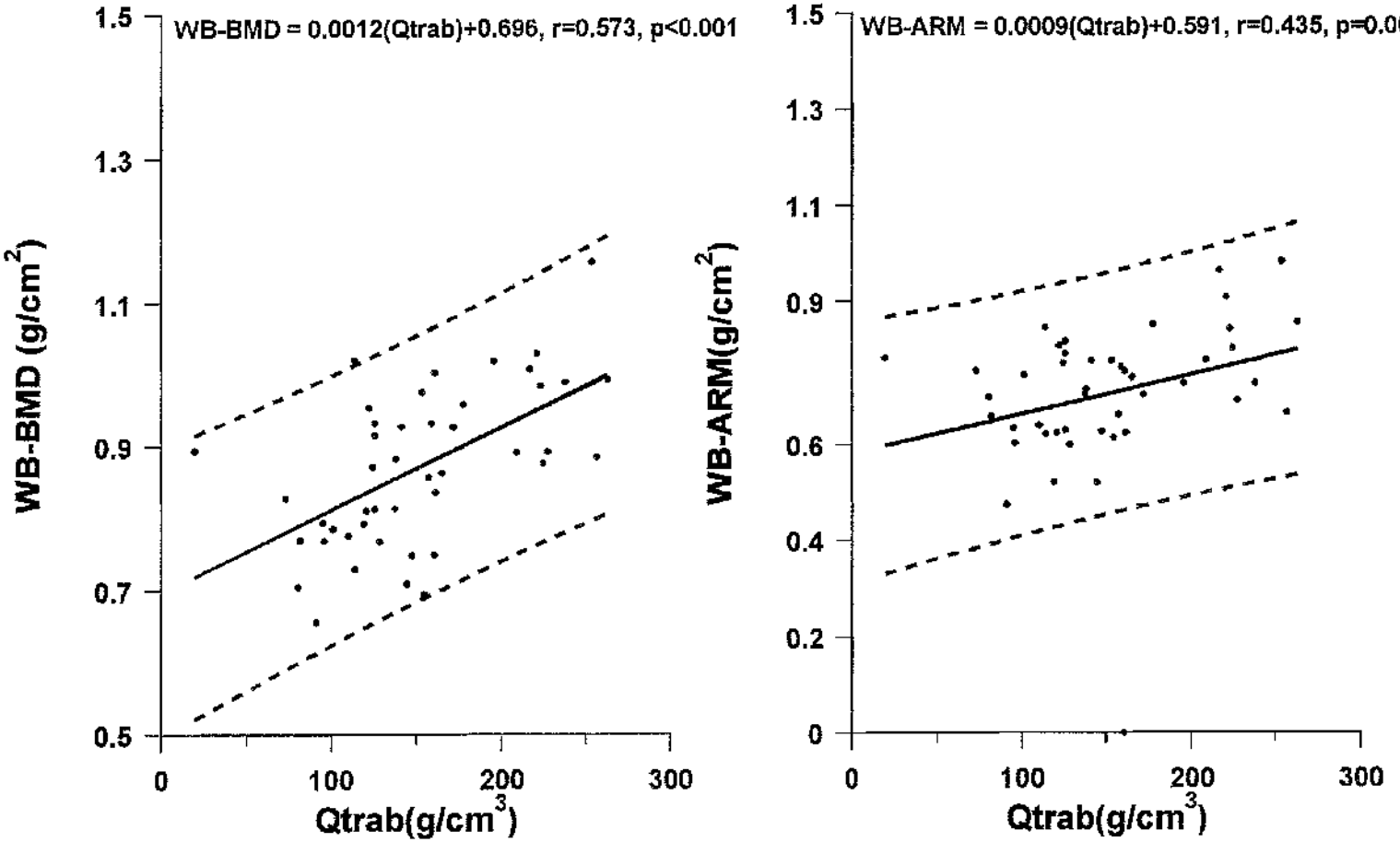
95% confidence limits for the regression equations shown

Fig 6.10: Relationships of pQCT Qtrab with ultrasound BUA and VOS



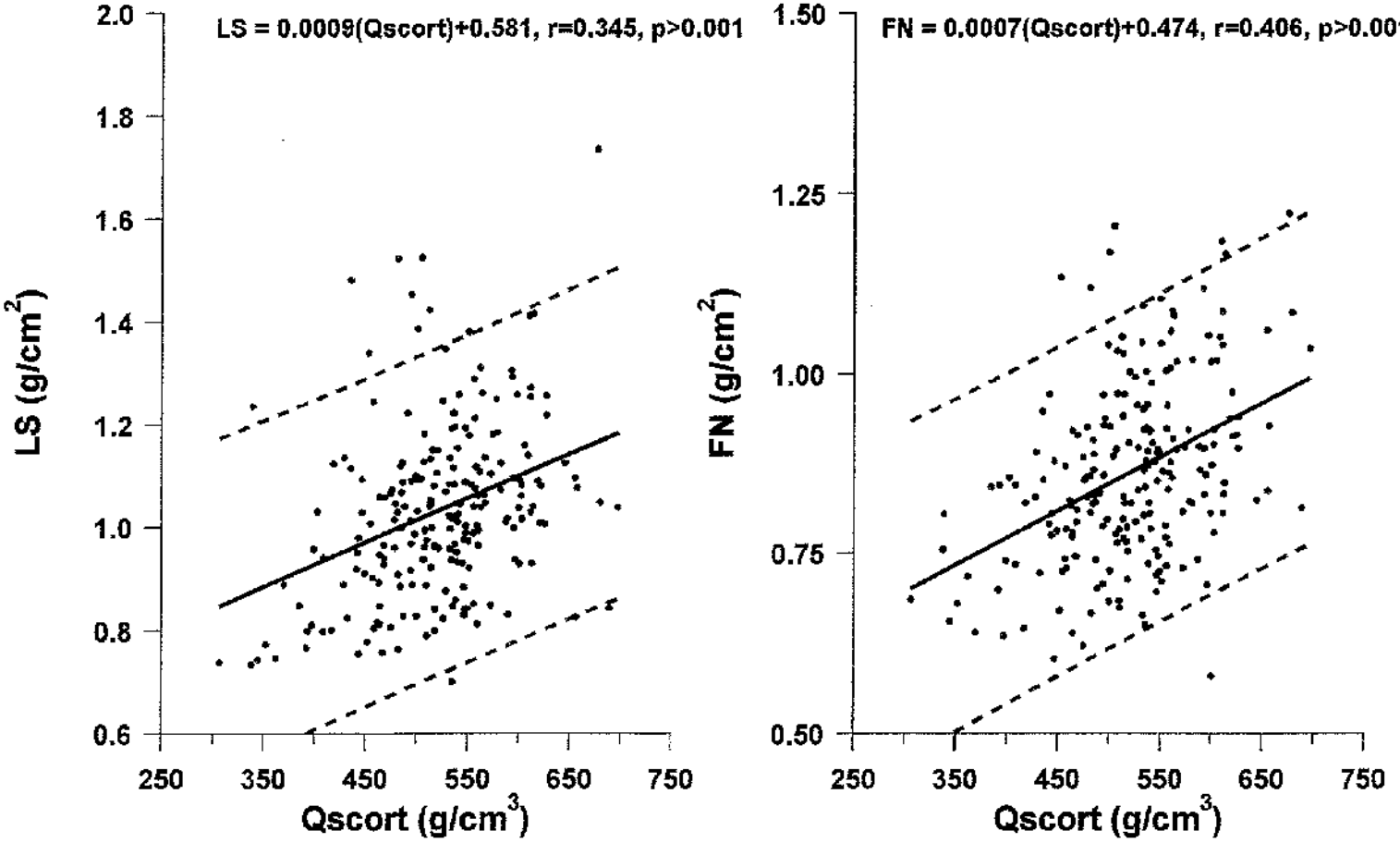
95% confidence limits for regression equations shown

Fig 6.11: Relationships of pQCT Qtrab with DXA WB-BMD and WB-ARM



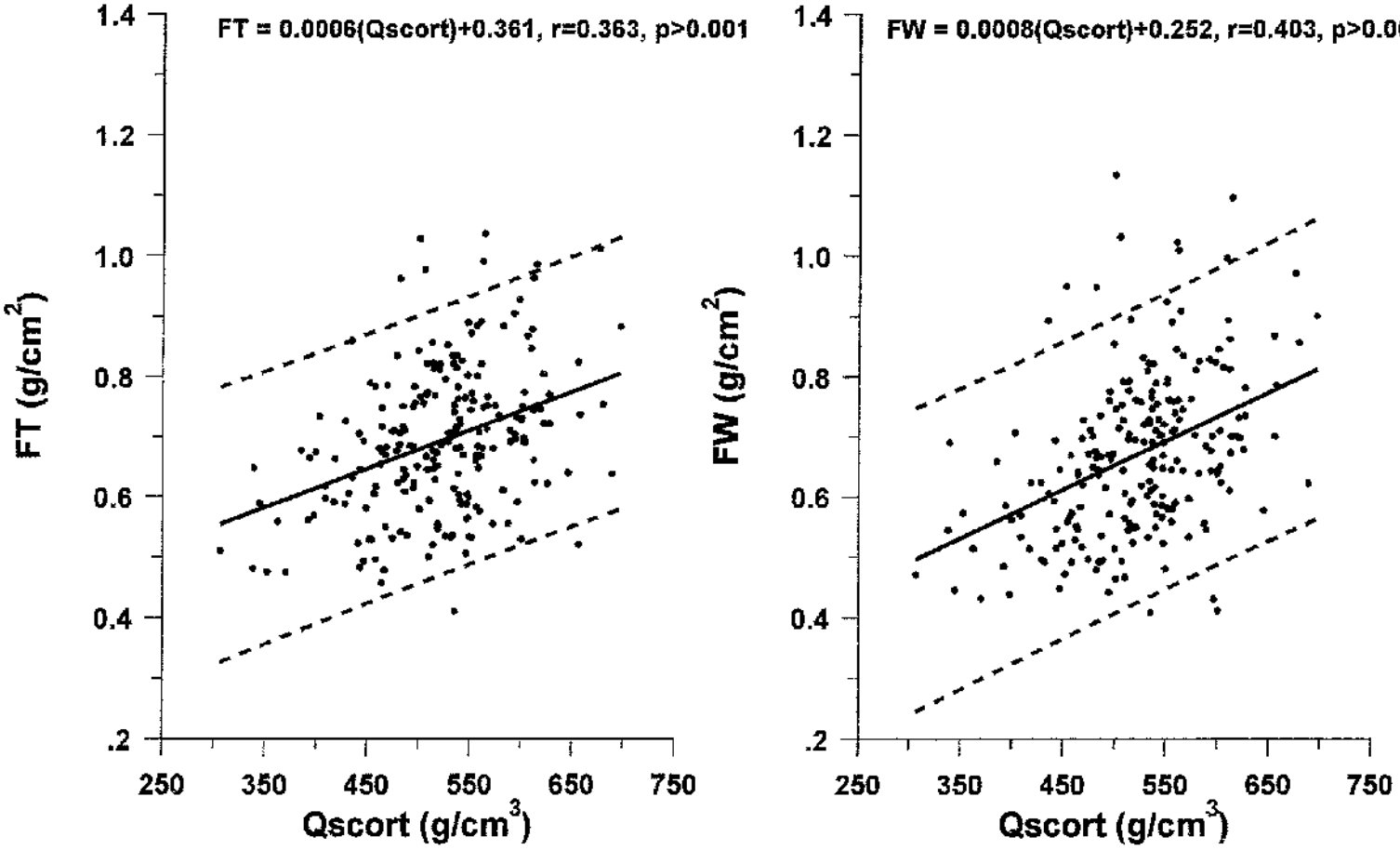
95% confidence limits for regression equations shown

Fig 6.12: Relationships of pQCT Qscort with DXA LS and FN



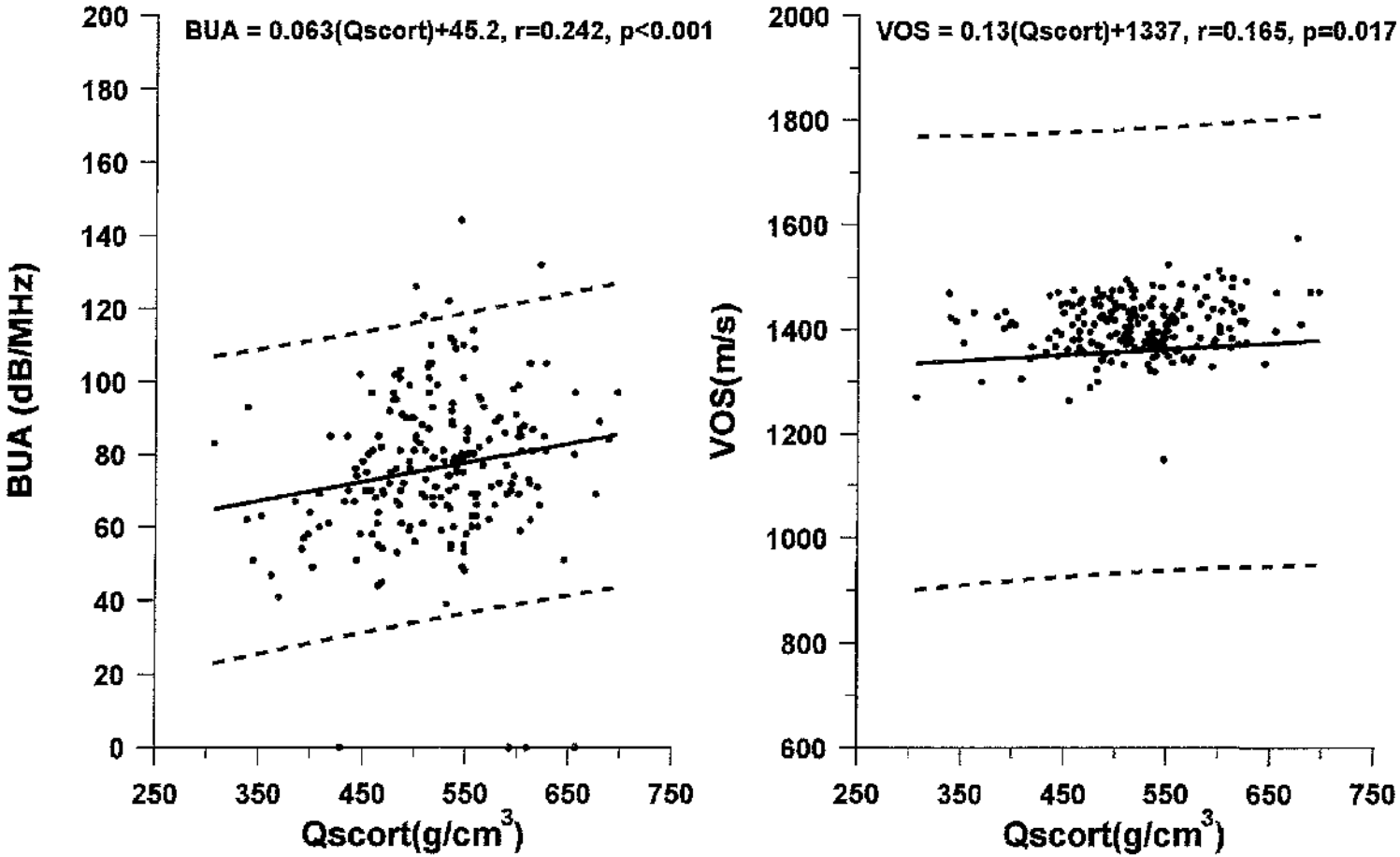
95% confidence limits for regression equations shown

Fig 6.13: Relationships of pQCT Qscort with DXA FT and FW



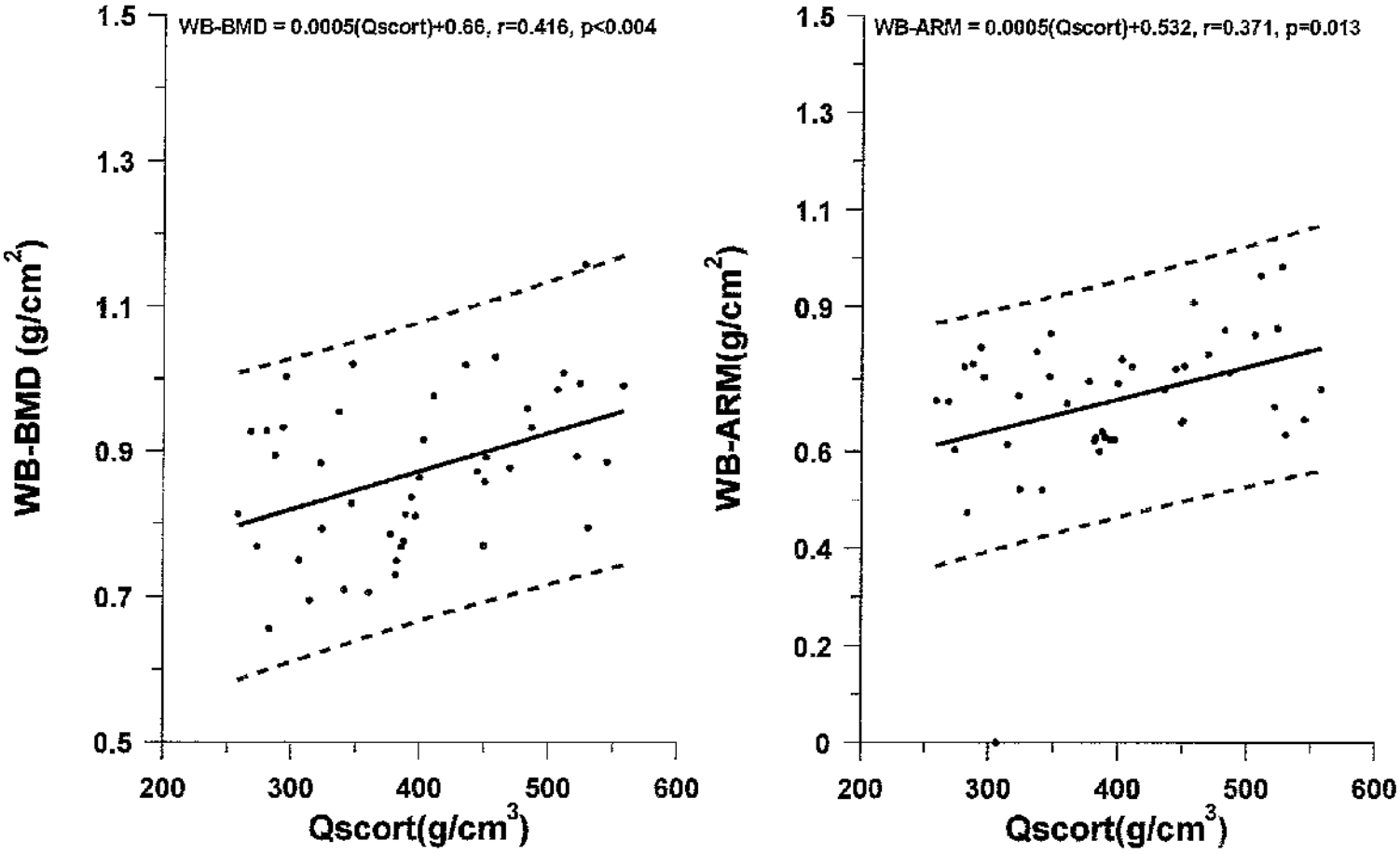
95% confidence limits for regression equations shown

Fig 6.14: Relationships of pQCT Qscort with ultrasound BUA and VOS



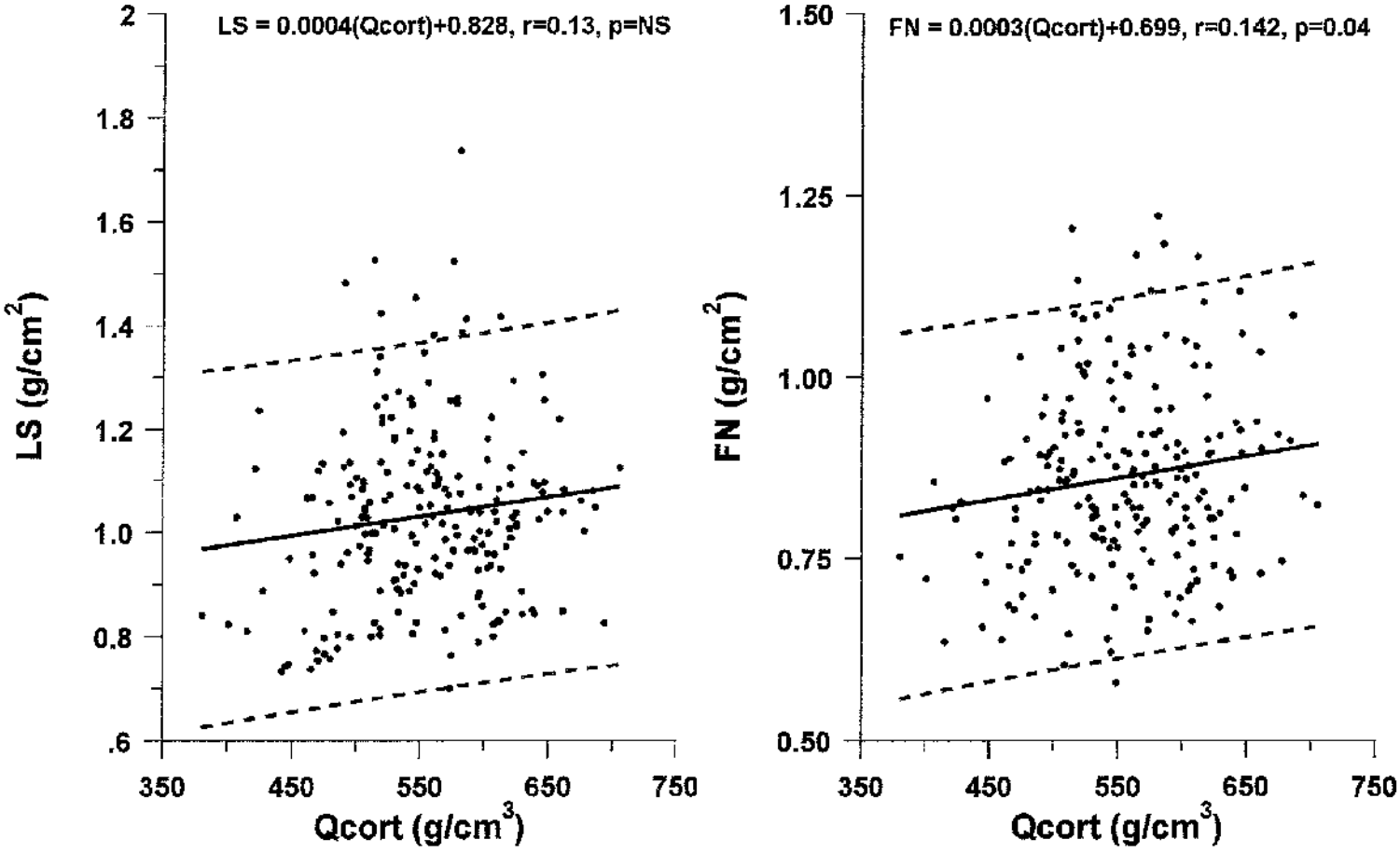
95% confidence limits for regression equations shown

Fig 6.15: Relationships of pQCT Qscort with DXA WB-BMD and WB-ARM



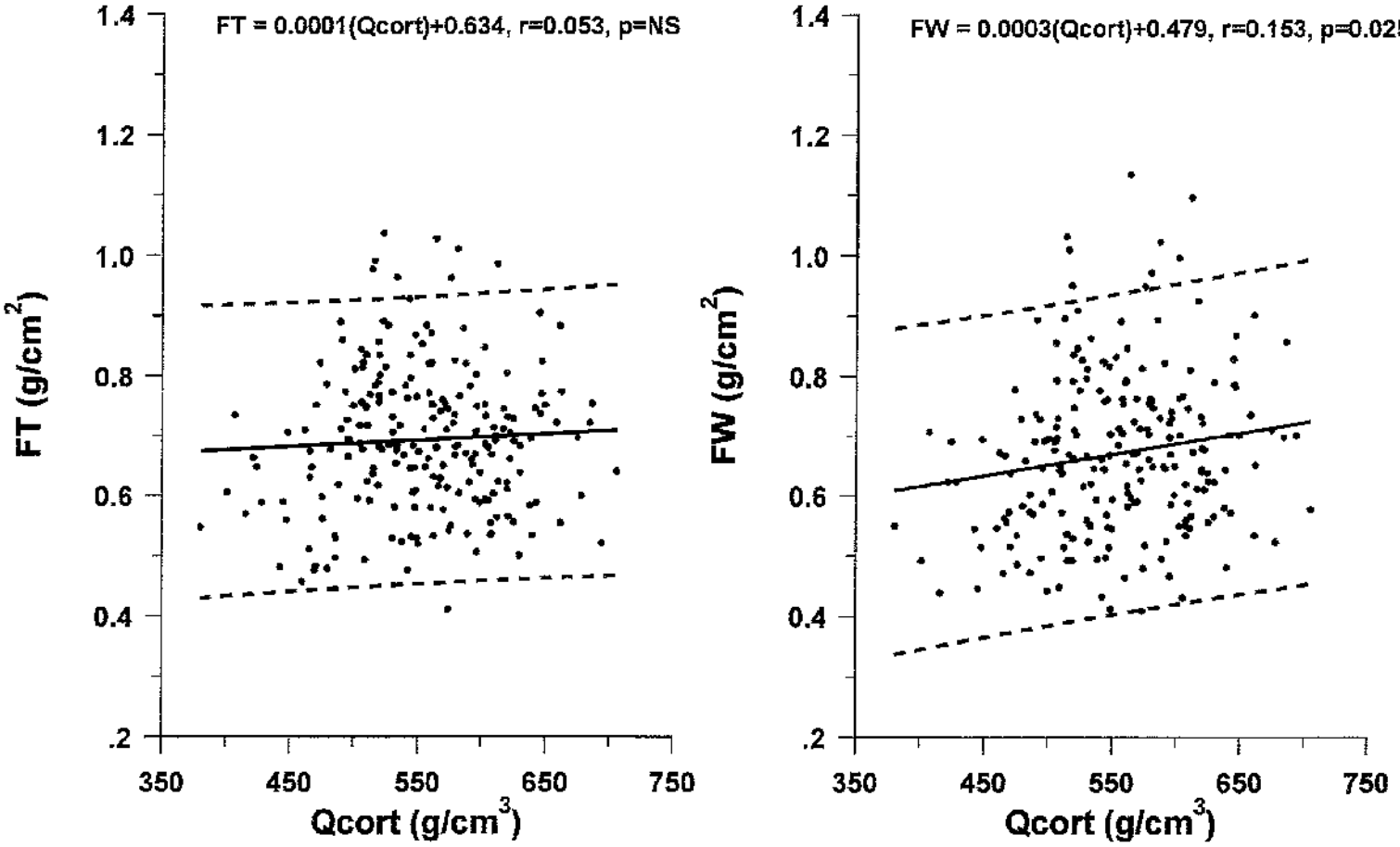
95% confidence limits for regression equations shown

Fig 6.16: Relationships of pQCT Qcort with DXA LS and FN



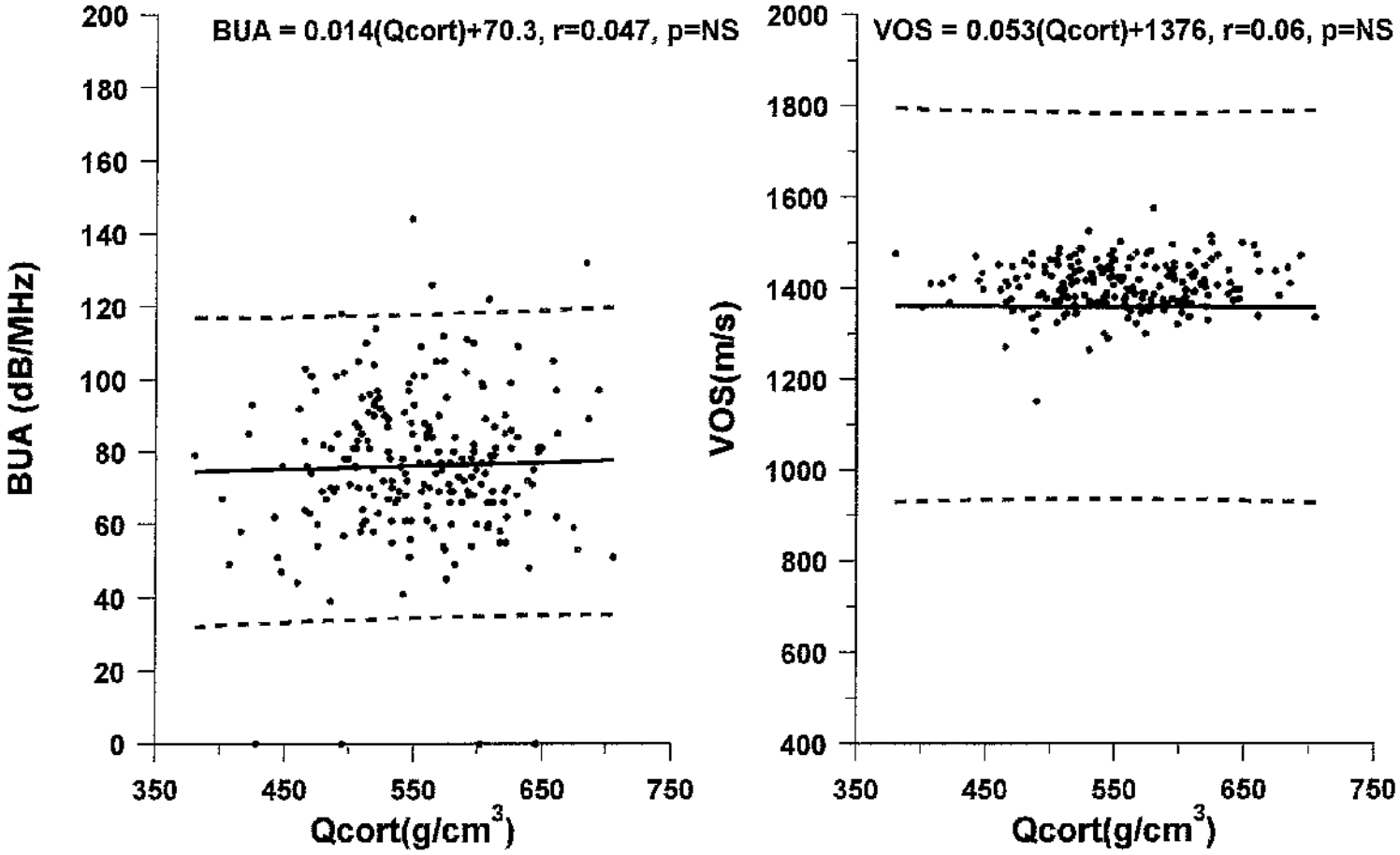
95% confidence limits for the regression equations shown

Fig 6.17: Relationships of pQCT Qcort with DXA FT and FW



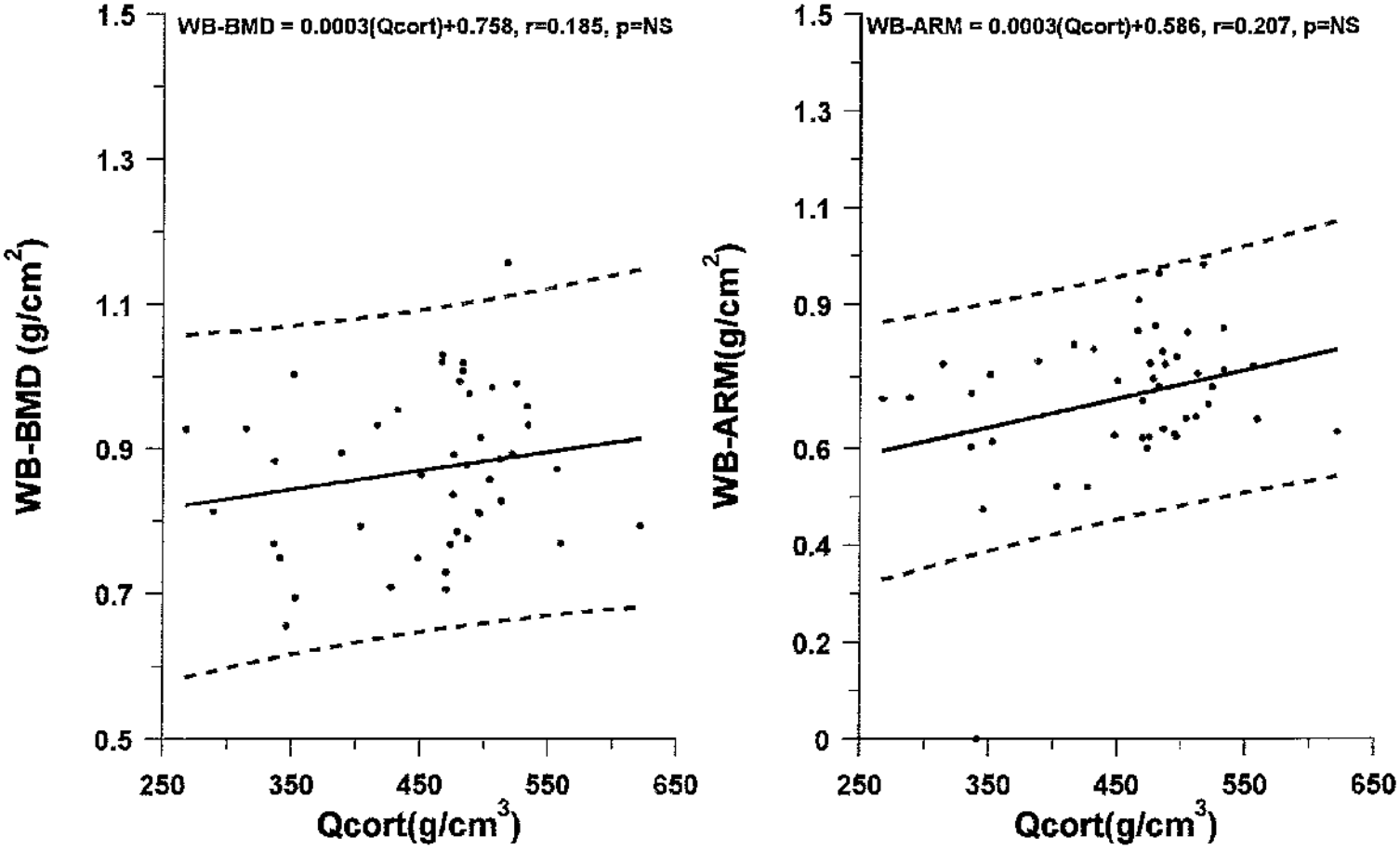
95% confidence limits for regression equations shown

Fig 6.18: Relationships of pQCT Qcort with ultrasound BUA and VOS



95% confidence limits for regression equations shown

Fig 6.19: Relationships of pQCT Qcort with DXA WB-BMD and WB-ARM



95%confidence limits for regression equations shown

Fig 6.20: Proportions of females in the lowest quartiles of DXA hip (FN, FT, FW) and spine (LS) measurements also in the lowest quartiles of other mutually exclusive DXA measurements, and pQCT measurements (Qtot, Qtrab, Qscort, Qcort)

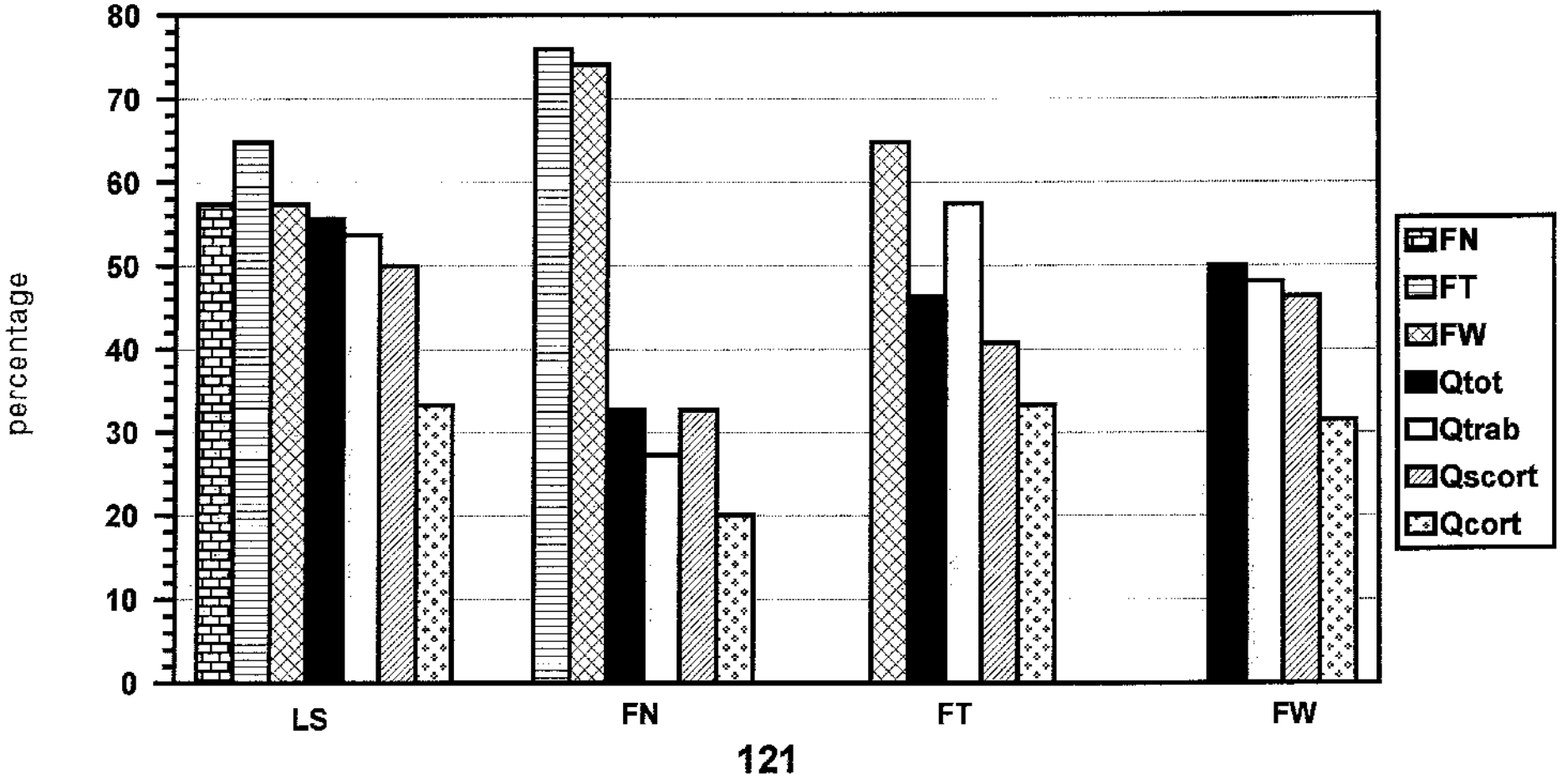
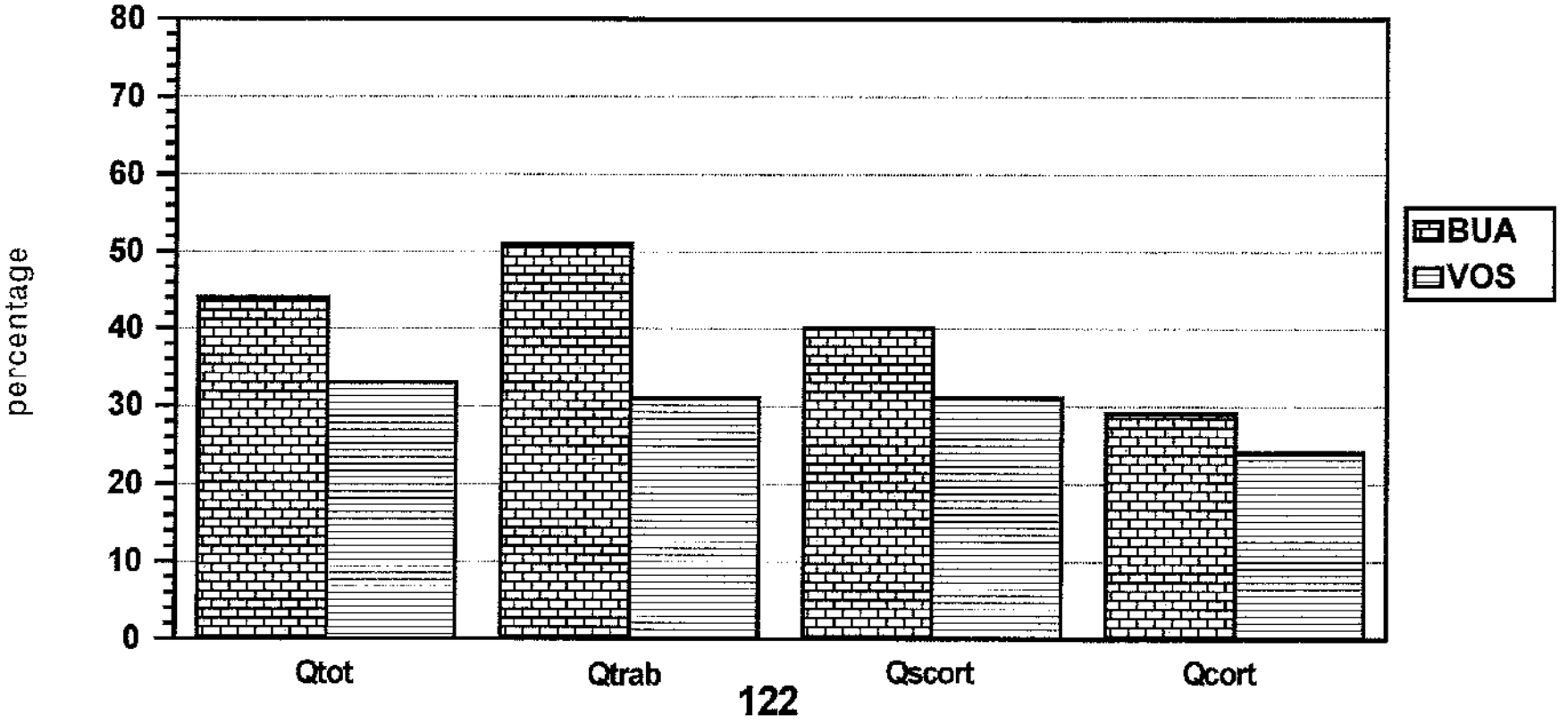


Fig 6.21: Proportions of females in the lowest quartiles of pQCT measurements (Qtot, Qtrab, Qscort, Qcort), also in the lowest quartiles of ultrasound measurements (BUA, VOS)



CHAPTER 7

AGE RELATED CHANGES IN RADIAL pQCT BMD MEASUREMENTS: COMPARISON WITH OTHER SKELETAL SITES.

7.1 Introduction

Changes in bone mass throughout the lifetime of an individual have been discussed in detail in chapter 1.1.3, and are depicted in figure 1.2. Peak bone mass (PBM) is now generally considered to be achieved by the end of the second decade (1.44,1.60-1.65), and possibly a few years later (age 25) at the radius (1.40). PBM is generally maintained throughout the following 2-3 decades before bone loss commences. Controversies regarding the age at which PBM is achieved, and timing of bone loss from PBM are also discussed in chapter 1.1.3. Generally, age related bone loss occurs in all individuals from all skeletal sites, and affects both trabecular and cortical bone. This type of bone loss leads to what has been termed Type 2 osteoporosis, leading eventually to hip fractures (1.67). Due to ovarian failure and subsequent oestrogen deficiency, women experience an accelerated phase of bone loss following the menopause. Although all skeletal sites are affected, there is controversy, especially at axial sites, as to the exact timing and degree of bone loss (1.51,1.68-1.72,1.74,1.79-1.82,5.1,5.2). Trabecular bone is metabolically more active than cortical bone, and is therefore thought to be preferentially affected during this phase of accelerated bone loss. Consequently, bone loss is greater from skeletal sites rich in trabecular bone. This type of bone loss leads to what has been termed Type 1 osteoporosis, and fractures especially of the wrist and vertebrae (1.67).

Most of the work done to date examining patterns of radial bone loss have employed either SPA or DXA, which give a composite

assessment of trabecular and cortical BMD at the measurement site. pQCT, with its ability to quantify trabecular and cortical BMD independently may give additional information as to the timing, pattern and extent of bone loss at the radius. It should be more sensitive than radial SPA or DXA to subtle BMD change, particularly within the trabecular component. It should be borne in mind however, that for any given individual, a change in BMD of ±2.8 x the co-efficient of variation is necessary before a BMD change can be accepted as being outwith precision error (1.88,7.1). The pattern of bone loss as determined by pQCT was therefore examined in 4 different female populations, which are detailed below. Changes in pQCT radial BMD were compared to axial measurements in three of the groups

7.2 Study Populations and Bone Mass Measurements

The following different female populations were studied.

Cross-Sectional Design

Group 1. Changes in pQCT measurements alone were obtained from analysis of the study population used to create our normal range. This population was defined in chapter 5.2, and has an age range of 18-90 years. 213 females were premenopausal (defined as ongoing menses) and 119 were postmenopausal (defined as no menses for at least 12 months)

Group 2. Changes in pQCT BMD measurements were compared to DXA lumbar spine and hip BMD measurements in a perimenopausal group aged 45-55 years. The study population described in chapter 6.2 (group 1) was analysed further. From the original 216 females, those with a known history of thyroid disease, diabetes, asthma and inflammatory arthritis were excluded as were those taking drugs known to affect bone metabolism and those who had undergone hysterectomy, leaving 119 normal women. 79 women were

premenopausal, and 40 postmenopausal.

Longitudinal Design

Group 3. 23 normal premenopausal females who were attending an osteoporosis screening programme (described in chapter 5: 5.2-point 2) were invited to return approximately one year later for re-scanning. None were known to have any condition or were taking medication which could influence bone mass. pQCT was performed within 8 weeks of DXA lumbar spine and hip measurements at the baseline visit, but both were performed on the same day at the follow-up visit. All women were menstruating regularly at both baseline and follow-up visits.

Group 4. 26 normal postmenopausal females underwent pQCT and DXA hip and spine measurements on the same day at baseline and approximately 18 months later. None were known to have any condition or were taking medication which could influence bone mass. This study population is derived from that described in chapter 5: 5.2-point 3. Of the original 31 females, 26 females agreed to return for re-scanning, to form the basis of this study population.

For the follow-up pQCT measurements, the "trending" function, which is discussed in chapter 3, was utilised. The cut-off value used for the difference in voxel numbers between baseline and follow-up scans was set at 30. This should have ensured accurate positioning of the scanner in follow-up scans, thus minimising the influence of change in scan site on follow-up pQCT BMD measurements.

7.3 Statistical Analyses

Results for continuous variables were expressed as the mean with standard deviation if the data were normally distributed,

otherwise as the median with ranges.

7.3.1 Cross-sectional Designs

The relationships of pQCT BMD values with age in the whole population aged 18-90 years (group 1), were examined using linear and non-linear regression, exponential and logarithmic analyses. The model which best fitted the data was determined by minimising the residual sum of squares and improving the correlation co-efficient. Similar analyses were performed on premenopausal women as a function of age, and postmenopausal women as a function of years since the menopause. From the resultant equations, annual rates of change were determined, as a function of age for premenopausal women, and years postmenopause for postmenopausal females at 5, 10, 20, 30 and 40 years postmenopause.

In group 2, between group comparisons were performed using the unpaired t-test. Differences between premenopausal and postmenopausal subgroups were expressed as percentages. Taking into account the differing ranges for BMD measurements, T-scores were also generated and compared for the postmenopausal group, using the premenopausal group as the young normal population. The differences are expressed as T-scores rather than Z-scores, as obviously the populations were not aged matched, and pQCT BMD in premenopausal women studied cross-sectionally showed little change (see results section of this chapter).

7.3.2 Longitudinal Designs

In the longitudinal designs, between group comparison of baseline BMD measurements were performed using the unpaired t-test. Annualized rates of change in BMD were calculated, and within group annualized percentage BMD changes from baseline were compared using the paired t-test.

7.4 Results

7.4.1 Cross-sectional studies

The changes in pQCT BMD values in a female population aged 18-90 (group 1) are shown in figures 7.1 - 7.4. For the whole population, cubic regression was superior to other models in describing age related changes for all pQCT BMD measurements as a function of age (see figures 7.1-7.4 for regression equations). There was a decrease in BMD from peak bone mass to that of old age of 34.3%, 31.7%, 33.7% and 24.4% for Qtot, Qtrab, Qscort and Qcort respectively [excluding the age range 30-39 years, which is probably not representative of the general population, due to the small number of subjects studied (n=6)]. Linear regression equations of the premenopausal females showed that there was little change in any of the pQCT BMD measurements as a function of age between the end of the second and fifth decades. The relationship with age was positive for Qtot (Qtot = 376.4 + 0.3(age), r=0.053, p=NS), and negative for Qtrab (Qtrab = 186.4 - 0.01(age), r=-0.003, p=NS), Qscort (Qscort = 545 - 0.17(age), r=-0.024, p=NS) and Qcort (Qcort = 567.7 - 0.11(age), r=-0.016, p=NS). The resultant annual rates of changes in premenopausal women were small: Qtot (+0.3mg/cm^3/yr; 0.08%/yr), Qtrab (-0.01mg/cm^3/yr; -0.005%/yr), Qscort (-0.17mg/cm^3/yr; -0.03%/yr) and Qcort (-0.11mg/cm^3/yr; -0.02%/yr).

For postmenopausal females, all BMD measurements were negatively related to the duration since menopause, and are shown in figures 7.5 and 7.6. A cubic regression model best fitted Qtot, Qscort and Qcort BMD data, whereas a parabolic model best fitted Qtrab BMD (see figures 7.5 and 7.6 for regression equations). The annual rates of changes for postmenopausal women at 5, 10, 20, 30 and 40 years postmenopause (YPM) derived from the regression equations for each of the BMD measurements are shown in table 7.1. For Qtrab, the rate of loss gradually increased from -0.53%/yr at 5 YPM to -0.76%/yr at 40 YPM. The greatest rate of loss in the early postmenopause years (5 and 10 YPM) was found for Qscort (-

0.72%/yr and -1.12%/yr respectively) and Qtot (-0.79%/yr and -1.12%/yr respectively), with that for Qcort being less (-0.5%/yr and -0.95%/yr respectively). The greatest overall rates of loss for Qtot, Qscort, and Qcort were found at 20 YPM: -1.36%/yr, -1.39%/yr and -1.39% respectively. Qtot, Qscort and Qcort all increased at 40 YPM: +0.85%/yr, +1.43%/yr and +0.75%/yr respectively.

Changes in radial BMD around the menopause were further examined in a perimenopausal population (group 2) and compared to DXA spine and hip BMD. 79 premenopausal females (PRE subgroup) were compared to 40 postmenopausal females (POST subgroup). Details of the study population are shown in table 7.2. The PRE group was 4.1 years younger and 3 cm taller than the POST group, but were well matched for weight. The median duration since the menopause in the POST subgroup was 35 months (range 12-180). All bone mass measurements were lower in the POST subgroup and are shown in table 7.2, and figures 7.7 and 7.8. There were statistically significant differences in all BMD measurements except Qcort and Qtrab. Percentage BMD differences for axial DXA measurements [-13.48%, -11%, -9.81% and -9.78% for FW, FT, FN and LS respectively] were greater than those for pQCT [-7.63%, -6.43%, -5.49% and -1.75% for Qtrab, Qtot, Qscort and Qcort respectively]. T-score differences between the premenopausal and postmenopausal subgroups (using the premenopausal subgroup as the reference population) followed a similar pattern to the percentage differences and are shown in figures 7.7 and 7.8. Differences [T-score(SD),p value] for axial DXA measurements: FT [-0.81(1.29),p<0.001], FW [-0.77 (1.01),p<0.001], FN [-0.76(1.09),p<0.001] and LS [-0.61(1.26),p=0.005] were greater than those found for pQCT measurements: Qscort[-0.58(1.34),p=0.018], Qtot [-0.54(1.3),p=0.013], Qtrab [-0.35(1.2),p=0.1] and Qcort [-0.29(1.24),p=0.17].

7.4.2 Longitudinal Studies

Demographic and BMD data for groups 3 and 4 are shown in table 7.3. At baseline, the premenopausal group (group 3) were younger (16.3 yrs), taller (4.7cm) and heavier (2.7kg) than their postmenopausal counterparts (group 4). Accordingly, BMD for all radial, hip and spine measurements were greater in group 3, although this failed to reach significance for Qtrab and FN. Correcting for the influence of height and weight, significant differences remained for all except for Qtrab ($p=0.198$), FN ($p=0.065$) and FT ($p=0.057$). The variance of all BMD measurements was greater in group 4 than in group 3. There were no significant changes in height or weight in either group between baseline and the follow-up visits (group3: height 1.613 ± 0.062m vs 1.614 ± 0.06m; weight 65.9 ± 12.5kg vs 66.2 ± 12kg) (group 4: height 1.566 ± 0.063m vs 1.568 ± 0.063m; weight 63.2 ± 10.7kg vs 62.9 ± 11kg). Annualized rates of change in pQCT radial BMD and DXA hip and spine BMD for both groups are shown in table 7.4, and figures 7.9 and 7.10. There were statistically significant annualized decreases in Qtot in both groups, and in Qscort in group 3. Mean changes in other pQCT measurements were negative in both groups with the exception of Qtrab in group 4, but none reached significance. There were no significant changes in DXA hip or spine BMD measurements in groups 3 or 4 with the exception of FN in group 4. The variance in percentage change was large for all measurements and tended to be greater in group 4. As can be seen for figures 7.9 and 7.10, very few individual changes fell outwith the 2.8 x CV band indicating that a real change could only be confirmed in very few patients. The postmenopausal group (group 4) was further analysed according to the duration since menopause. There was no difference in the annualized rates of change between those within 10 years of their menopause (n=9), and those more than 10 years from their menopause (n=15), although the numbers in each subgroup were small.

The relationship between the annualized percentage rates of

change in pQCT measurements and those of LS and FN for premenopausal females (group 3) are shown in table 7.5, and for postmenopausal females (group 4) are shown in table 7.6. Similar relationships were found with FT and FW BMD measurements, but are not shown. There were no significant relationships between annualized rate of change between pQCT and DXA LS and FN measurements in either premenopausal or postmenopausal groups. The relationships between changes in Qtot and LS in premenopausal and postmenopausal females are shown in figure 7.11, as are those for Qtot and FN in figure 7.12. The relationships of other pQCT measurements were similar but are not shown. However, the relationships between annualised percentage rates of change at LS and FN in both group 3 and 4 were also insignificant, and are shown in figure 7.13.

7.5 Discussion

All radial pQCT BMD measurements decreased with age, the reduction between peak bone mass and old age being 24.4%-34.3% depending upon the measurement. Studying a population with a wide age range, as there was in group 1 (18-90 years), a cubic regression model was found to best fit all pQCT BMD measurements. This has been found previously for trabecular BMD determined by QCT at the radius (7.2) and lumbar spine (1.74,7.2). When the cross-sectional data derived from group 1 were examined by decades (see tables 5.1 & 5.2), the various BMD values seem stable until the end of the sixth decade. This method of analysing data can mask the effects of the menopause upon BMD, as its age of onset varies between women. Dividing the population by menopausal status should help clarify the effect of the menopause upon radial BMD. In the premenopausal subgroup of group 1, there must be doubt whether those females in the age group 30-40 years (n=6) are representative of the general population. This negates any meaningful attempt to determine the timing of peak bone mass in this population. Nevertheless, fitting a linear regression model should allow

the trend of BMD in premenopausal women to be determined, as the 10 year age bands on either side of the 4th decade are sufficiently large to be representative of the premenopausal population. Such a model showed that all radial pQCT BMD measurements were effectively stable in the premenopausal subgroup. This is in keeping with almost all of the published work done using both SPA (1.63,1.51,1.68,1.69,1.70,1.79) and pQCT (1.50,1.78). However, reduced radial trabecular BMD has been found in regularly menstruating women with evidence of declining ovarian function (7.3).

In contrast to the premenopausal subgroup, there was clear evidence of significant reductions in pQCT BMD measurements in the postmenopausal subgroup of group 1. A cubic regression model best fitted Qtot, Qscort and Qcort BMD data as a function of years since the menopause, whereas a parabolic model best fitted Qtrab. Surprisingly, the derived rate of loss for Qtrab gradually increased from 5 to 40 years postmenopause, which is contrary to the theory that an accelerated phase of trabecular bone loss occurs immediately following the menopause, at least at the radius. Additionally, derived rates of loss for Qtrab were much lower than those for Qtot, Qscort and Qcort in the early postmenopausal years (5 to 20 years postmenopause). The greatest rates of loss were found for Qtot, Qscort and Qcort at 20 years postmenopause(-1.36%/yr - -1.39%/yr). These findings for Qtot, Qscort and Qcort can be explained by the recent observation that postmenopausal remodelling occurs at the inner aspect of the cortical shell with trabecularisation of endosteal cortical bone. Consequently, progressive expansion of the cross-sectional area of trabecular bone occurs at the expense of cortical area in postmenopausal women (1.75,6.6). A more pronounced decrease in pQCT total BMD compared to trabecular BMD has been noted previously from cross-sectional data (1.50,6.6). The estimated rates of bone loss (from cross-sectional data) for the postmenopausal subgroup of group 1 in this thesis, are comparable to other estimated rates of loss

(cross-sectional data) determined using pQCT (1.50,6.6), SPA (1.68,1.69), and DXA (7.4), and observed rates of loss (longitudinal data) determined using pQCT (1.75,1.78) and SPA (1.73). There was also evidence of ongoing loss for all pQCT BMD measurements in the elderly. Estimated rates of loss in women 30 years postmenopause were between -0.59%/yr and -0.93%/yr depending upon the measurement, supporting the claims of others that significant bone loss continues into old age (1.86). In contrast, the estimated rates of change at 40 years postmenopause, suggested that radial Qtot, Qscort and Qcort BMD increased in the very elderly. However, many of the women more than 40 years postmenopause were recruited through an advertising campaign requesting elderly, fracture free women to act as normal controls for hip fracture patients. They were not randomly selected from the elderly population, and were therefore liable to several biases, which could have falsely increased BMD, thus reducing or reversing estimated rates of bone loss (1.86). These biases have been discussed in more detail in chapter 1.1.3.

Profound changes in bone metabolism occurs immediately following the menopause due to falling oestrogen levels. This results in increased bone resorption and subsequent bone loss. The effect of the menopause upon radial pQCT BMD was compared to DXA hip and spine BMD measurements, in a cross-sectional study. The study population was a randomly selected group of perimenopausal females aged 45-55 years of age, which was then divided into premenopausal and postmenopausal subgroups based upon menstrual history (group 2). 90% of the postmenopausal females studied in this group were within 8 years of the menopause and thus represent early postmenopausal females. In view of the differences in mean BMD values and ranges between pQCT and DXA measurements, comparison of differences is best achieved if the differences are expressed as T-scores (using the premenopausal subgroup as the young normal reference population) rather than percentages. BMD was found to be

significantly lower at all skeletal sites in postmenopausal females. The greatest differences (based upon T-scores) were found for the three DXA hip measurements, particularly the trochanteric site and Ward's area, which are the trabecular rich sites within the hip. Differences for all pQCT BMD measurements were lower than those found at the hip and spine. At the radius, the greatest differences (based upon T-scores) were found for Qtot and Qscort (both statistically significant), whereas those for Qtrab and Qcort were insignificant. This suggests that perimenopausal and early postmenopausal bone loss is less marked from radial compared to axial sites, supporting the findings of others (1.77,7.4). These findings also suggest that perimenopausal bone loss at the radius primarily occurs from the subcortical region, supporting the findings above derived from group 1, and previously reported work (1.75,6.6). A similar insignificant reduction in radial trabecular BMD has also been reported previously from a comparable study, with a population similar but smaller to group 2 reported here (7.5).

Longitudinal studies should resolve the issues of timing and rate of bone loss. Almost all longitudinal studies have shown that there is no significant premenopausal loss in radial bone mass when assessed using SPA (1.63,1.69,1.70,1.79). The premenopausal females studied longitudinally in this thesis (group 3), are all older than 45 and are therefore likely to be nearing the menopause. Observed annualized rates of change showed mean total and subcortical BMD reductions of -1.04% and -1.35% respectively, both of which were statistically significant. Trabecular and cortical BMD changes were much smaller and insignificant. This suggest that there may be radial bone loss immediately preceding the menopause within the subcortical area, in a similar manner to that described in postmenopausal women above (Chapter 7: groups 1 & 2), and previously (1.75,6.6). It may well be that although these premenopausal women were still menstruating regularly, their

oestrogen levels were diminishing, but unfortunately they were not assessed as part of this study.

There is convincing evidence from longitudinal studies using both SPA (1.70,1.73,1.80,5.3) and pQCT (1.75) that bone loss occurs from the radius in postmenopausal females. The studies using SPA have found rates of bone loss around 1%/yr. The study using pQCT (1.75) found a greater annual rate of loss of 2.3% for total BMD and 2.8% for trabecular BMD, whilst cortical BMD remained stable. This latter study examined females within 4 years of the menopause, and supports the concept of accelerated bone loss immediately following the menopause which preferentially affects trabecular bone. In comparison, there was no significant change in trabecular BMD (+0.3 ± 3.04 %/yr) in the group of postmenopausal females studied longitudinally in this thesis (group 4: table 7.4). Although observed mean annual rates of loss were noted for subcortical (-4.1%/yr) and cortical BMD (-4.1%/yr), these annual changes failed to reach statistical significance due to the large variances observed. The observed mean rate of loss for pQCT total BMD was 1.36%/yr which reached statistical significance. The large variance in rates of change found generally in the postmenopausal females could be related to the precision of the scanner, but also probably reflects inter-individual variation in rates of bone loss, and differing rates of bone loss in postmenopausal females at different time points from the menopause. The disparity from previous results using pQCT (1.75) can be explained by the different study populations as our population was older, and the mean duration since menopause was 13.3 years with a large variance.

The mean annual rates of change found at the radius using pQCT in all these populations (groups 1-4) would be clinically insignificant if found in an individual, bearing in mind a change of ± 2.8 times the coefficient of variation for each BMD measurement is necessary before it can be assumed that a

clinically relevant change in BMD has occurred, and that the change is not due to scanner error (1.88). Based upon the changes observed in group 3, an interval of around 3 years would be necessary between scans for detection of clinically important changes in total and subcortical BMD in an individual premenopausal female nearing the menopause. It is more difficult to be accurate about the corresponding interval in postmenopausal females, as this would be determined by the precision of pQCT in such females. Unfortunately this has not been formally assessed by us, but the precision is likely to be between that of normal young females, and that of postmenopausal females with severe osteoporosis and vertebral fracture (see chapter 3). If this assumption is accepted, then, based upon the observed annual rates of change in group 4 (longitudinal data in postmenopausal women), and the estimated annual rates of change in the postmenopausal subgroup of group 1(cross-sectional data in postmenopausal women), the corresponding interval in normal postmenopausal females would again be at least 3 years, with total and subcortical BMD measurements being the most useful measures of change.

Existing evidence from the literature suggests that changes in BMD at the radius differs from that at the axial skeleton both in timing and rate. Whilst radial BMD is stable until the menopause, there is some evidence to suggest premenopausal bone loss at both hip (1.63,1.68,1.72,5.1,5.2) and spine (1.51,1.63,1.69,1.70,1.71,1.74,1.83). Others have found spine (1.68,1.77,1.79,5.1) bone mass stable until the menopause with loss limited to postmenopausal females. An accelerated phase of bone loss at the hip (1.81,5.1,5.2) and spine (1.51,1.71,1.73,1.74,1.81,5.1,5.3) immediately after the menopause has been recorded, whilst others have found a linear decline at hip (1.72,5.3) and spine (1.68,1.69,1.70). The percentage difference between PBM and BMD of old age, and rates of loss, have been found to be greater at the hip and spine compared to radius in most of the previous work. Generally,

annual rates of loss at axial sites exceed 1% and tend to be greater in postmenopausal females in both cross-sectional and longitudinal studies, with rates of loss at the spine as great as 6%/yr being found in the early postmenopausal years.

Hip and spine BMD in the premenopausal females (group 3) studied longitudinally in this thesis were found to be stable, with no evidence of bone loss. Similarly, there was no evidence of spinal bone loss in the postmenopausal group. There was however a significant annual decline of 2.47%/yr in femoral neck BMD, although changes in femoral trochanter and Ward's area were insignificant. The small numbers studied in each group, the composition of the postmenopausal group (see above), the interval between repeat measurements and the precision of the DXA scanner are likely to be responsible for the largely stable DXA measurments in groups 3 and 4. As for radial pQCT measurements, the precision of DXA and rates of change recorded at axial sites are such that annual changes are not outwith scanner error, and an interval between scans greater than that studied in this thesis (median value: 15 months for group 3, 18 months for group 4) is necessary for clinically significant change to be detected in an individual.

The relationships between the observed rates of change in the longitudinal studies (groups 3 & 4) for radial pQCT BMD measurements and changes at either lumbar spine or hip were very poor. In the premenopausal group, the relationships between radial, and lumbar spine and femoral neck BMD changes were all positive except radial trabecular BMD versus lumbar spine, but none reached statistical significance. The relationships in the postmenopausal group were even poorer, such that all changes in pQCT measurements were negatively related to changes at the femoral neck. Although the corresponding relationships with lumbar spine changes were all

positive, none reached significance. A similar relationship has been found before between lumbar spine and radial BMD changes measured by DPA and SPA respectively (1.70). It is worth noting however, that the relationship between changes at the femoral neck and lumbar spine was equally poor in both premenopausal and postmenopausal populations studied in this thesis. The relationship was stronger in the postmenopausal compared to the premenopausal group, but failed to reach significance in either. This suggests that BMD changes occurring at one skeletal site are not necessarily representative of changes at another over the short-term. Change must therefore be determined from site specific measurements, and cannot be extrapolated from measurements at other sites.

Table 7.1. Annualized percentage rates of change of pQCT BMD measurements in women aged 18-90 years (group 1). Rates are derived as a function of age in premenopausal (PRE) women, and years since the menopause (5,10,20,30 & 40 years) in postmenopausal (POST) women.

	PRE	POST				
		5yrs	10yrs	20yrs	30yrs	40yrs
Qtot	+0.08	-0.79	-1.12	-1.36	-0.77	+0.85
Qtrab	-0.005	-0.53	-0.56	-0.62	-0.68	-0.76
Qscort	-0.03	-0.72	-1.12	-1.39	-0.59	+1.43
Qcort	-0.02	-0.5	-0.95	-1.39	-0.93	+0.75

values are %/year.

Table 7.2 Details of age, height, weight, radial pQCT BMD measurements for premenopausal (PRE) and postmenopausal (POST) subgroups of group 2. Values are mean (SD) unless stated otherwise.

	PRE (n=79)	POST (n=40)	t-test p value	%diff
Age (yrs)	47.1 (1.29)	51.2 (2.46)	< 0.001	-
Height (cm)	162 (6)	159 (6)	0.013	-
Weight (kg)	66.9 (12.3)	66.0 (11.59)	0.698	-
pQCT (gm/cm^3)				
Qtot	391.8 (52.9)	366.6 (68.6)	0.013	-6.43
Qtrab	187.5 (38.8)	173.2 (46.6)	0.098	-7.63
Qscort	533.6 (59.4)	504.3 (79.8)	0.018	-5.49
Qcort	561.0 (53.4)	551.2 (66.0)	0.174	-1.75
DXA (gm/cm^2)				
LS	1.063 (0.16)	0.959 (0.20)	0.003	-9.78
FN	0.897 (0.12)	0.809 (0.13)	<0.001	-9.81
FT	0.718 (0.10)	0.639 (0.13)	0.001	-11.0
FW	0.705 (0.13)	0.610 (0.13)	< 0.001	-13.48

Table 7.3 Demographic data of group 3 (n=23) and 4 (n=26), with baseline pQCT and DXA spine and hip BMD data. Values are: mean (SD), § is median (range). YPM: is years postmenopause. Time: is duration in months between baseline and follow-up visit. ANOVA: is analysis of covariance controlling for height and weight

	Group 3	Group 4	t-test	ANOVA
Age (yrs)	47.2 (1.7)	63.5 (6.8)	<0.001	-
Height (cm)	1.613 (0.162)	1.566 (0.063)	0.011	-
Weight (kg)	65.9 (12.5)	63.2 (10.7)	NS	-
YPM (yrs)	-	13.3 (7.9)	-	-
Time (mo)§	15 (13-17)	18 (15-19)	-	-
pQCT (gm/cm^3)				
Qtot	395.2 (47.1)	349.5 (75.3)	0.011	0.032
Qtrab	190.6 (27.2)	179.1 (44.4)	NS	NS
Qscort	542.8 (70.8)	474.1 (99.2)	0.008	0.037
Qcort	563.2 (63.4)	503.7 (86.4)	0.009	0.035
DXA (gm/cm^2)				
LS	1.08 (0.126)	0.893 (0.16)	<0.001	<0.001
FN	0.868 (0.094)	0.799 (0.15)	NS	NS
FT	0.714 (0.093)	0.631 (0.128)	0.014	NS
FW	0.693 (0.101)	0.583 (0.170)	0.01	0.024

Table 7.4. Annualized rate changes in pQCT radial and DXA hip and spine BMD measurements for groups 3 (premenopausal, n=23) and 4 (postmenopausal, n=26). Values are mean (SD). p-value is for the paired t-test (follow-up vs baseline). CV is co-efficient of variation.

	Group 3	Group 4	p value		2.8 x CV
pQCT (gm/cm^3)			(gp3)	(gp4)	
Qtot	-1.04 (2.11)	-1.36 (3.06)	0.027	0.032	± 3.5%
Qtrab	-0.19 (3.17)	0.33 (3.04)	NS	NS	± 3.7%
Qscort	-1.35 (2.67)	-4.09 (12.9)	0.024	NS	± 4.4%
Qcort	-0.95 (2.8)	-4.09 (12.9)	NS	NS	± 5.3%
DXA (gm/cm^2)					
LS	-0.34 (3.17)	0.32 (2.47)	NS	NS	± 2.5%
FN	0.02 (2.97)	-2.47 (4.33)	NS	0.007	± 7.8%
FT	0.63 (2.72)	0.94 (4.59)	NS	NS	± 3.6%
FW	2.15 (6.72)	5.62 (13.8)	NS	NS	± 13.7%

Table 7.5 Linear regression equations for group 3 (premenopausal females, n=23) examining the relationships between annualized percentage rates of change (Δ) in pQCT Qtot, Qtrab, Qscort and Qcort BMD measurements with DXA LS and FN BMD measurements.

ΔLS	SE slope	r	p	ΔFN	SE slope	r	p
0.406(ΔQtot) + 0.09	0.316	0.269	0.22	0.509(ΔQtot) + 0.55	0.287	0.360	0.09
-0.057(ΔQtrab) - 0.35	0.218	-0.057	0.80	0.273(ΔQtrab) + 0.08	0.196	0.292	0.17
0.282(ΔQscort) + 0.05	0.252	0.238	0.28	0.269(ΔQscort) + 0.39	0.236	0.242	0.27
0.206(ΔQcort) - 0.14	0.243	0.182	0.41	0.168(ΔQcort) + 0.18	0.229	0.159	0.47

SE slope = standard estimate of the mean of the slope of regression equation.

r = correlation coefficient, p = significance of the regression equation

Table 7.6 Linear regression equations for group 4 (postmenopausal females, n=26) examining the relationships between annualized percentage rates of change (Δ) in pQCT Qtot, Qtrab, Qscort and Qcort BMD measurements with DXA LS and FN BMD measurements.

ΔLS	SE slope	r	p	ΔFN	SE slope	r	p
0.004(ΔQtot) + 0.33	0.164	0.005	0.98	-0.237(ΔQtot) - 2.79	0.284	-0.167	0.41
0.081(ΔQtrab) + 0.29	0.165	0.100	0.63	-0.098(ΔQtrab) - 2.44	0.290	-0.069	0.74
0.013(ΔQscort) + 0.38	0.039	0.068	0.74	-0.087(ΔQscort) -2.82	0.066	-0.255	0.21
0.012(ΔQcort) + 0.31	0.059	0.041	0.84	-0.143(Qcort) - 2.350	0.098	-0.284	0.16

SE slope = standard estimate of the mean of the slope of regression equation.

r = correlation coefficient, p = significance of the regression equation

Figure 7.1: Age related changes in Qtot for normal women aged 18-90 years

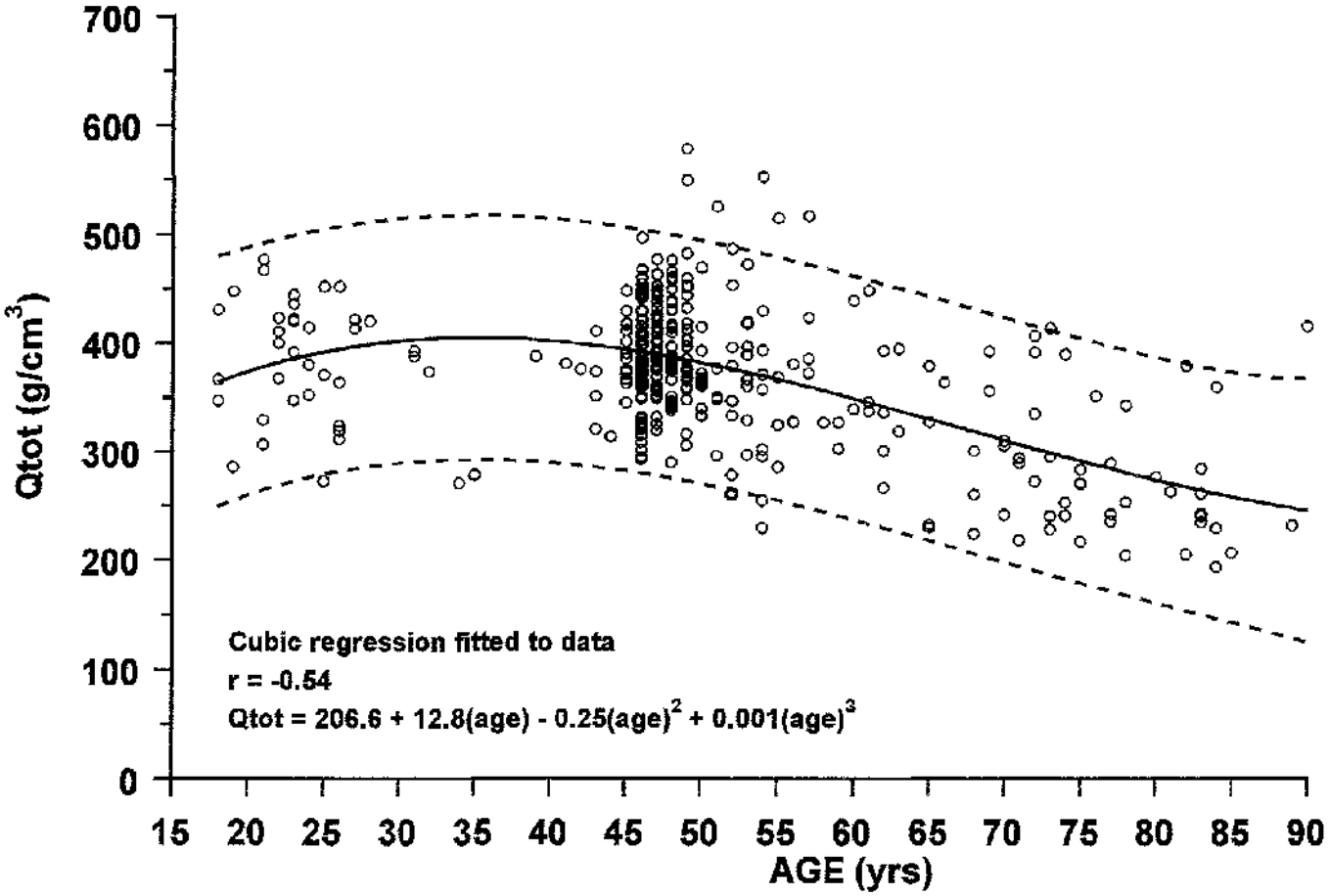


Figure 7.2: Age related changes in Qtrab for normal women aged 18-90 years

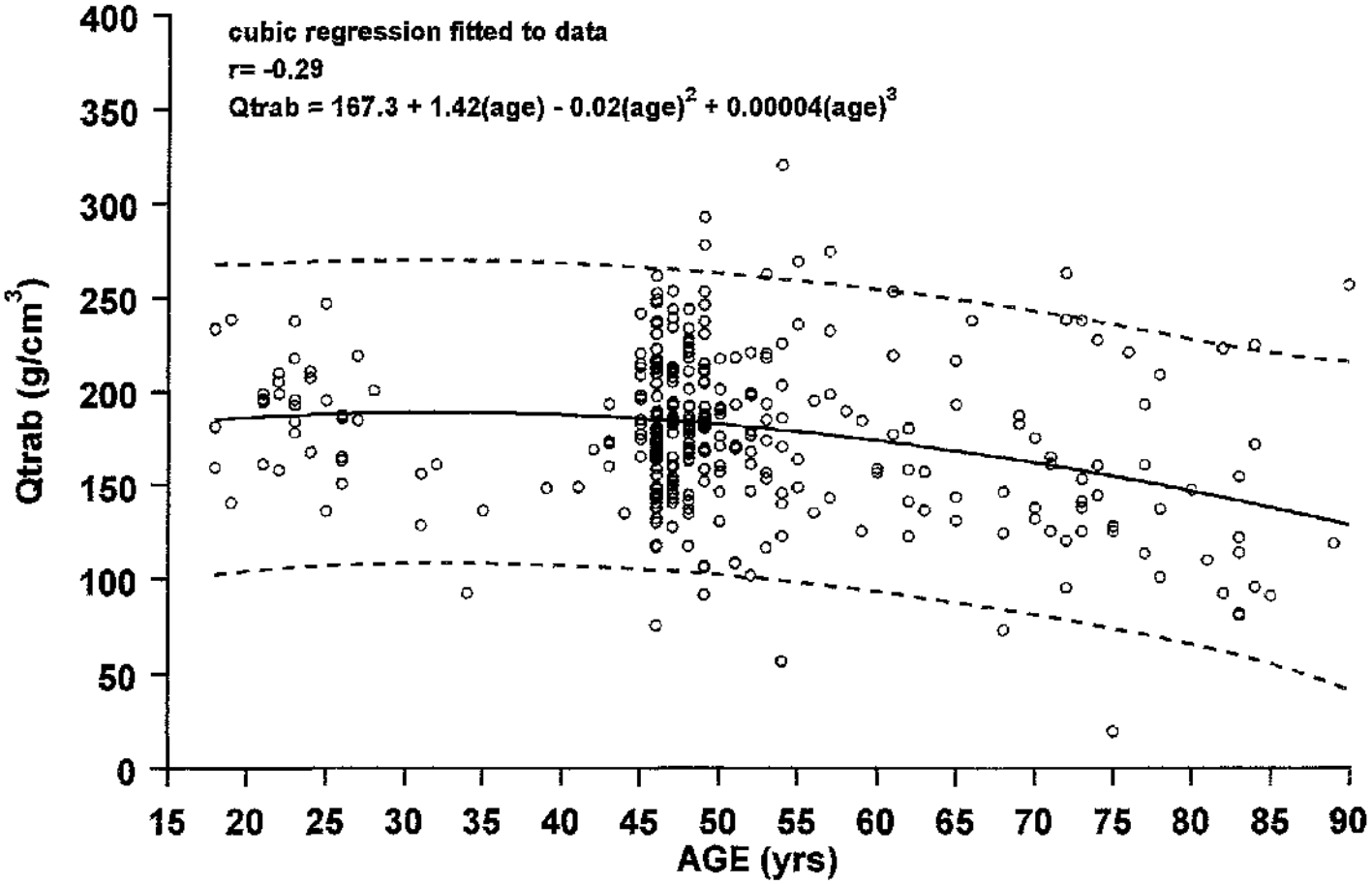


Fig 7.3: Age related changes in Qscort for normal women aged 18-90 years

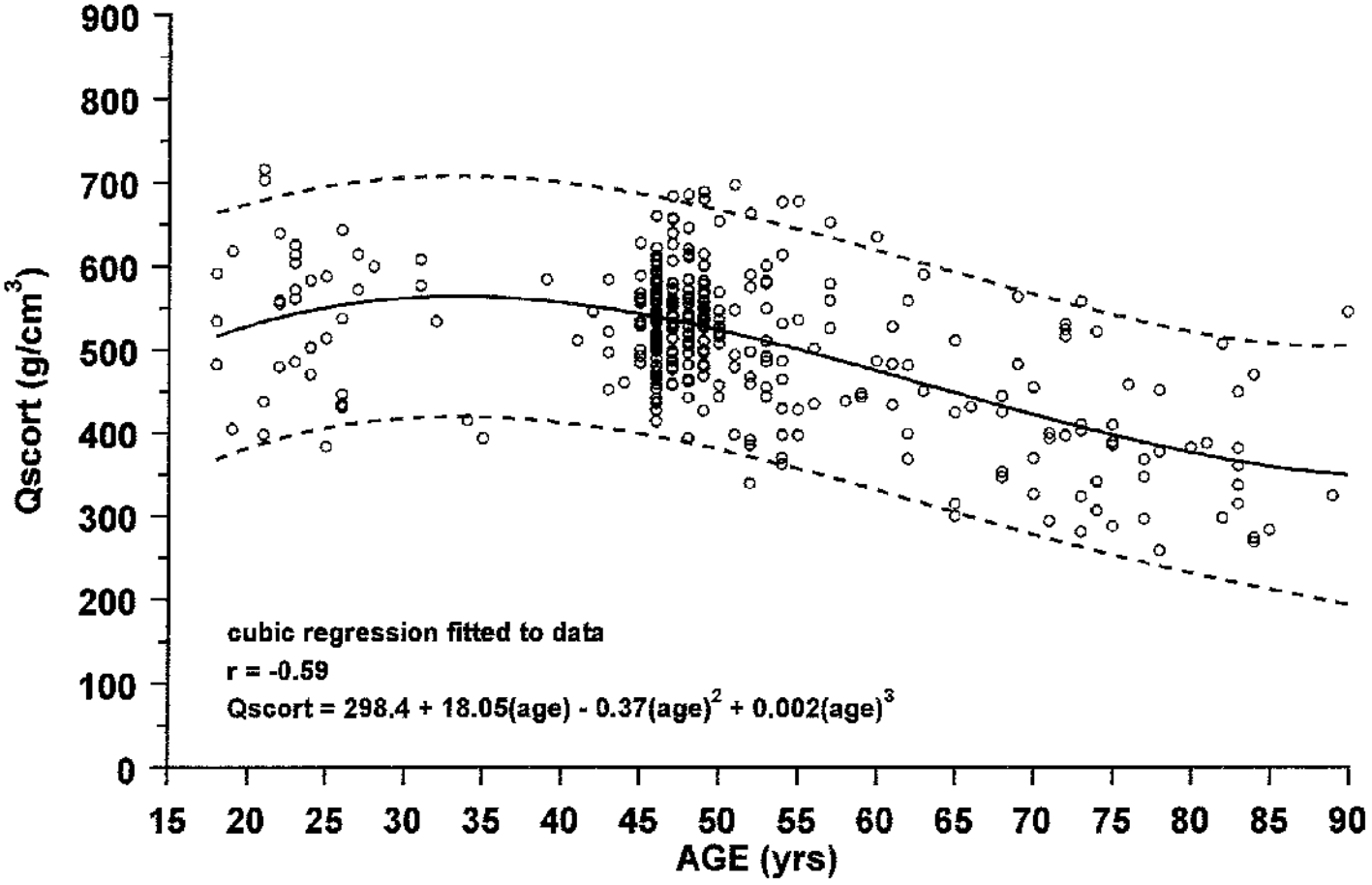


Fig 7.4: Age related changes in Qcort for normal women aged 18-90 years

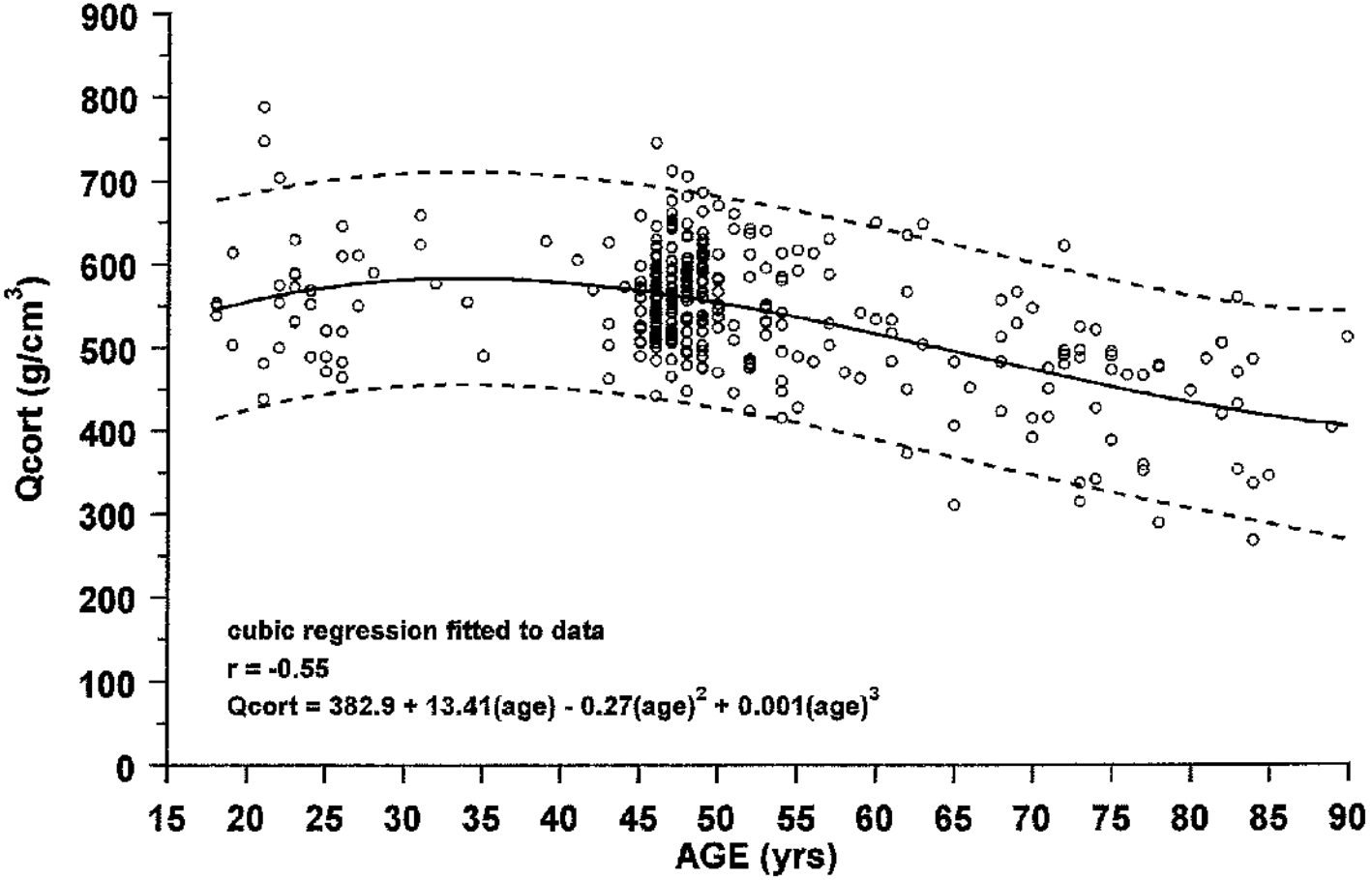


Figure 7.5: Qtot and Qtrab BMD in postmenopausal women as a function of years since menopause

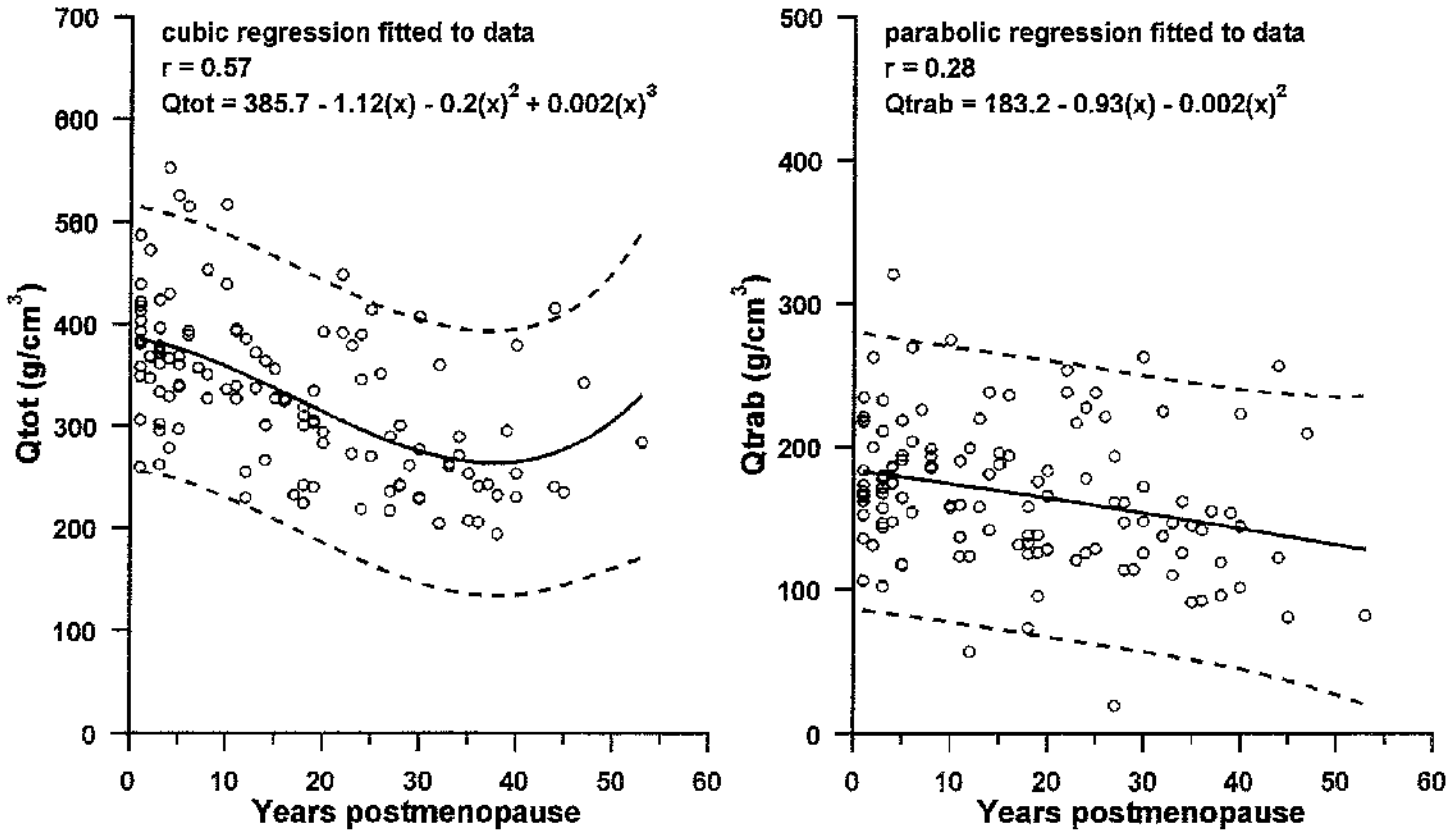


Figure 7.6: Qcort and Qscort BMD in postmenopausal women as a function of years since menopause

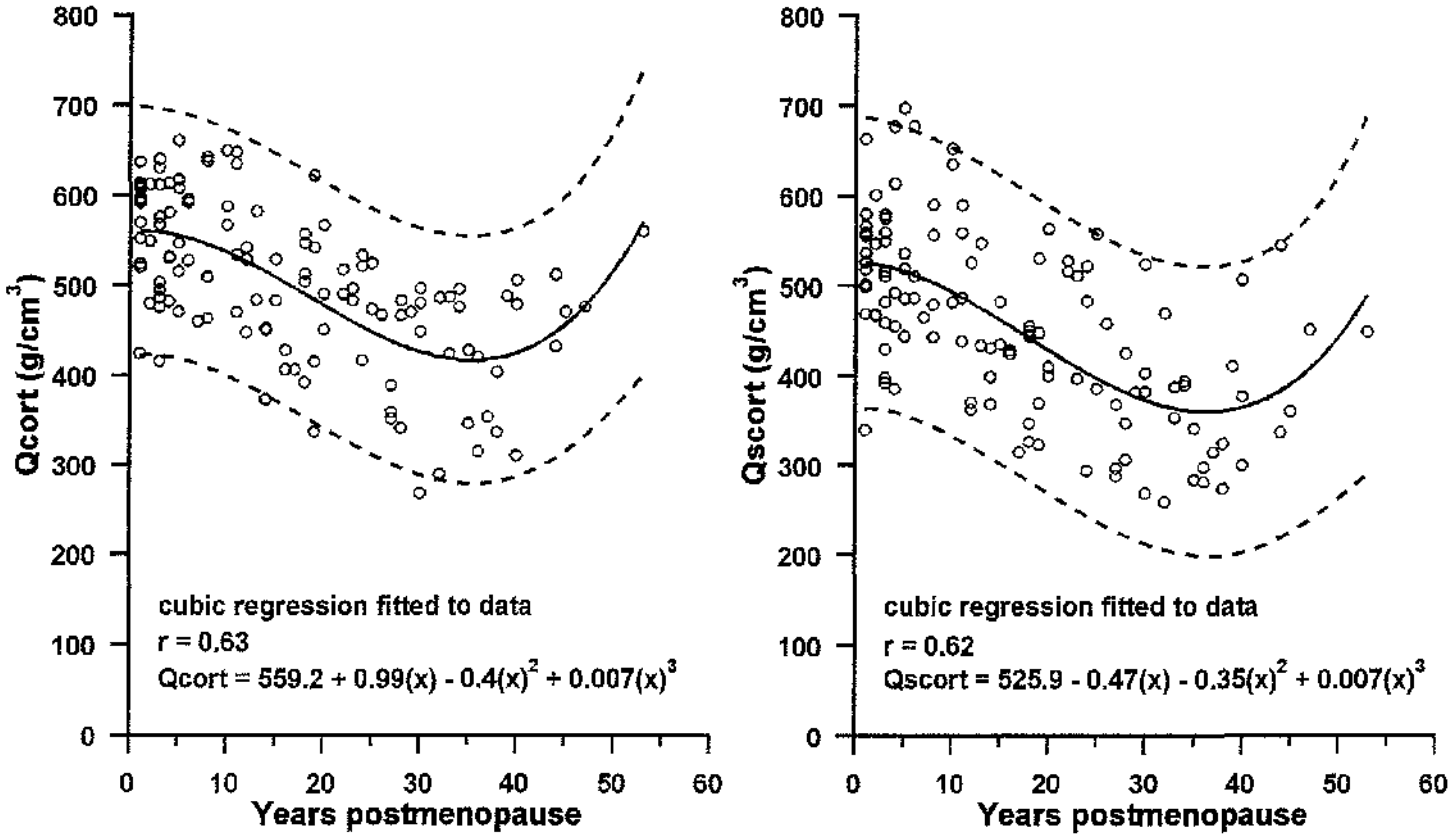
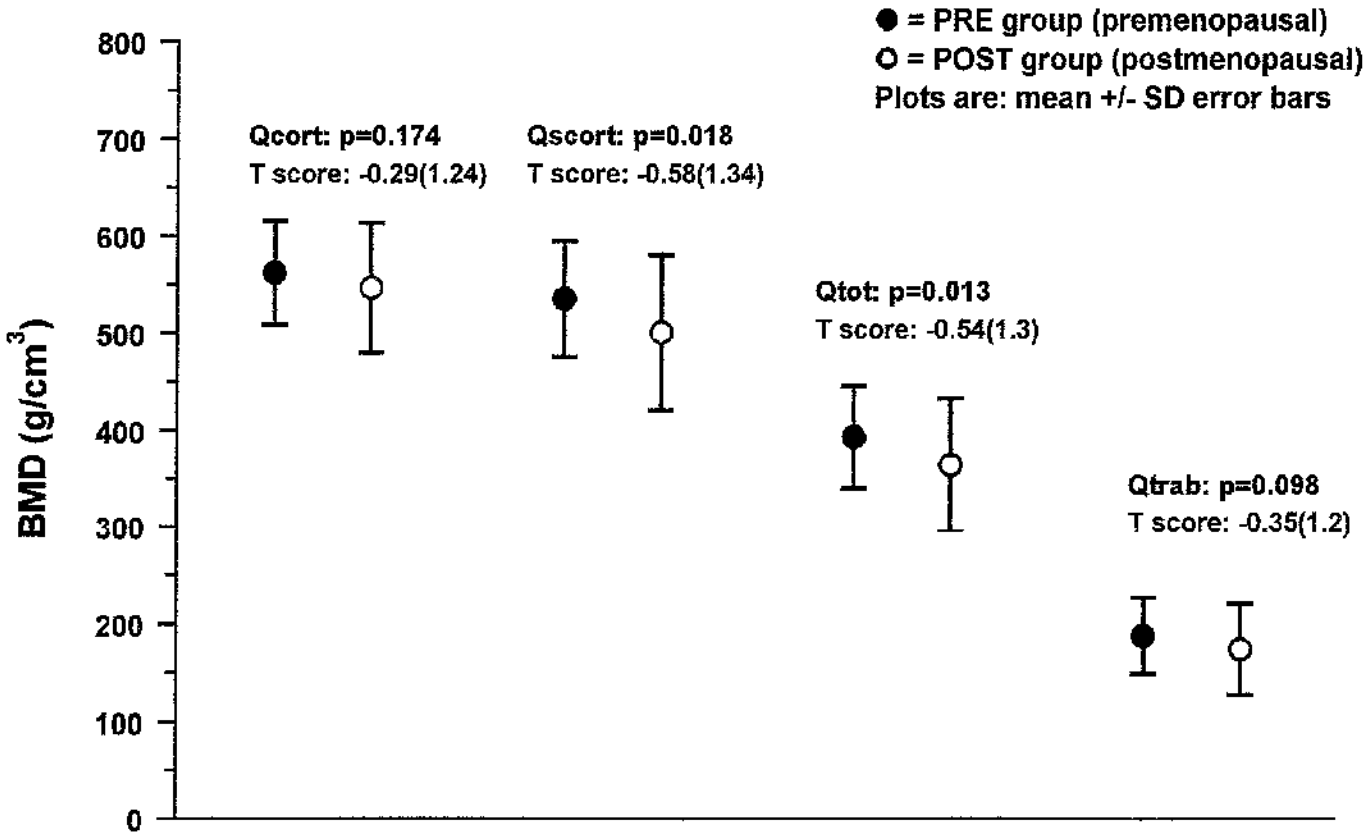


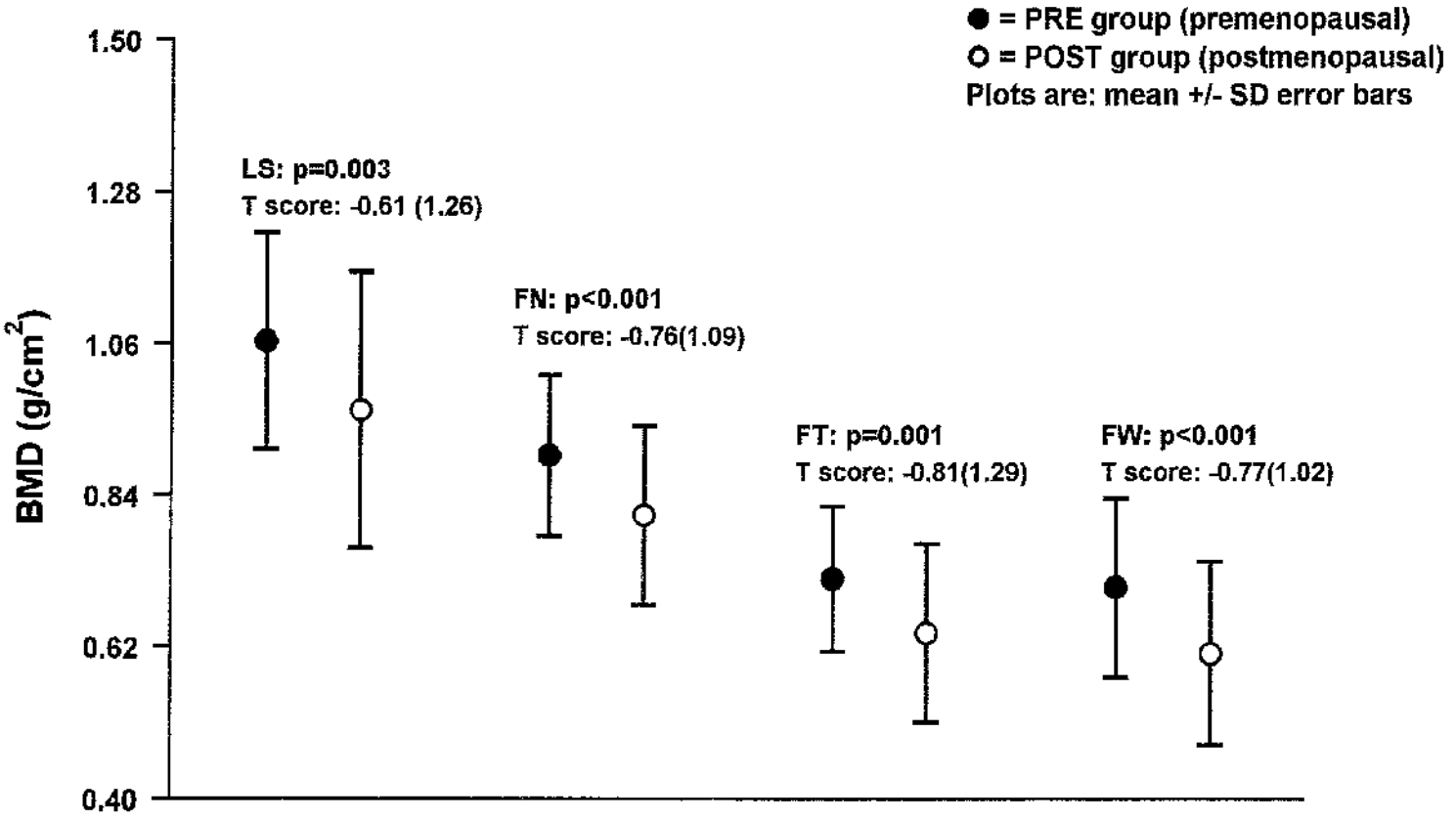
Fig 7.7: Differences in pQCT BMD values between PRE and POST females



p values are for unpaired t-test

T score: SD difference between groups using the PRE group as the reference population

Fig 7.8: Differences in DXA BMD values between PRE and POST females



p values for unpaired t-test

T score: SD difference between groups using the PRE group as the reference population

Fig 7.9: Annualized rates of change in pQCT BMD measurements

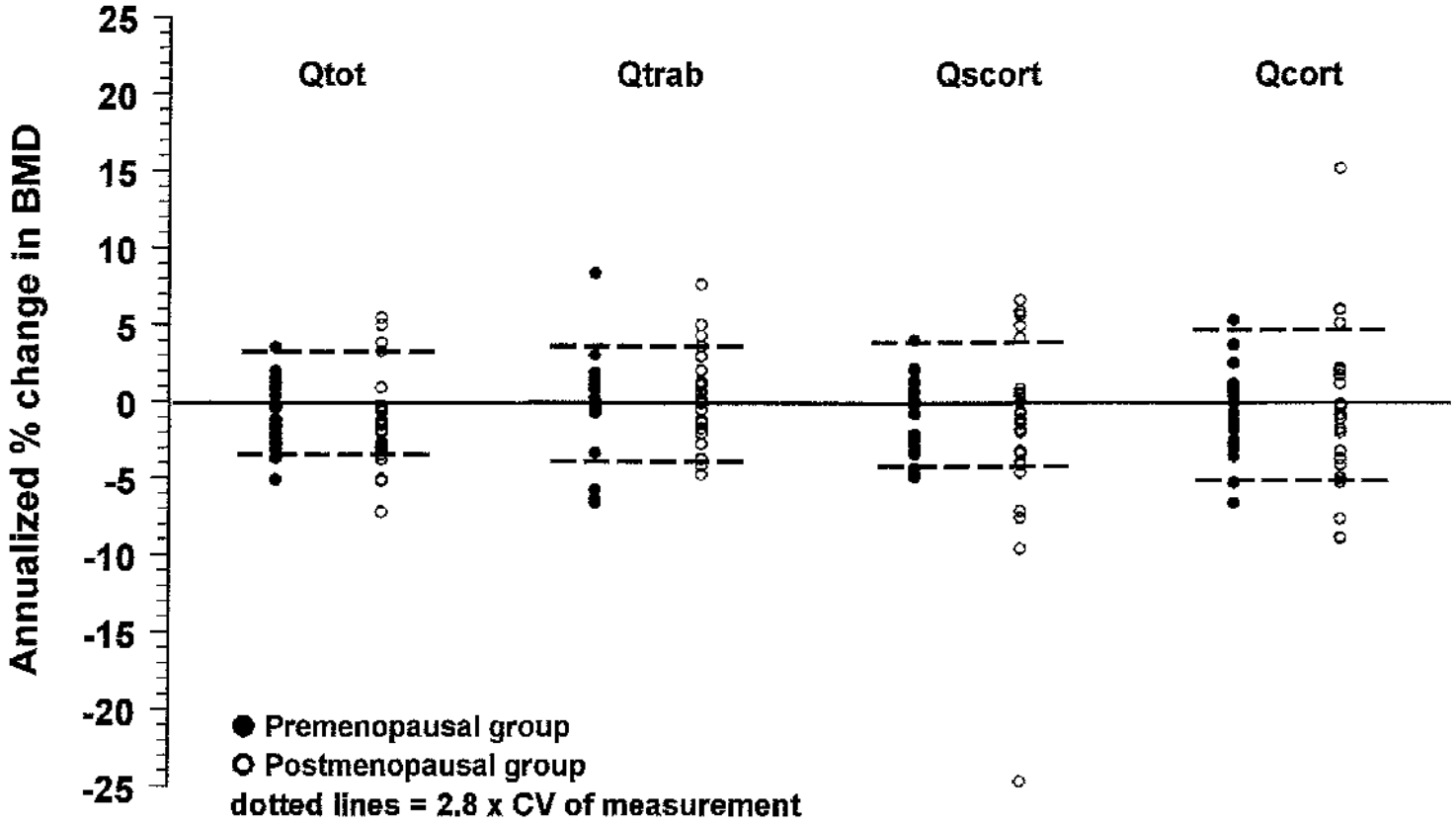


Fig 7.10: Annualized rates of change in DXA hip and spine BMD measurements

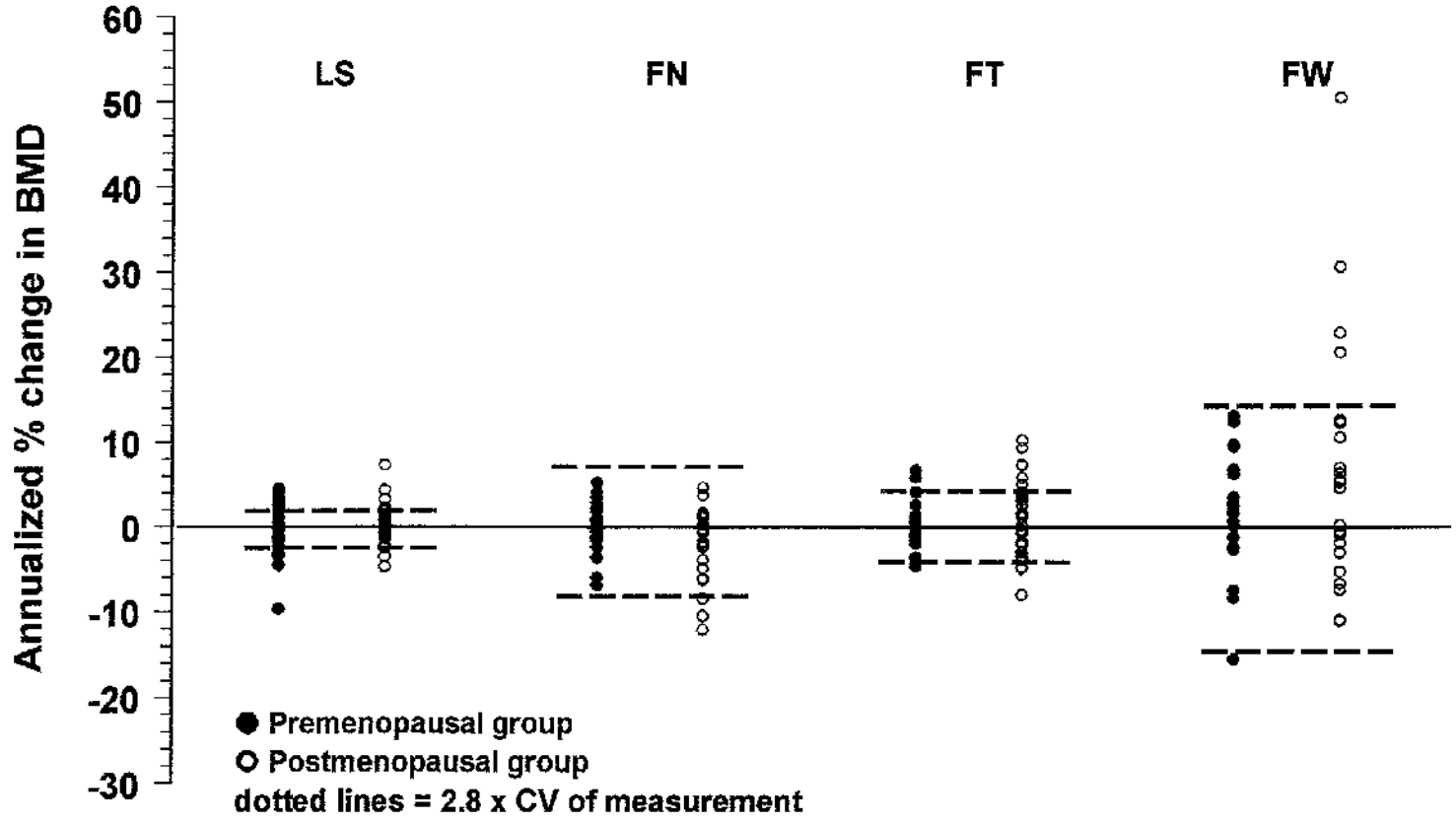
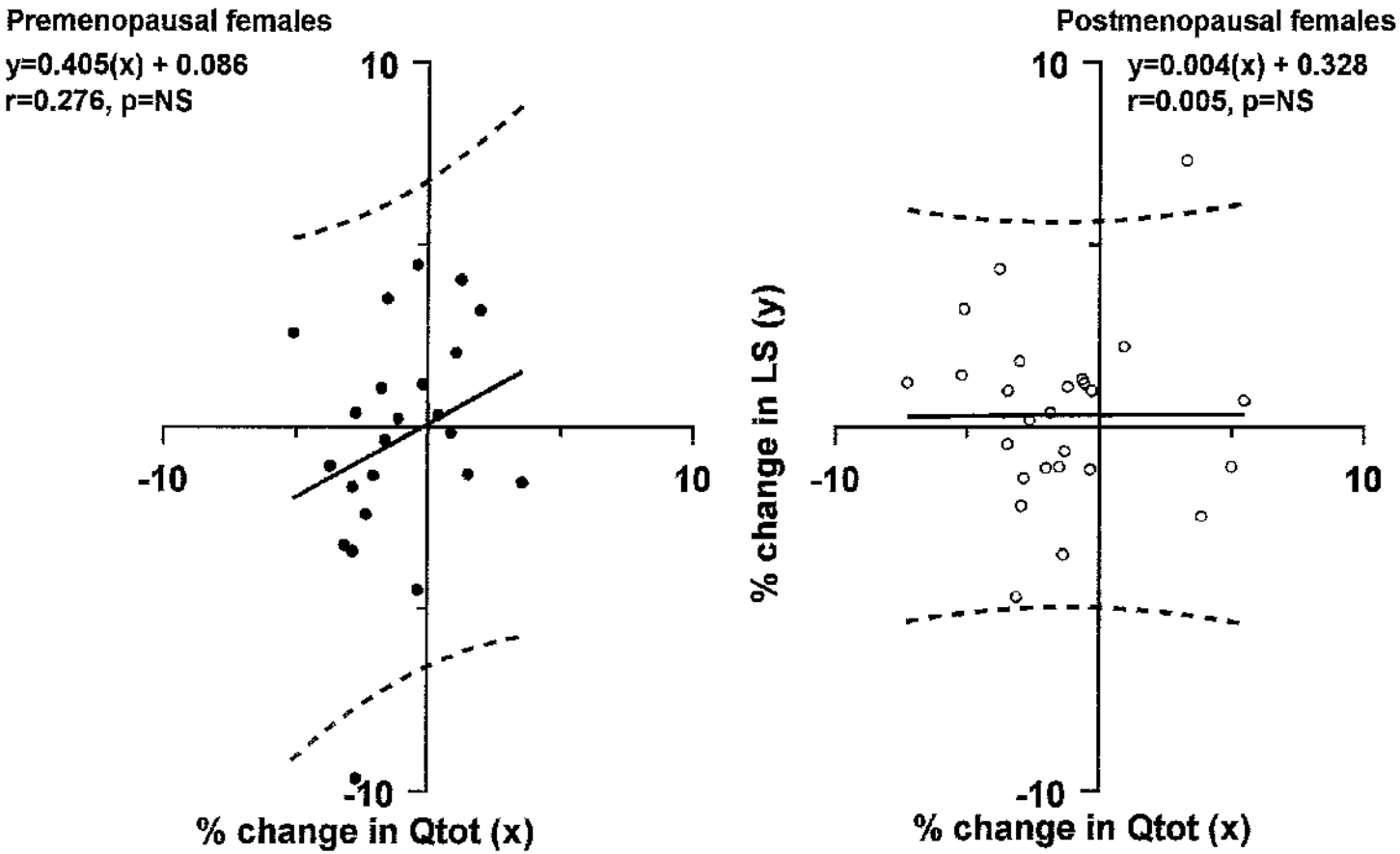
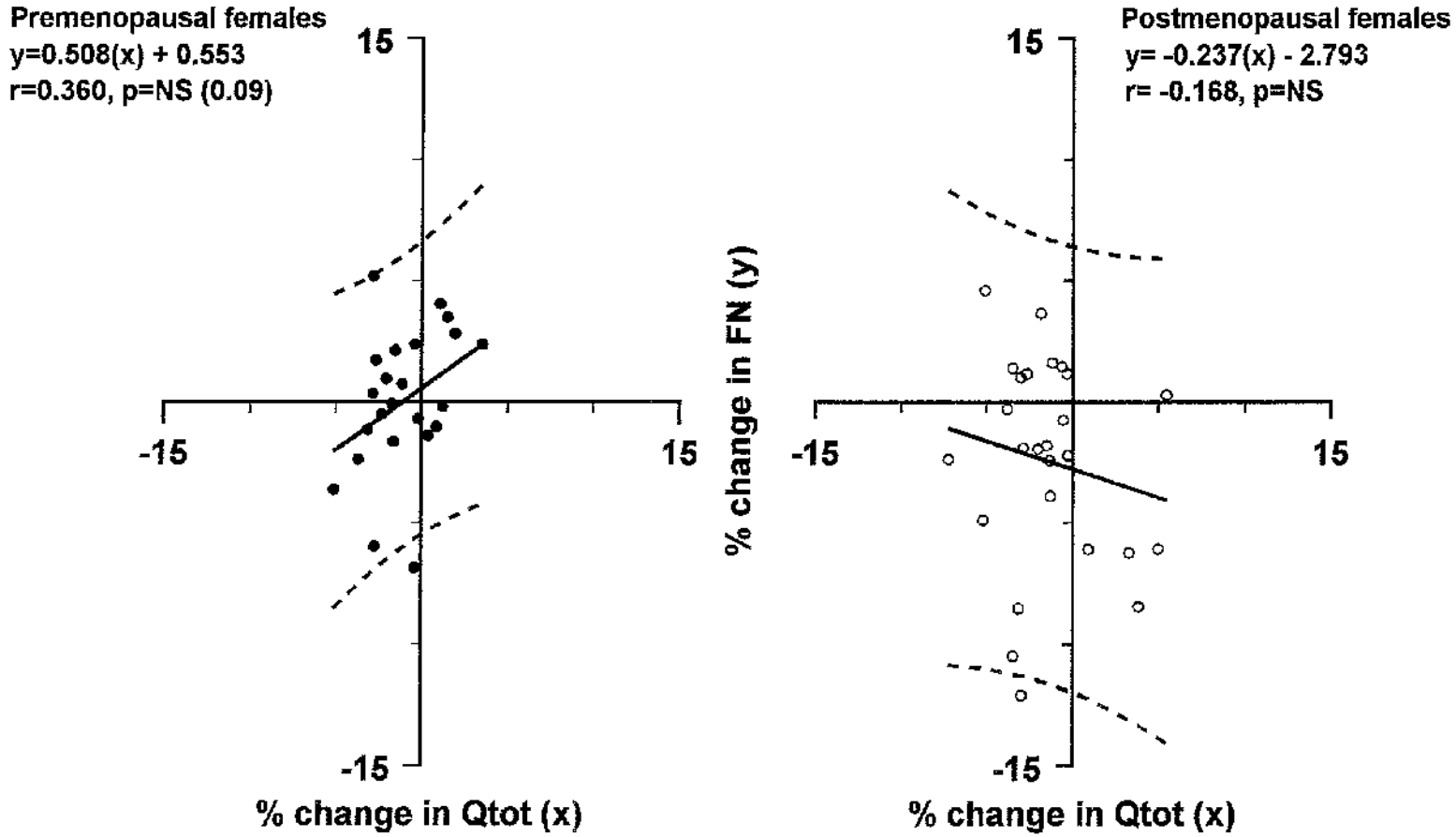


Fig 7.11: Relationship between annualized percentage changes in Qtot and LS



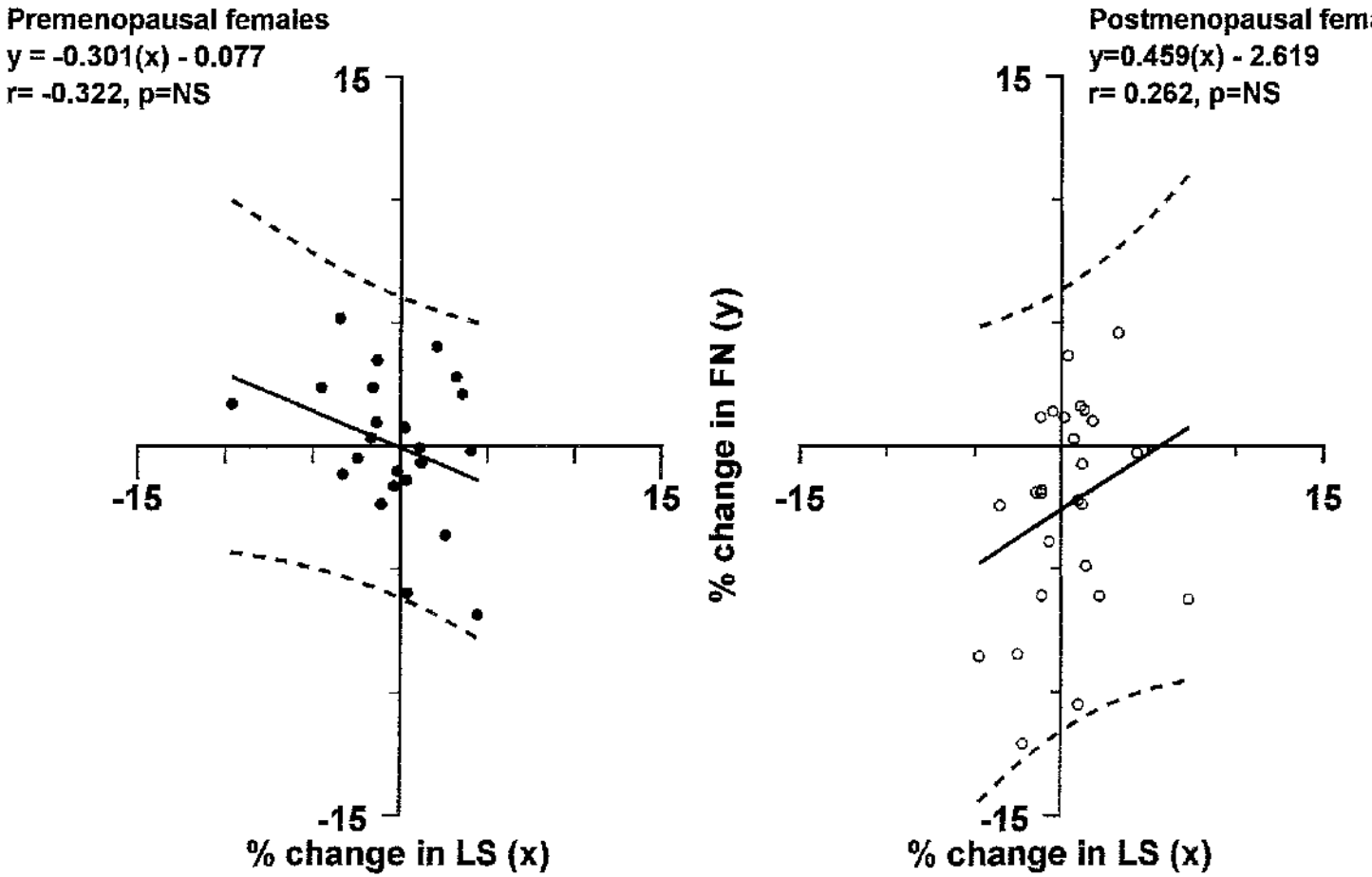
95% confidence limits for the regression equations shown

Fig 7.12: Relationship between annualized percentage changes in Qtot and FN



95% confidence limits for the regression equations shown

Fig 7.13: Relationship between annualized percentage changes in LS and FN



95% confidence limits for the regression equations shown

CHAPTER 8

THE ABILITY OF pQCT TO DISCRIMINATE FRACTURE AND NON-FRACTURE POPULATIONS: COMPARISON WITH OTHER BONE MASS MEASUREMENTS

8.1 Introduction

Osteoporotic fracture is the ultimate event affecting individuals with low BMD. Accordingly, such individuals are categorised as suffering from severe osteoporosis (6.4). Osteoporotic fractures characteristically affects the distal radius, thoracolumbar spine and proximal femur. Such fractures cause significant morbidity and cost the NHS an estimated £740 million per year (8.1). Additionally, the latter two types of fracture are associated with a reduced 5 year survival of 0.82 (8.2) and 0.83 (1.94) respectively, when compared to age matched non-fracture controls. With our increasingly aged population, the problems and financial burden imposed by osteoporotic fractures will undoubtedly rise (1.98).

One of the most important roles of osteo-densitometry is prediction of future fracture, as individuals considered at risk based upon a bone mass measurement can be targeted for life style and therapeutic intervention. There is convincing evidence that radial bone density measurements are useful in determining fracture risk. Although hip fracture risk is best determined by a site specific measurement (1.192), prospective studies have shown that radial BMD measurements, using techniques other than pQCT, can predict fracture risk at the hip (1.192,8.3) and spine (6.5,8.3). It is recognised that there is an overlap in BMD assessed at axial sites between age matched non-fracture populations and both hip (1.155,8.4,8.5) and vertebral (1.54,8.6) fracture populations, with the overlap being greater for the former type of fracture. Also, lumbar spine measurements can be falsely elevated by overlying aortic

calcification (1.168,1.169,1.170), and age related spondylosis and osteophytosis (1.171-1.177), thus limiting its discriminatory power (1.177). Inspite of these problems, spinal BMD measurements have been shown to discriminate vertebral fracture and non-fracture populations (1.173), with spinal QCT being considered the best method (8.9,8.10). Similarly, prospective studies have shown spinal BMD to predict osteoporotic fractures (1.192,6.5,6.10,8.11), with a recent study showing that spinal (and hip) DXA BMD predicts fragility fractures in perimenopausal females (1.203).

There has been much recent interest in the value of calcaneal ultrasound in fracture discrimination and prediction. In the case of hip fracture, the discriminatory power of calcaneal ultrasound attenuation and velocity measurements has been established (8.12,8.13,8.14,8.15), and both prospective (8.16,8.17,8.18,8.19) and retrospective (8.20) studies have shown their predictive power. In the case of vertebral fractures, they have been shown to discriminate (8.8,8.14) and predict prospectively (8.21),and retrospectively (8.22) fracture populations. Generally ultrasound measurements are thought to be more useful in hip than vertebral fracture discrimination and prediction. A preliminary prospective study has also shown ultrasound attenuation to predict fragility fractures in perimenopausal females (1.204), although less well than DXA lumbar spine BMD.

Prospective studies in fracture prediction are required for pQCT. Such studies are clearly longterm, and not really feasible within the time scale of work for this thesis. However, an important related function is the discrimination of fracture and non-fracture populations. Almost invariably discriminatory studies have demonstrated approximately the same relationship between specific sites of BMD assessment and

fracture risk as subsequent longitudinal studies. As the vertebral body is predominantly trabecular bone, as is up to 50% of the proximal femur, independent assessment of trabecular and cortical bone at the radius by pQCT may allow differentiation of fracture and non-fracture populations by one or other of the pQCT BMD measurements. The ability of pQCT to discriminate groups of individuals who had suffered a previous vertebral or hip fracture from non-fracture controls was therefore studied, comparing the results with DXA and ultrasound measurements done at other skeletal sites.

8.2 Study Populations and Bone Mass Measurements

8.2.1 Vertebral fracture study

45 postmenopausal females with vertebral fractures proven on lateral thoracolumbar spine x-ray were recruited from a bone clinic. None had any underlying condition or were taking medication known to influence bone mass. 30 normal postmenopausal females formed the control group. The recruitment of these females has been discussed previously (Chapter 5: 5.2 point 3). Lateral thoracolumbar spine x-rays were performed to exclude vertebral fracture in this control group (1 of the original 31 females had a vertebral fracture and was excluded from this study). All of these females had radial pQCT and DXA of hip and spine performed on a single visit. 30 of the fracture population were scanned using a Norland DXA scanner, whilst the remaining 15 females were scanned using a Lunar DPX-α scanner. The whole control population was scanned using the Norland DXA scanner. Fractured vertebral bodies within the DXA lumbar spine region of interest (L2-L4) were excluded from the analysis. As two different DXA scanners were used in the assessment of the vertebral fracture group, and there are known to be differences in data acquisition between these scanners (8.23), DXA hip and spine

BMD data were standardised using a conversion equation (8.23). These equations have been derived from extensive cross-calibration experiments allowing for the expected deviations between the measured BMD's on each scanner. This allows direct comparison of data derived from the two scanners. The following equations were used for both hip and spine measurements:

$$sBMD_N = 1.0761\ BMD_N$$

$$sBMD_L = 0.9522\ BMD_L$$

where s = standardised

$_N$ = Norland

$_L$ = Lunar

8.2.2 Hip fracture study

300 females who had suffered a hip fracture were recruited into a study designed to examine the power of calcaneal ultrasound and different DXA measurements in discriminating hip fracture patients from a control population. Patients who had suffered a previous hip fracture patients were obtained from a search of admission records to Aberdeen Royal NHS Trust for the five year period prior to the study. Individuals were invited by letter to attend for scanning. 64 postmenopausal female controls were recruited from advertising in the local press. None had a history of previous fracture, although thoracolumbar spine x-rays were not done to exclude asymptomatic vertebral fractures. All females had the following measurements done on the same day: (1) DXA of the left hip in the control group, and the hip contralateral to the fracture site in the fracture group, (2) ultrasound of the left calcaneus. When personnel trained to perform pQCT were available, including myself, pQCT was also performed. 165 of the hip fracture group, and 45 of the control

group had pQCT performed. These females formed the study populations which are reported in this thesis.

8.3 Statistical Analyses

Similar analytical methods were used for both vertebral and hip fracture groups. Continuous variables are expressed as mean and standard deviation when normally distributed, median with range otherwise. Comparison between groups was performed by the unpaired t-test. Bone mass measurements were examined having corrected for the influence of age, height and weight by analysis of co-variance. Percentage differences between measurements were calculated, and taking into account differing ranges for these measurements, Z-scores (number of standard deviations above or below the normal mean) were calculated. These z scores were generated using the control group as the reference population in each corresponding studies. Receiver operator curves (ROC) for the different bone mass measurements were created. These reflect sensitivity versus specificity for multiple cut off values. The area under the resultant curve (AUC) indicates the ability of that measurement to discriminate fracture from non-fracture populations. The greater the area under the curve, the more discriminatory the measurement. ROC's were generated, AUC's calculated, and subsequent comparisons made using the "ROCKER" statistical package.

8.4 Results

8.4.1 Vertebral fracture study

Details of the study populations are shown in table 8.1. The fracture group was 4.1 years older ($p<0.05$), 3.8 cm shorter ($p<0.05$), 3.2 kg lighter (p=NS) and 6.5 years more postmenopause ($p<0.01$) than the non-fracture group. The median number of vertebral fractures was 2 (range 1-8). All pQCT BMD values were significantly lower in the fracture group and are shown in figure 8.1: (Qtot: 341.8 ± 76.3 vs 269.8 ± 56.3 g/cm^3;

Qtrab: 174.7 ± 44.9 vs 114.1 ± 45.8 g/cm³, both p<0.001; Qscort: 465.1 ± 105.6 vs 390.5 ± 85.4 g/cm³, p=0.002) with the exception of Qcort (498.2 ± 91.7 vs 475.9 ± 87.3 mg/cm³). DXA measurements were also lower in the fracture group and are shown in figure 8.2: (standardised (S) LS: 0.958 ± 0.174 vs 0.726 ± 0.133 g/cm²; SFN: 0.843 ± 0.164 vs 0.667 ± 0.089 g/cm²; SFT: 0.667 ± 0.138 vs 0.526 ± 0.1 g/cm²; SFW: 0.616 ± 0.176 vs 0.458 ± 0.92 g/cm², all p<0.001). After correcting for differences in age, height, weight and years postmenopause between the groups, significant differences in BMD remained (see figures 8.1-8.2), with the exception of Qscort (ANOVA, p=0.063). The greatest percentage difference between groups (see figures 8.1 & 8.2) was found for Qtrab (-34.7%), with difference in Qtot, SLS, SFN, SFT and SFW being of a similar magnitude (-21.1%, -24.2%, -26.4%, -21.1% and -25.6% respectively). A smaller difference was found in Qscort (-16%) and Qcort (-4.5%). Taking into account differing measurement ranges, z-score differences between fracture and non-fracture groups (see figures 8.1 & 8.2) were greatest for standardised LS [mean(SD): -1.37(0.78)] and Qtrab [-1.35(1.02)]. Z-score differences were of a similar magnitude for standardised DXA hip BMD measurements and Qtot (-0.9 - -1.08), whilst that for Qscort [-0.71(0.81)] was lower, and that for Qcort [-0.24(0.95)] lowest.

The receiver operator (ROC) curves generated for pQCT and DXA measurements, with the corresponding area under the curves (AUC), are shown in figure 8.3. Comparisons of the AUC's for each of the measurements are shown in table 8.2. The largest AUC was for Qtrab (0.853), which was significantly greater than that for Qscort (0.715, p=0.035) and Qcort (0.572, p<0.002), but not Qtot (0.782, p=0.139). The AUC for SLS (0.847) was greater than that for SFN, SFT and SFW (0.822, 0.787 and 0.784 respectively). However, there were no significant differences between the AUC's for the DXA measurements. There was a slight

numerical difference between the AUC for Qtrab and SLS in favour of the former, but this was insignificant (p=0.976). The AUC for Qcort was significantly less than all other pQCT and DXA measurements. Otherwise, there were no significant differences in the AUC's comparing pQCT with DXA measurements, except for SLS which was greater than Qscort (p=0.035).

8.4.2 Hip fracture study

Details of the hip fracture and non-fracture groups are shown in table 8.1. The fracture group was 1.2 years younger, 0.8cm shorter, 2.5 kg lighter and 1.4 year less postmenopausal than their non-fracture counterparts, none of which were statistically significant. The mean duration between fracture and study was 3 years. 1 of the control group, and 26 of the hip fracture group self-reported a history of rheumatoid arthritis (χ^2 test, p=0.02). Their exclusion did not change the results, so they are included in the subsequent analyses. Differences in bone mass measurements between groups are shown in figures 8.4-8.6. DXA hip BMD data is missing on 17 of the fracture group due to bilateral hip prostheses. Ultrasound data are missing from 1 control and 11 fracture subjects due to machine malfunction. All pQCT measurements were significantly lower in the fracture group and are shown in figure 8.4: (Qtot: 288.8 ± 66.1 vs 243 ± 60.7 g/cm^3 and Qscort: 397.6 ± 86.1 vs 334.7 ± 81 g/cm^3, both p<0.001; Qcort: 455.2 ± 77.7 vs 403.4 ± 94.1 g/cm^3, p=0.001; Qtrab: 151.6 ± 54.5 vs 126.1 ± 47.7 g/cm^3, p=0.002). All DXA hip measurements were significantly lower and are shown in figure 8.5: (FN: 0.686 ± 0.106 vs 0.576 ± 0.095 g/cm^2; FT 0.549 ± 0.114 vs 0.458 ± 0.113 g/cm^2; FW: 0.462 ± 0.105 vs 0.39 ± 0.096 g/cm^2, all p<0.001), as were ultrasound measurements which are shown in figure 8.6: (BUA: 62.3 ± 15.8 vs 52.1 ± 19.6 dB/MHz, p=0.002; VOS: 1485 ± 49 vs 1423 ± 64 m/s, p<0.001). Correction for differences in age, height, weight and years postmenopause between the groups did not alter

the results. The percentage differences were of a similar magnitude for all pQCT (-16.8%, -15.8% -15.6% and -11.4%, for Qtrab, Qscort, Qtot and Qcort respectively), DXA hip (-16.6%, -16% and -15.6% for FT, FN and FW respectively)and BUA (-16.4%) measurements. There was only a -4.2% difference for VOS. Again, taking into account differing measurement ranges, z-score differences between fracture and non-fracture groups (see figures 8.4 - 8.6) were greatest for FN [-1.04 (0.86)] and VOS [-0.91(4.68)], followed by FT [-0.83 (1.03)] and Qscort [-0.73 (0.94)]. Those for the remaining pQCT measurements, FW and BUA were all of a similar magnitude [-0.64 - -0.68], with Qtrab differences being lowest [-0.48 (0.88)].

The receiver operator (ROC) curves generated for pQCT, DXA and ultrasound measurements, with the corresponding area under the curves (AUC), are shown in figure 8.7. Comparisons of the AUC's for each of the measurements are shown in table 8.3. The AUC for the ROC curve was greatest for FN (0.796), which was significantly greater than those for all pQCT measurements: (Qtot: AUC=0.693, p=0.028; Qtrab: AUC=0.648, p<0.002; Qscort: AUC=0.698, p=0.037; Qcort: AUC=0.675, p=0.027), FW (AUC=0.738, p=0.01) and BUA (AUC=0.663, p=0.007). Although the AUC for FN was greater than those for FT (0.751, p=0.062) and VOS (AUC=0.783, p=0.818), the differences were statistically insignificant. The AUC for Qscort was greater than other pQCT measurements, but not statistically superior. The AUC for VOS was greater than all of the pQCT measurements, but this reached significance only against Qtrab (p=0.026). The AUC for BUA was similar to those for pQCT, but significantly less than that for VOS (p=0.009).

8.5 Discussion

These results show that trabecular BMD measured by pQCT at the ultra-distal radial site was the most powerful measurement in

discriminating patients with vertebral fracture from non-fracture controls, by virtue of the greatest AUC of the ROC curve. However there was no statistical superiority over the discriminatory power of DXA lumbar spine and hip measurements for which the AUC's were only slightly less. In contrast, the discriminatory power of the cortical BMD measurement was low, and significantly poorer than all other pQCT, as well as DXA hip and spine measurements. When the discriminatory power of pQCT measurements were compared, that for trabecular BMD was significantly better than that of cortical and subcortical, but not total BMD measurements. These finding largely mirror the z-score differences between fracture and non-fracture groups for each of the BMD measurements - the greatest difference being found for radial trabecular BMD, and the smallest for radial cortical BMD.

In contrast, the power of pQCT to discriminate a hip fracture population from a non-fracture population was less than it was for a vertebral fracture population, as shown by the smaller AUC's. This was true for all individual pQCT BMD measurements comparing the AUC's in the vertebral fracture and hip fracture populations, with the exception of the cortical BMD. The most discriminatory pQCT measurement in the hip fracture study was subcortical BMD, whilst the least was trabecular BMD. Overall, the best discriminatory measurement for hip fracture was DXA femoral neck BMD, which was statistically superior to all pQCT measurements, and calcaneal ultrasound attenuation, but not velocity. In general, the discriminatory power of the pQCT and DXA was poorer for hip fractures than it was for vertebral fractures. This could be explained in part by the smaller z-score differences between fracture and non-fracture groups for corresponding BMD measurements in the hip fracture study compared to the vertebral fracture study (except for Qscort and Qcort). It also suggests that although BMD is an important

discriminant of fracture, it is more important in vertebral fracture than in hip fracture.

It is apparent that factors other than BMD are important in determining fracture risk. More recently, other features of the proximal femur have been cited as being important in fracture predisposition - namely femoral neck length (8.24,8.25,8.26,8.27,8.28), and distribution and architecture of bone (8.24,8.28,8.29,8.30), as assessed on x-ray and DXA images. Bone turnover rate also predicts hip fracture independently of BMD (8.31). The mechanics of a fall are also important for hip fracture (1.26,1.27,1.94,8.32,8.33). The orientation and energy of the fall, the location of impact, and protective mechanisms are all important in determining whether a hip fracture will occur or not (8.32). The importance of falls, which is the most important risk factor for hip fracture, is less important in vertebral fractures (1.94,8.1). For the latter type of fracture, architectural factors have also been found to be of some importance. A smaller cross-sectional area of unfractured vertebrae results in an increased mechanical strain for equivalent loads (8.34), and morphometric differences in spinal trabecular bone predispose to fracture (8.35).

To date, very little data has been published on the discriminatory or predictive power of pQCT in fracture populations, especially hip fracture. The superiority of pQCT derived trabecular BMD over DXA lumbar spine BMD in the discrimination of a vertebral fracture population has been cited previously (8.36). In contrast, Grampp et al (8.37) found pQCT to be inferior to spinal BMD measured by QCT, and radial total BMD superior to radial trabecular BMD. The cross-sectional area of radial cortical bone was found to be equally discriminatory as total radial BMD. Several workers have

reported pQCT BMD in vertebral fracture populations (1.78,3.1,6.7,8.38). Grampp et al (3.1) found differences of 10% for trabecular, 8% for total and 1.5% for cortical BMD, which are lower than those reported in this thesis. There was also a greater age difference between their groups than ours. Schneider et al (6.7) found a difference of 21% between groups, but they compared a postmenopausal fracture group (mean age 59 years) with a premenopausal control group (aged 20-40) which are clearly not comparable. However, Ruegsegger et al have found differences of 15-33% in age matched controls (1.78, 8.38) which are comparable to those reported in this thesis.

To date, no prospective cohort study exist in which fracture risk has been determined by pQCT. Numerous studies have shown that radial BMD, as measured by SPA, has predictive value for hip (1.192,8.3,8.39,8.40) and vertebral (6.5,6.10,8.3) fractures. One standard deviation decrease in radial BMD results in a 1.6-2.6 increased risk of hip fracture (1.192,8.3,8.11), and a 1.3-2.4 increased risk of vertebral fracture (6.5,6.10,8.3,8.11). It is however generally accepted that fracture risk is best determined by a site specific measurement (1.192,8.11,8.41). If this applies to the radius, then radial pQCT measurements should be useful in predicting distal forearm fracture, although this was not formally assessed as part of the work for this thesis. The discriminatory power of pQCT trabecular and total BMD measurements in vertebral fracture suggests that pQCT may also be of value in the prediction of vertebral fracture. pQCT may be of particular value when lumbar spondylosis is evident, when the discriminatory power of spinal DXA is diminished (8.52). The power of pQCT to discriminate hip fracture was less than that of hip DXA and calcaneal ultrasound, suggesting that pQCT would be of less value in the prediction of hip fracture.

Prospective studies are now required to determine the clinical usefulness of pQCT in fracture prediction.

The fact that BUA was a poor discriminator of hip fracture was surprising and difficult to explain, as it is contrary to the findings of others (8.12-8.15), who found differences between groups of a similar magnitude to that presented here. BUA has also been shown to predict future hip fracture (8.16-8.19), and correlate with the failure load of human cadaveric femurs during simulation of a fall onto the trochanter (8.42). The finding that ultrasound velocity discriminates hip fracture from non-fracture populations as well as hip BMD, inspite of smaller percentage differences, is in keeping with previous work (8.12,8.14). When the differences in mean values and the range of absolute values are taken into account, and fracture and non-fracture groups are compared using z-scores, differences in DXA femoral neck BMD [-1.04 (0.86)] and VOS [-0.91(4.68)] are not dissimilar. The power of ultrasound velocity was superior to all pQCT measurements in the discrimination of hip fractures, although this reached statistical significance only against pQCT trabecular BMD. The finding that ultrasound attenuation was no better than pQCT, and significantly poorer than DXA hip and ultrasound velocity was surprising, and contrary to previous findings comparing DXA and BUA. One possible explanation is the interval between fracture and scanning in the work presented in this thesis (mean: three years), as the fracture and subsequent immobility, could have resulted in greater bone loss at the hip than at the calcaneus. A recent, large, prospective study showed that calcaneal ultrasound attenuation and velocity predicted hip fracture as well as, and independently of, DXA femoral neck BMD in 7575 (5662 underwent ultrasound assessment) community dwelling, elderly (at least 75 years of age) women (8.19). Of the ultrasonic measurements, BUA was found to be the most

independent of femoral neck BMD, yet the most predictive of hip fracture. Additionally, for women in whom both BUA and femoral neck BMD was low (less than the median), the fracture risk was much greater than in those with only one low measurement. This suggests that fracture risk is best determined by measuring both femoral neck BMD and calcaneal BUA.

There are several confounding factors in the studies presented in this thesis. In the vertebral fracture study, the groups were not entirely comparable, with the fracture group being older, shorter and further beyond the menopause than the non-fracture group. However, correcting for these differences did not greatly change the highly significant differences for most BMD measurements between groups. Also, as discussed in chapter 7, age related rates of bone loss are greater at the spine and hip compared to the radius. Therefore any age difference between groups would affect DXA more than pQCT measurements, and as such should not detract from the finding that pQCT trabecular BMD discriminates best between vertebral fracture and non-fracture groups. An additional problem was performing axial measurements on two DXA scanners manufactured by different companies, which is less than ideal. However, correction equations have been extensively validated to allow comparison of data acquired from these different scanners (8.23). Additionally, there was no quantification of lumbar spondylosis on the spinal x-rays. If significant osteoarthritic changes were present, this would have diminished the discriminatory power of the DXA lumbar spine measurement.

In the hip fracture study, the control group is much smaller than the fracture group, whilst the reverse is the ideal. Unfortunately it proved impossible to recruit more non-fracture controls. Also, only a subgroup of the population originally recruited underwent pQCT as discussed in chapter 8.2.2. There

was no preselection of this subgroup, as pQCT was performed whenever personnel trained in pQCT were available, and this is unlikely to have biased the subgroup which formed the populations presented here. The differences in bone mass measurements between hip fracture and non fracture groups for hip DXA and ultrasound measurements are comparable to those previously published (8.12,8.13,8.15), which supports the concept that both groups were representative.

Finally, the ability of pQCT to predict hip, vertebral and distal forearm fractures must now be determined by prospective studies.

Table 8.1. Demographic data of the hip (HIP-F) and vertebral (VERT-F) fracture groups with the corresponding hip (HIP-C) and vertebral (VERT-C) control groups.

	HIP-C (n=45)	HIP-F (n=165)	VERT-C (n=30)	VERT-F (n=39)
Age (yrs)	75.1 (7.7)	73.9 (9.1)	64.1 (7.1)	68.2 (6.9)[a]
Height (m)	1.565 (0.064)	1.557 (0.074)	1.569 (0.06)	1.531 (0.061)[a]
Weight (kg)	61.4 (9.6)	58.9 (11.4)	62.9 (10.1)	59.7 (10.2)
Years Postmenopause	30.4 (9.7)	29.0 (10.2)	15.3 (9.3)	21.8 (6.8)[b]
Interval between hip fracture and study (yrs)	-	3.0 (1.5)	-	-
No. of vertebral fractures §	-	-	0	2 (1-8)

Values are mean (SD), except § which is median (range).

[a]:0.05>p>0.01; [b]:0.01>p>0.001, for unpaired t-test versus controls. Otherwise not significant

Table 8.2 Area (AUC) under the receiver operator curves (ROC) indicating the power of pQCT and DXA to discriminate vertebral fracture from non-fracture populations. Comparison against mutually exclusive measurements are also shown.

	Qtot	Qtrab	Qscort	Qcort	LS	FN	FT	FW
AUC	0.782	0.853	0.715	0.572	0.847	0.822	0.787	0.784
Qtrab	0.139							
Qscort	0.134	**0.035**						
Qcort	**<0.002**	**<0.002**	**<0.002**					
LS	0.211	0.976	**0.035**	**<0.002**				
FN	0.395	0.631	0.057	**<0.002**	0.582			
FT	0.842	0.294	0.159	**<0.002**	0.246	0.395		
FW	0.905	0.308	0.254	**0.003**	0.234	0.368	0.952	

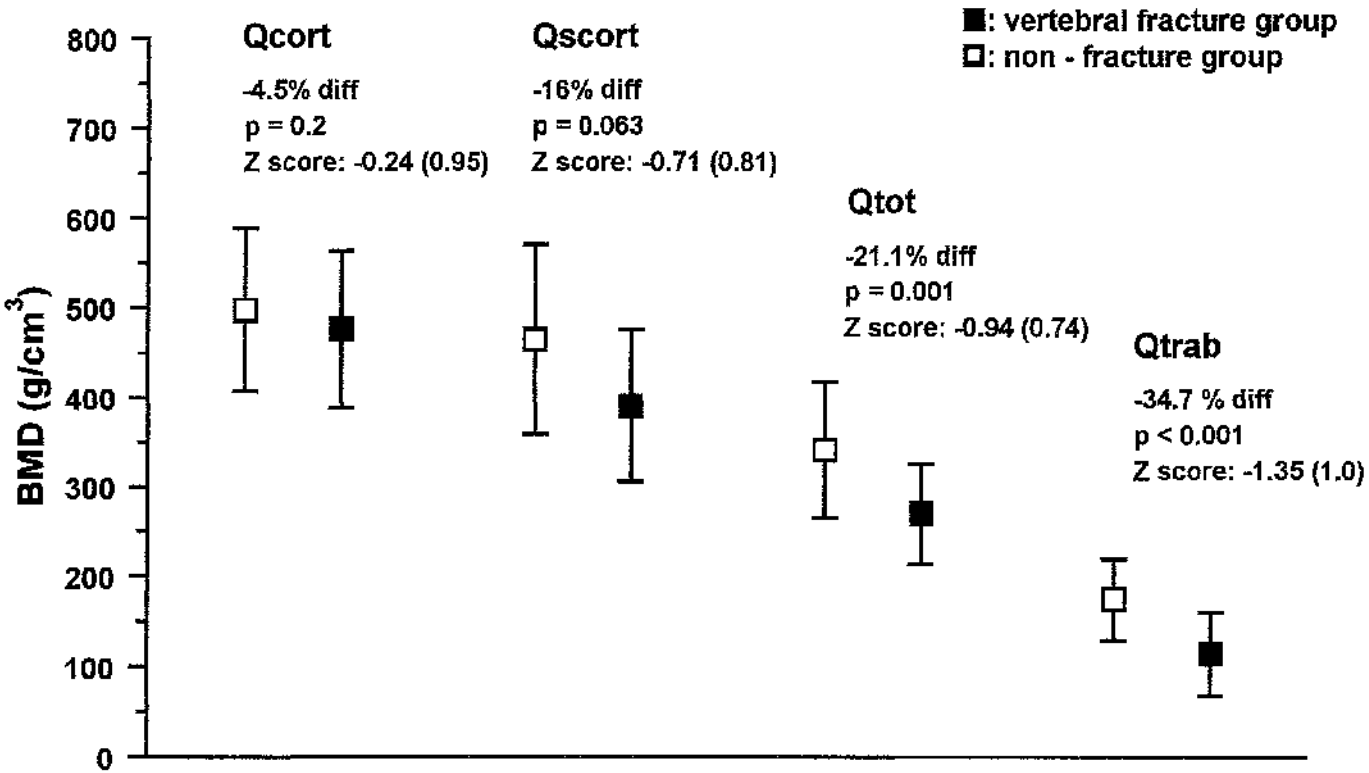
Values are p-values for comparison of AUC of ROC.

Table 8.3 Area (AUC) under the receiver operator curves (ROC) indicating the power of pQCT, hip DXA and calcaneal ultrasound to discriminate hip fracture from non-fracture populations. Comparison against mutually exclusive measurements are also shown.

	Qtot	Qtrab	Qscort	Qcort	FN	FT	FW	BUA	VOS
AUC	0.693	0.648	0.698	0.675	0.796	0.751	0.738	0.663	0.783
Qtrab	0.201								
Qscort	0.841	0.271							
Qcort	0.653	0.689	0.39						
FN	**0.028**	**<0.002**	**0.037**	**0.027**					
FT	0.254	**0.042**	0.284	0.184	0.062				
FW	0.358	0.07	0.424	0.276	**0.01**	0.624			
BUA	0.589	0.787	0.542	0.857	**0.007**	0.082	0.144		
VOS	0.142	**0.026**	0.162	0.093	0.818	0.582	0.447	**0.009**	

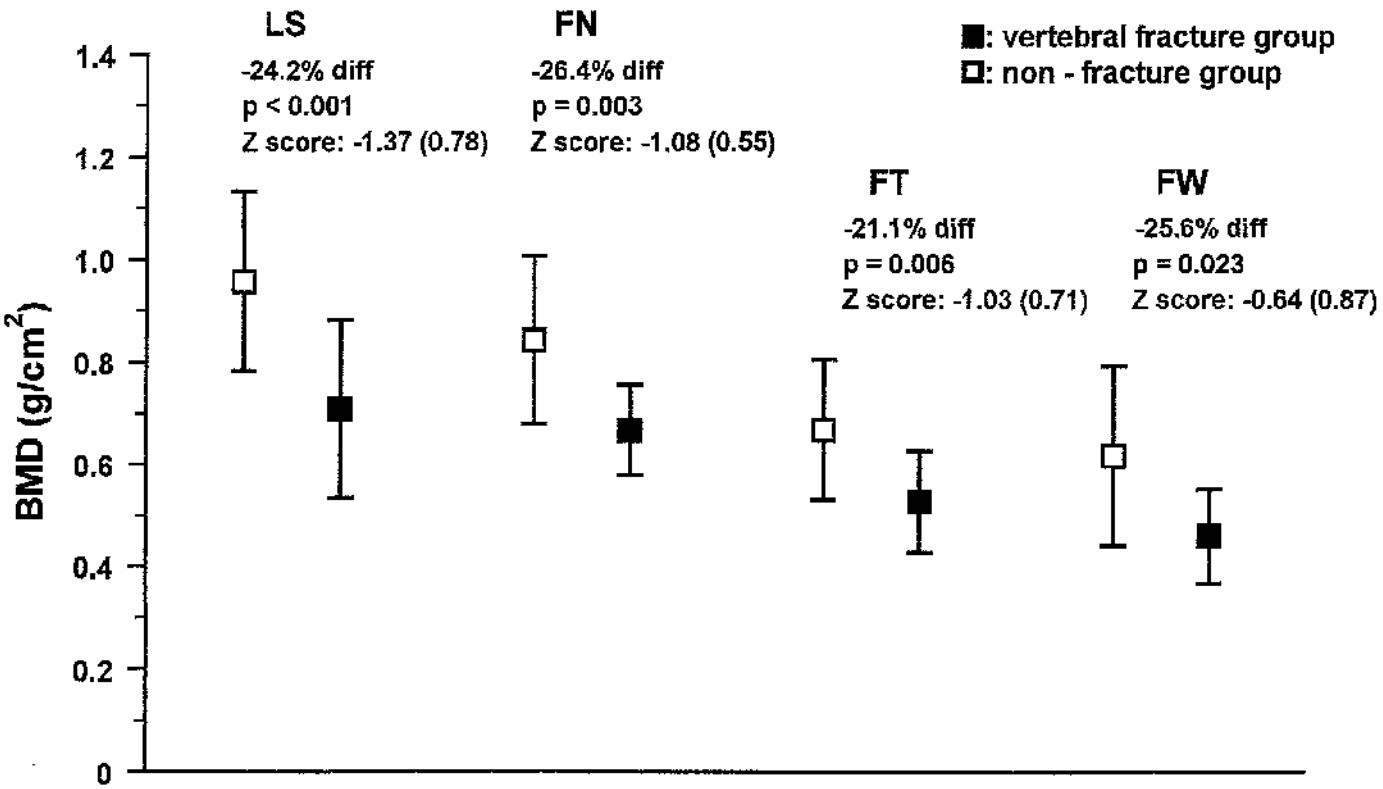
Values are p-values for comparison of AUC for ROC.

Fig 8.1: Differences in pQCT BMD measurements between vertebral fracture and non-fracture groups



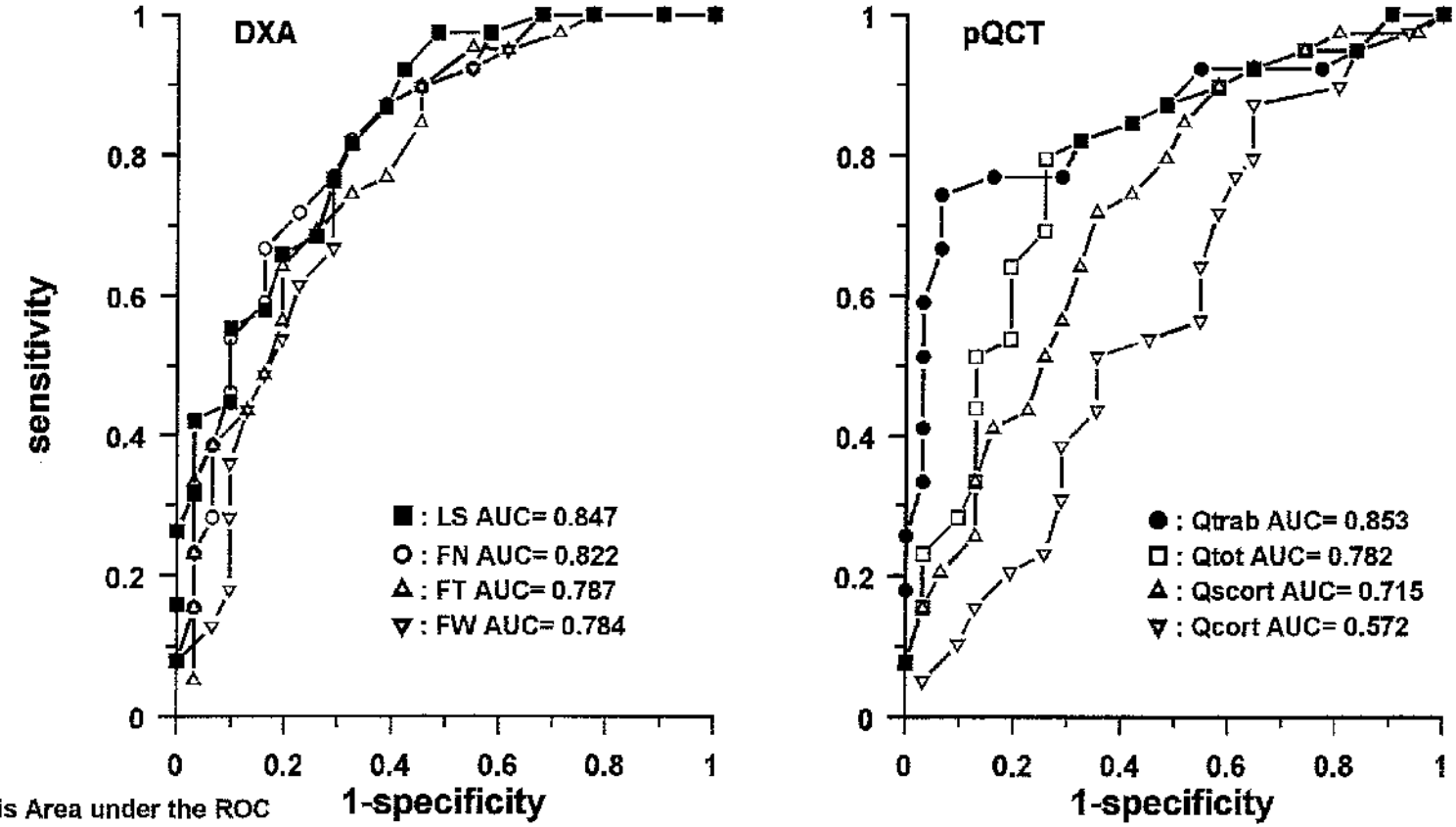
plots are mean +/- SD. Percentage differences between groups shown.
p value is for covariate analysis controlling for age, height, weight and years postmenopause.
Z score: mean (SD) standard deviation difference of the fracture group relative to the control group

Fig 8.2: Differences in DXA BMD measurements between vertebral fracture and non-fracture groups



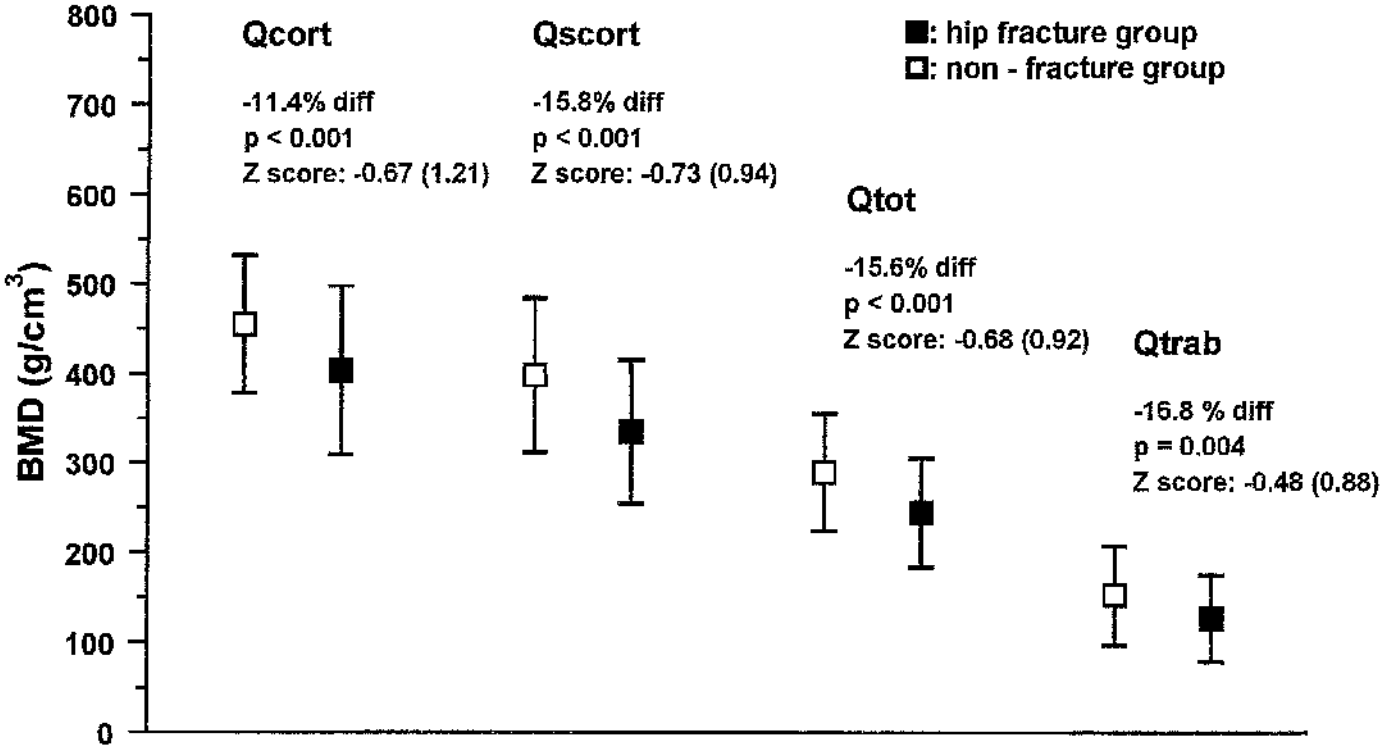
plots are mean +/- SD. Percentage differences between groups shown.
p value is for covariate analysis controlling for age, height, weight and years postmenopause.
Z score: mean (SD) standard deviation difference of the fracture group relative to the control group

Fig 8.3: Receiver operator curves (ROC) showing the power of DXA and pQCT to discriminate vertebral fracture and non-fracture populations.



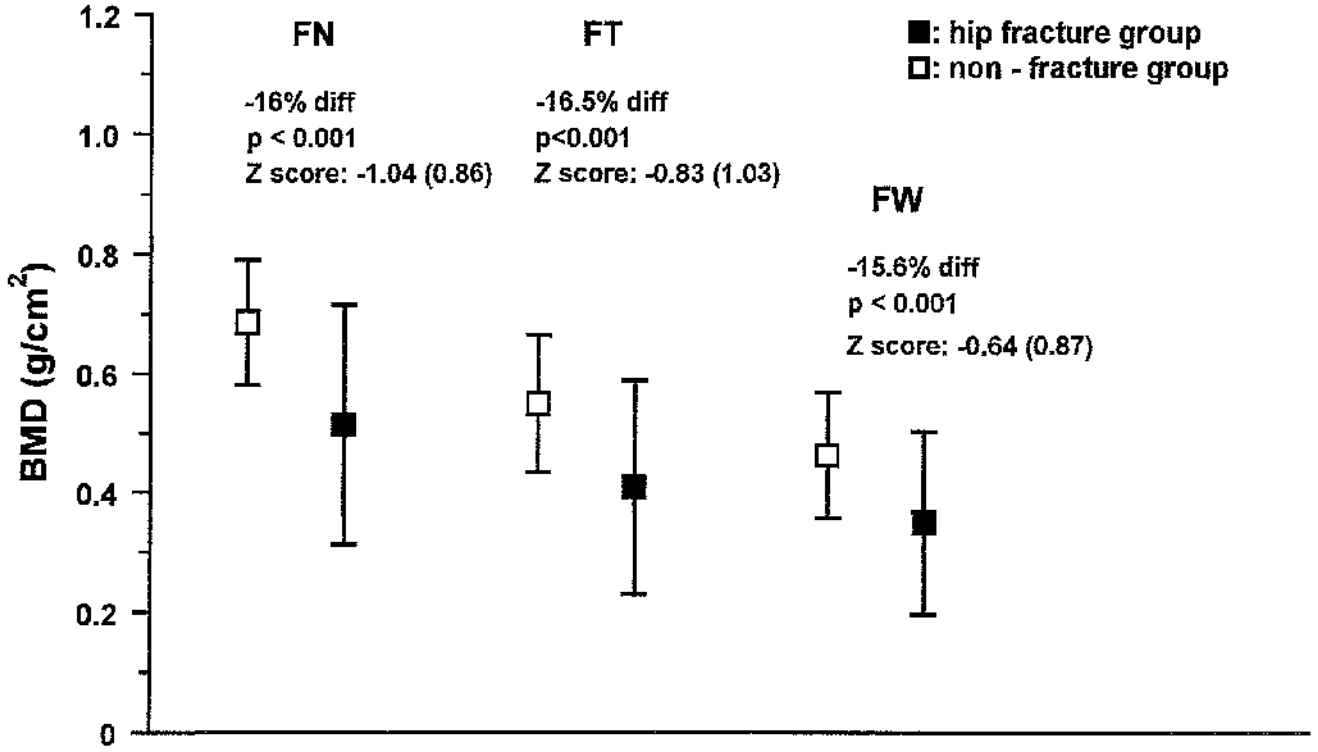
AUC is Area under the ROC

Fig 8.4: Differences in pQCT BMD measurements between hip fracture and non-fracture groups



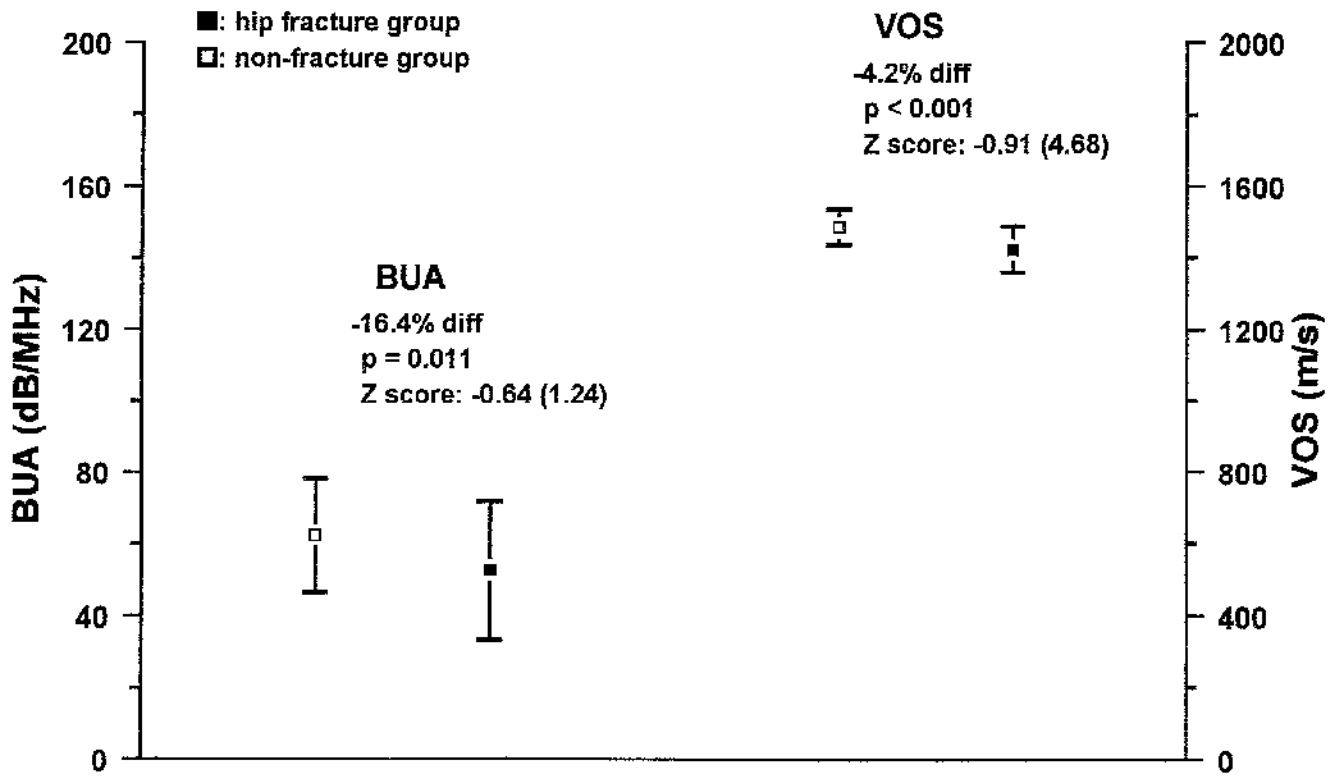
plots are mean +/- SD. Percentage differences between groups shown.
p value is for covariate analysis controlling for age, height and weight differences.
Z score: mean (SD) standard deviation difference of the fracture group relative to the control group

Fig 8.5: Differences in DXA BMD measurements between hip fracture and non-fracture groups



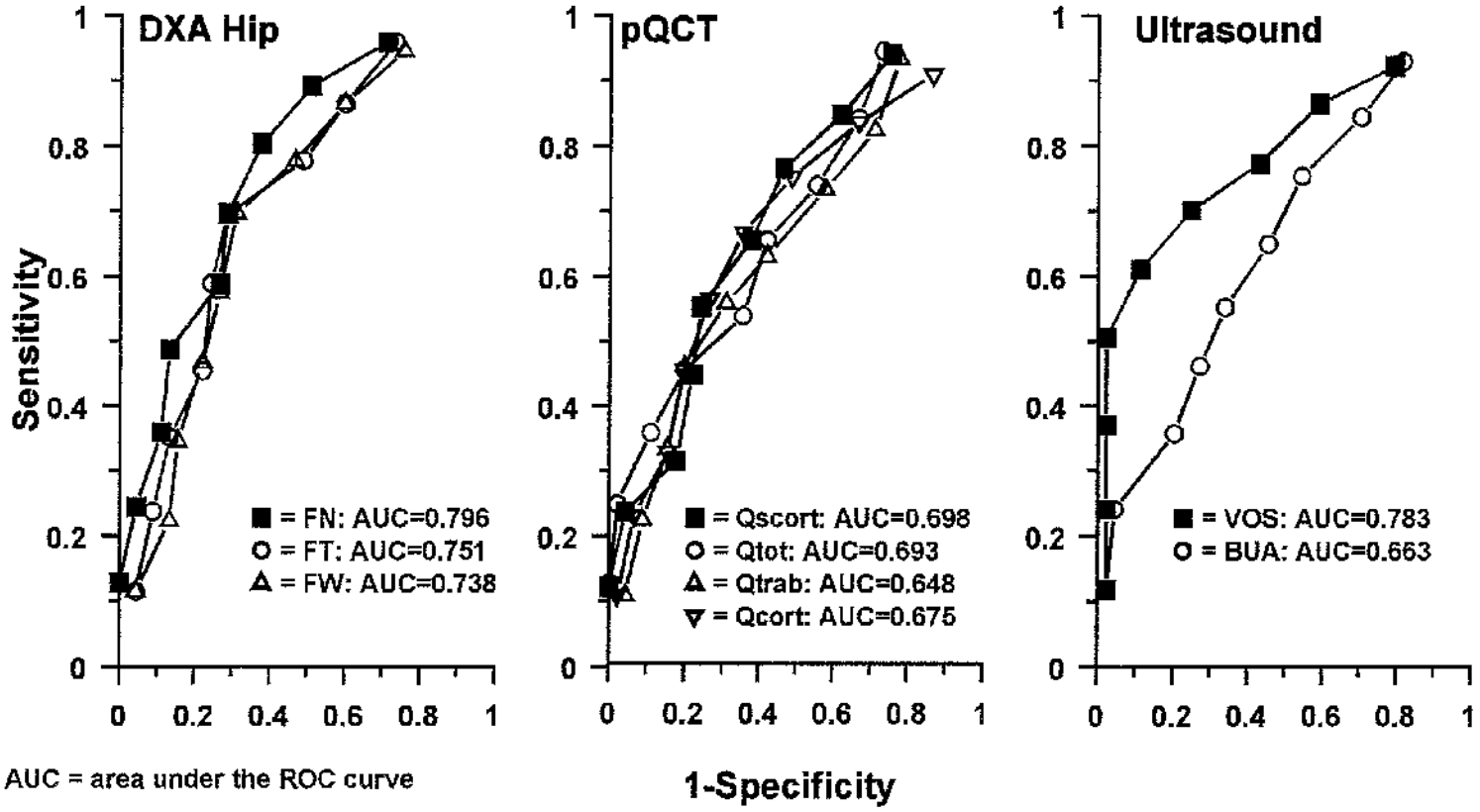
plots are mean +/- SD. Percentage differences between groups shown.
p value is for covariate analysis controlling for age, height and weight differences.
Z score: mean (SD) standard deviation difference of the fracture group relative to the control group

Fig 8.6: Differences in ultrasound measurements between hip fracture and non-fracture groups



plots are mean +/- SD. Percentage differences between groups shown.
p value is for covariate analysis controlling for age, height and weight differences.
Z score: mean (SD) standard deviation difference of the fracture group relative to the control group

Fig. 8.7: Receiver operator curves (ROC) showing the power of hip DXA, pQCT and calcaneal ultrasound to discriminate hip fracture and non-fracture populations.



AUC = area under the ROC curve

CHAPTER 9

CHANGES IN RADIAL pQCT BMD MEASUREMENTS IN RESPONSE TO DRUG THERAPY: COMPARISON WITH MEASUREMENTS AT OTHER SKELETAL SITES.

9.1 Introduction

One of the most important functions identified for bone densitometry is monitoring of drug therapy (1.145,1.146,1.153,1.154,9.1). This is as equally applicable to drugs which have a beneficial effect upon bone mass and are used in the treatment of osteoporosis, as it is to those which have an adverse effect upon bone mass, such as corticosteroids. Both hormone replacement therapy (HRT) and cyclical etidronate with calcium are used in the treatment of osteoporosis. HRT has been shown to reduce fracture rates at the hip, spine and radius in postmenopausal women (1.198,1.199,9.2-9.5), increase axial (9.6-9.13) and maintain radial (9.8,9.11,9.14) BMD. Cyclical etidronate and calcium increase spinal BMD and is of proven value in the treatment of established postmenopausal osteoporotic vertebral fracture by reducing vertebral fracture rates (9.15,9.16,9.17) and increasing spinal BMD (9.7,9.13,9.15,9.16,9.17). The desired interval between repeat measurements for monitoring response is largely determined by the precision of the scanner and the expected rate and magnitude of change. As the precision of pQCT is comparable to DXA lumbar spine and femoral trochanter measurements, and better than femoral neck and Ward's area measurements (see chapters 2 and 3), the response to these treatments may be better monitored at the radius by following changes in trabecular BMD. This is especially attractive as both HRT and etidronate preferentially affect trabecular bone which has an increased metabolic rate. As DXA measures a composite of trabecular and cortical bone unlike pQCT which allows direct quantification of trabecular BMD, DXA may be less sensitive to

smaller changes in trabecular bone than pQCT. Whilst spinal QCT is also a technique which allows measurement of trabecular bone independently, its use, especially when repeat measures are necessary, is limited by radiation considerations (see chapter 1). The use of pQCT for monitoring purposes would however be dependent upon drug induced change at the radius being of a similar timing and magnitude to that at other skeletal sites. At present, BMD assessment every 2 years is recommended (1,145). A hypothesis can be raised pQCT will allow earlier detection of responders, and equally importantly, non-responders to HRT and etidronate. The work in this chapter addresses this hypothesis, the issue of timing of bone mass changes at different skeletal sites in response to HRT and etidronate during the first year of treatment, and whether changes in radial trabecular BMD measured by pQCT can predict axial changes measured by DXA.

9.2 Study Populations and Bone Mass Measurements

11 postmenopausal women (defined as no menses for at least 2 years) were treated by their general practitioners with HRT preparations (Prempak-C, n=4; Livial and Estracombi n=2; Trisequens, Estraderm and Cycloprognova each n=1) for the prevention of osteoporosis (HRT Gp). 6 of these women were identified from the ongoing osteoporosis screening programme which has been described previously (Chapter 5: 5.2-point 2). They either had lumbar spine or femoral neck BMD in the lowest quartile of age matched controls and were targeted for intervention with HRT assuming no contra-indications, a cut-off point which has been proposed previously (1.88). The remaining women were referred directly by their general practitioner's for a DXA scan and were also found to have low bone mass for which HRT was recommended. All women were either osteopenic (T-score $\leq$ -1; n= 1) or osteoporotic (T-score $\leq$ -2.5; n= 10) as defined by the WHO (6.4), at either the femoral neck or lumbar

spine. None of these women had suffered an osteoporotic fracture and none had vertebral fractures on lateral thoracolumbar spine x-ray.

10 older postmenopausal women were referred by their GP's to a specialised bone clinic because of symptomatic osteoporotic vertebral fractures for which cyclical etidronate and calcium supplements was prescribed (ETD gp). All women were osteoporotic (T-scores ≤ -2.5 at either lumbar spine or femoral neck) with atraumatic vertebral osteoporotic fractures.

None of the women in either group had other conditions or were taking other medications which could affect bone mass or metabolism. Baseline pQCT and DXA of hip and spine measurements were made before treatment was started, and then 4, 8 and 12 months thereafter. All measurements were done on the same day except the baseline visit, where DXA preceded pQCT by no more than 8 weeks in some women - DXA was repeated if a longer delay was encountered. For the follow-up pQCT measurements, the "trending" function, which is discussed in chapter 3, was utilised. The cut-off value used for the difference in voxel numbers between baseline and follow-up scans was set at 30, thus ensuring accurate re-positioning of the scanner in follow-up scans and minimising the influence of change in scan site on repeat pQCT BMD measurements.

The co-efficients of variation (CV) for pQCT (see chapter 3) are generally poorer in postmenopausal women with vertebral osteoporotic fractures compared to young normal women (Qtot: 1.73% vs 1.24%, Qtrab: 2.96% vs 1.33%, Qscort: 1.57% vs 1.58%, Qcort: 5.18% vs 1.88%). The precision of axial DXA measurements was determined in 6 postmenopausal women [median (range) age: 68 (60 -71) years, and years postmenopause: 21 (13 - 25) years] with vertebral fractures on lateral thoracolumbar x-ray [median

(range) number of fractures: 2.5 (1-3)], by performing repeat hip and spine measurements on the same day with repositioning of the subject between scans. These women were different to those studied to determine the precision of pQCT in the a vertebral fracture group, and those studied in the etidronate treatment group. The CV's in the vertebral fracture group compared to young normals were: LS: 2.32% vs 0.9%, FN: 1.3% vs 2.8%, FT: 1.42% vs 1.3%, FW: 2.16% vs 4.8%. Fractured vertebral bodies within the DXA lumbar spine region of interest (L2-L4) were excluded from all relevant analyses.

9.3 Statistical Analyses

Results for continuous variables are expressed as median with ranges. Baseline lumbar spine and femoral neck BMD results are also expressed as T-scores and Z-scores (number of standard deviations above or below the mean relative to young, and age matched normal controls respectively). Between group comparison at baseline are performed using the Mann-Whitney U test. Within group percentage changes in bone mass measurements from baseline are compared using the Wilcoxon matched pairs test and one factor repeat measurement analysis. The relationships between annual rates of changes in BMD at different sites were examined using linear regression and correlation co-efficients.

9.4 Results

Baseline clinical and bone mass details of both groups are shown in Table 9.1. Although 4 women had undergone hysterectomy (hyst) previously [HRT gp: n=1(age 63,hyst 20 yrs previously)], [ETD gp: n=1(age 71,hyst 16 yrs previously), n=2(aged 60 & 73, hyst 30 yrs previously)], none had FSH, LH or oestradiol levels done to confirm their assumed postmenopausal status. The HRT group were younger and fewer years postmenopausal than the ETD group. Consequently all baseline BMD measurements were greater

in the HRT group with the exception of LS.

There were no significant changes in median height or weight values during the 1 year follow-up period in either HRT or ETD groups (see table 9.2). Percentage BMD changes for the pQCT radial and DXA hip and spine BMD measurements are shown in tables 9.3 and 9.4 respectively, and depicted in figures 9.1 and 9.2. There were no overall significant changes in any pQCT BMD measurements for either group. There was however a trend towards a fall in BMD at month 8 in the HRT group, which reached significance for Qtot and Qscort, with some recovery by month 12. Significant overall increase was found at LS in both groups, which was statistically significant within 4 months, and further increased after 12 months of treatment. Although there was a trend for all hip BMD measurements to increase, overall significance was only achieved for FN in the HRT group. The results remained unchanged after correction for changes in height and weight. There were no significant relationships between the percentage changes in any of the pQCT BMD measurements and DXA hip or spine BMD changes with either treatment. Comparisons of the percentage changes in pQCT measurements with LS BMD after 12 months of treatment with HRT ($r = 0.19, -0.35, 0.26$ and 0.19 for Qtot, Qtrab, Qscort and Qcort respectively; p = NS for all) and etidronate ($r = 0.14, 0.35, 0.01$ and -0.01 for Qtot, Qtrab, Qscort and Qcort respectively; p = NS for all) were typical of comparisons.

9.5 Discussion

These results shows that changes in BMD induced by both HRT and etidronate during one year of treatment varies between skeletal sites. The most significant and greatest changes occurred at the lumbar spine for both treatments, although there was considerable inter-individual variation. Also, for several

women in either group, lumbar spine BMD did not increase during the first year of treatment. Median increases of +6.6% and +5.3% after one year of treatment with HRT (9.6,9.9,9.10,9.11,9.18) and etidronate (9.15,9.16) respectively are in keeping with previous work. The work presented here suggests that statistically significant changes were detectable at the lumbar spine after only 4 months of treatment with either HRT or etidronate. Present recommendations are that BMD measurements should not be repeated until a patient has been on therapy for 1-2 years (1.145). This is based upon a change 2.8 times that of the co-efficient of variation (CV) being necessary before it can be regarded as real and not due to measurement error (1.88,9.1). The CV for DXA lumbar spine measurements in our centre is 0.9% in young healthy women, but 2.32% in older osteoporotic women. The median change in lumbar spine BMD after 4 months of treatment with HRT was +3.3% which could only be accepted as significant if the precision value for young normal women was applied (ie CV = 0.9% with significant change greater than ± 2.52%). If this figure was applied, then a repeat lumbar spine DXA scan as early as 4 months may indicate response to therapy. However, although the HRT group did not suffer from vertebral fractures, and major spondylosis was not a problem, it is unlikely that the precision value would be as low as 0.9%, due to the lower BMD values which would result in a higher CV. If the higher CV figure was applied, then a follow up scan after 1 year would be the earliest possible to detect significant change. In the etidronate group, the higher CV for DXA lumbar spine scans would have to be applied (CV = 2.32%, with significant change greater than ± 6.4%). Consequently, a repeat scan no earlier than 1 year would be indicated. This implies that the optimum length of time between scans when assessing the response to therapy is dependent upon both the age of the patient (which can affect the precision of the measurement),

and the expected magnitude and timing of the response to treatment.

It is surprising that the baseline lumbar spine BMD of the ETD group was greater than that of our HRT group bearing in mind they were older and more years postmenopausal. This could be due to age related spinal osteoarthrosis (1.171-1.177) and aortic calcification (1.168,1.169,1.170) elevating spinal BMD results in the ETD group. This should not influence the rate of response at the lumbar spine, although a state of low bone turnover has recently been observed in patients with lumbar spondylosis and osteoarthritis (1.174,1.178,1.179,9.19). Also, we cannot exclude a spurious rise in BMD from further fractures occurring within the area of interest (L2-4) during the first year of treatment, as lumbar spine X-rays were not repeated. This was an attempt to minimise radiation exposure, particularly as the purpose of this work was not to examine the effect of treatment upon fracture rates.

Although there was a trend towards an increase in all hip measurements for both groups, this only achieved overall significance for femoral neck BMD in the HRT group. Similar changes in proximal femur BMD have been documented previously with HRT (9.6,9.10,9.11,9.18) and etidronate (9.20,9.21), and tend to be lower than those found at the lumbar spine, presumably due to a smaller proportion of trabecular bone at the former site. Bearing in mind the poorer precision of DXA hip measurements, they would be of less value than spinal measurements for detecting early response to HRT and etidronate. If however, certain situations prevailed, such as heavy overlying aortic calcification, severe spondylosis or multiple vertebral fractures within the spinal region of interest, then hip measurements may be the better choice for monitoring response, with an appropriately longer interval

between scans.

Previous work has shown that radial BMD, as measured by single photon absorptiometry (SPA) is maintained but not increased significantly with HRT (9.8,9.11,9.14) and etidronate (9.7,9.15). Theoretically, by quantifying trabecular BMD independently, pQCT should be more sensitive than SPA in detecting change at appendicular sites, and may mirror or even antedate axial changes measured by DXA. Although radial BMD was maintained, there was no significant increase, even in trabecular BMD in either treatment group. This, and the fact that there were no meaningful relationships between percentage changes at the radius and spine or hip, suggests that the response to treatment at the radius, even within the trabecular component, is different from that at the lumbar spine. It is possible that trabecular BMD may change after more than 1 year of treatment, but previous studies using SPA have shown no significant increase in radial BMD after treatment with HRT for 2 years (9.22), and etidronate for 3 years (9.15).

Early demonstration of response to treatment is important because it may help improve patient compliance (1.201,1.202,9.1), and allow early detection of non-responders which have been found previously with both etidronate (9.20,9.23) and HRT (9.10,9.18,9.22). For such non-responders, compliance with therapy could be checked, the importance of treatment emphasised, or the treatment changed if necessary. Also, proof of response to therapy is important as there is now some evidence that the anti-fracture efficacy of treatment is determined by both a reduction in bone turnover and an increase in BMD (9.24). The work presented in this thesis suggests that a repeat measurement after one year would evaluate response to treatment with HRT and etidronate in the majority of cases. When changes smaller than 2.8x the CV are recorded, such

changes could also be interpreted as showing an improvement if there was a consistent upward trend, although this would have to be judged in the context of a given individuals treatment (9.1). In clinical practice, the interval between follow up scans is likely to be determined largely by individual clinical situations and resources. In most instances, due to the differential effect of HRT and etidronate on axial and appendicular bone, response to treatment would be best determined by a spinal BMD measurement.

Table 9.1 Baseline clinical, pQCT and DXA data for hormone replacement therapy (HRT) and etidronate (ETD) groups.

		HRT gp (n=11)	ETD gp (n=10)
Age		53 (46-63)	71 (60-79)
Years Postmenopause §		4 (2-10)	23 (14-30)
No. of fractures		-	2 (1-4)
pQCT (g/cm^3)			
Qtot		340.0(261.6-389.1)	279.6(198.3-397.8)
Qtrab		147.8(102.1-200.4)	125.1(87.8-225.7)
Qscort		476.3(383.9-562.3)	376.6(288.6-538.3)
Qcort		523.0(466.7-627.0)	463.3(399.1-565.3)
DXA (g/cm^2)			
LS		0.755(0.632-0.959)	0.783(0.526-0.934)
	T-score	-3.17(-4.23 - -1.41)	-2.93(-5.02 - -1.63)
	Z-score	-1.46(-1.84 - -0.43)	-0.70 (-2.55 - +0.36)
FN		0.723(0.540-0.905)	0.606(0.471-0.858)
	Tscore	-2.06(-3.58 - -0.54)	-3.03 (-4.16 - -0.94)
	Z-score	-1.01(-1.88 - +0.69)	-1.26 (-2.09 - +0.89)
FT		0.577(0.441-0.813)	0.497(0.276-0.619)
FW		0.533(0.373-0.760)	0.387(0.304-0.554)

Values are median (range) unless otherwise stated.

§ for non-hysterectomized women.

Table 9.2. Height and weight at months 0, 4, 8 and 12 in hormone replacement therapy (HRT), and etidronate (ETD) groups.

	Month 0	Month 4	Month 8	Month 12	p
Height (m)					
HRT	1.615m(1.485-1.708)	1.614(1.472-1.702)	1.61 (1.476-1.703)	1.615(1.471-1.705)	NS
ETD	1.547(1.451-1.621)	1.551(1.453-1.602)	1.541(1.452-1.621)	1.549(1.448-1.601)	NS
Weight (kg)					
HRT	66 (51-89.5)	66 (52-91.5)	65.5 (51-89)	64 (53-89)	NS
ETD	61.5 (44.5-83.5)	60 (45-78)	62.8 (45.5-82.5)	61.3 (47.5-82)	NS

Values are median (range)

p-value is for one factor repeat measurement analysis.

Table 9.3. Percentage changes in pQCT at 4, 8 and 12 months in hormone replacement therapy (HRT gp) and etidronate (ETD gp) groups, compared with baseline.

		Month 4	8	12	Overall-Sig
pQCT					
Qtot	HRT	-0.7 (-7.0 - +10.5)	-2.0 (-4.8 - +1.7)[0.07]	-1.1 (-9.8 - +4.9)	NS
	ETD	-0.4 (-2.7 - +7.4)	+0.5 (-2.8 - +8.6)	+0.2 (-3.7 - +7.8)	NS
Qtrab	HRT	+0.3 (-14.0 - +4.2)	-1.3 (-18.2 - +3.9)	-0.7 (-9.3 - +2.8)	NS
	ETD	+0.9 (-8.5 - +14.2)	-0.5 (-16.4 - +8.2)	-1.0 (-12.9 - +13.1)	NS
Qscort	HRT	-1.0 (-6.7 - +14.5)	-1.8 (-5.6 - +3.3)[0.04]	-1.1 (-9.9 - +7.1)	NS
	ETD	-0.8 (-4.1 - +11.5)	+0.8 (-5.2 - +11.3)	+0.6 (-4.1 - +9.8)	NS
Qcort	HRT	-1.2 (-6.7 - +4.6)	-2.4 (-7.8 - +2.8)	-2.2 (-4.9 - +5.5)	NS
	ETD	-0.3 (-3.0 - +11.5)	+0.4 (-5.4 - +11.3)	-0.2 (-6.0 - +9.2)	NS

Values are median (range) [p-value for Wilcoxon paired test versus month 0]

Overall significance is for one factor repeat measurement analysis.

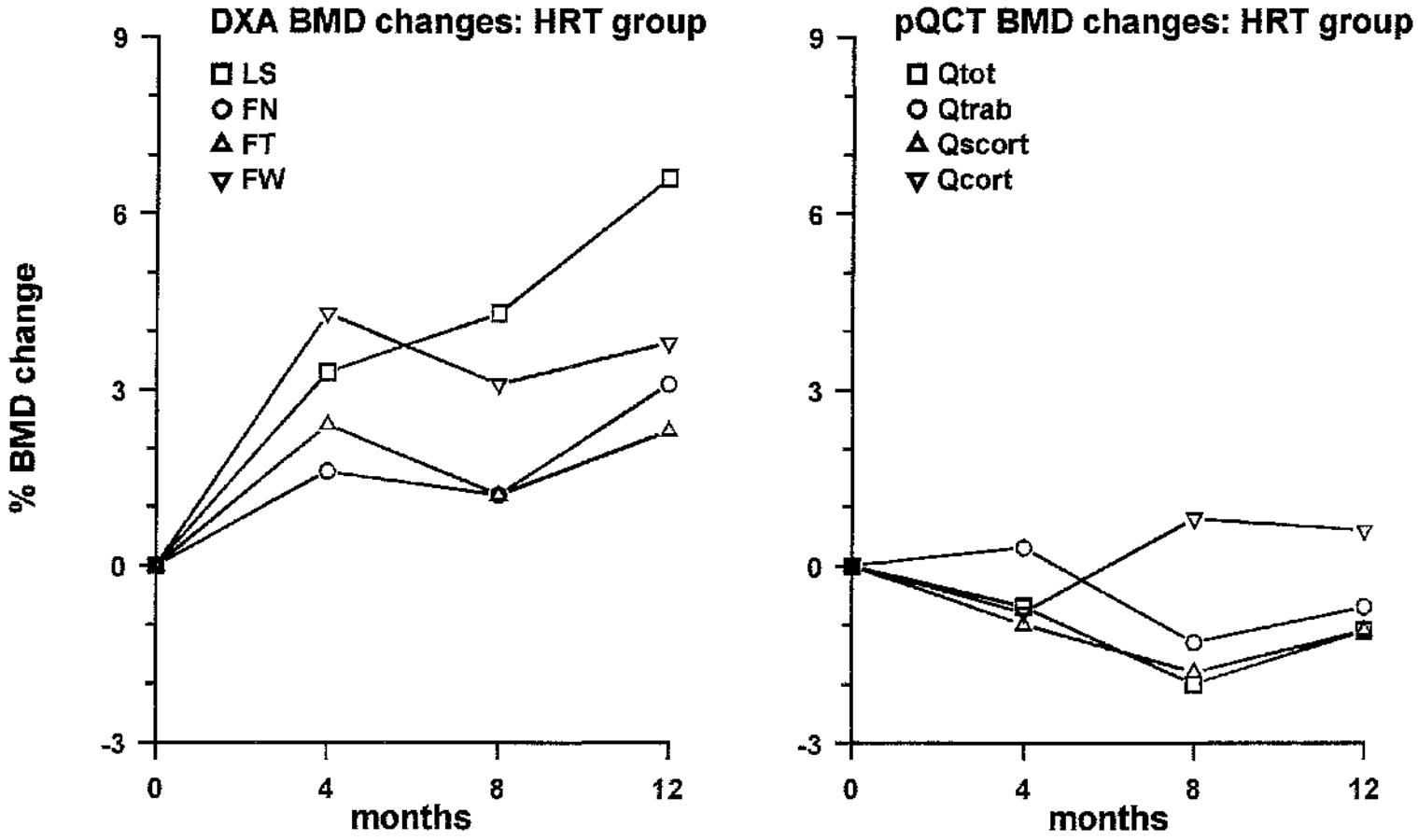
Table 9.4. Percentage changes in DXA spine and hip BMD measurements at 4, 8 and 12 months in hormone replacement therapy (HRT gp) and etidronate (ETD gp) groups, compared with baseline.

		Month 4	8	12	Overall-Sig
DXA					
LS	HRT	+3.3 (-4.8 - +9.8)[0.02]	+4.3 (-2.7 - +8.8)[0.01]	+6.6 (-3.2 - +13.1)[0.01]	< 0.001
	ETD	+3.8 (-1.5 - +10.2)[0.01]	+5.0 (-2.8 - +8.4)[0.01]	+5.2 (-4.3 - +12.8)[0.02]	0.013
FN	HRT	+1.6 (-4.1 - +5.6)	+1.2 (-3.2 - +7.9)	+3.1 (-5.7 - +7.7)	0.026
	ETD	-0.6 (-5.1 - +13.1)	+1.0 (-4.0 - +6.8)	+2.1 (-3.7 - +7.6)	NS
FT	HRT	+2.4 (-4.9 - +12.7)	+1.2 (-6.1 - +13.7)	+2.3 (-8.8 - +19.5)[0.026]	NS
	ETD	+4.2 (-17.7 - +29.3)	+4.2 (-8.0 - +33.3)	+5.3 (+0.5 - +15.2)[0.005]	NS
FW	HRT	+4.3 (-7.9 - +22.4)	+3.1 (-15.1 - +22.9)	+3.8 (-1.8 - +20.8)[0.01]	NS
	ETD	+5.9 (-6.7 - +45.1)	+7.8 (-14.5 - +50.3)	+5.4 (-8.1 - +44.2)	NS

Values are median (range) [p-value for Wilcoxon paired test versus month 0]

Overall significance is for one factor repeat measurement analysis.

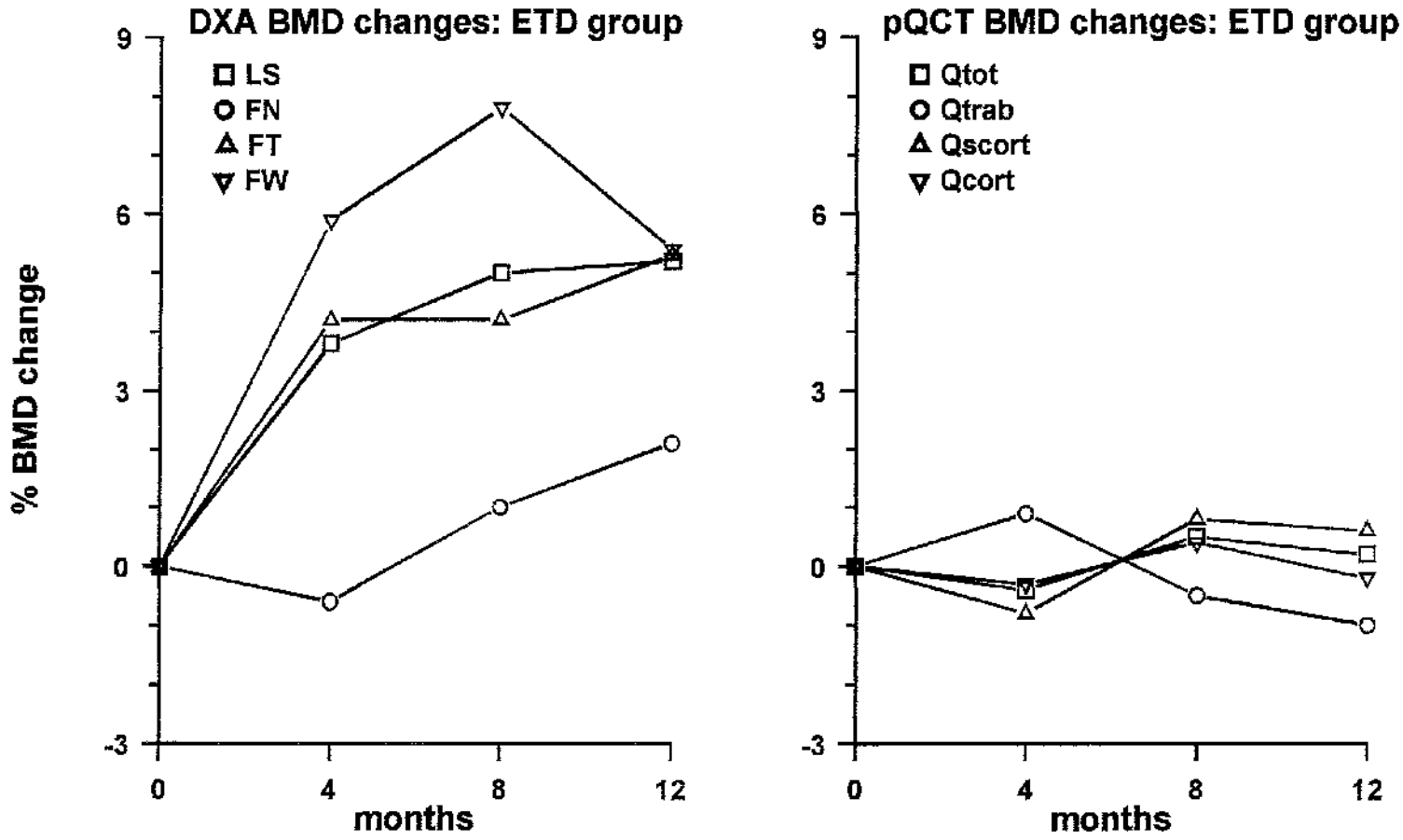
Fig 9.1: Percentage changes in pQCT and DXA BMD measurements with HRT



values are median % BMD changes

error bars not shown. See tables 9.3 and 9.4 for ranges

Fig 9.2: Percentage changes in pQCT and DXA BMD measurements with etidronate



values are median % BMD changes
error bars not shown. See tables 9.3 and 9.4 for ranges

CHAPTER 10

THE EFFECT OF LONGTERM WARFARIN THERAPY ON RADIAL AND AXIAL BMD.

10.1 Introduction

It is well recognised that heparin can cause bone loss (10.1). Warfarin is known to affect the development of foetal bone with stippled epiphyses and hypoplasia of the nose and extremities being observed in the off-spring of mothers treated during pregnancy (10.2,10.3). The effect of warfarin on adult bone is less well documented, but there is a suggestion that courmarins do have an adverse effect (10.4,10.5). In these previous studies reduced bone mass was found, but assessment was limited to the radius using SPA, and the more clinically important sites of hip and spine were not examined. Warfarin is thought to affect bone metabolism through its effect on osteocalcin, the non-collagenous bone matrix protein which is synthesised by osteoblasts and considered to be a marker of bone formation. Osteocalcin contains gamma-carboxyglutamic acid (gla), which is derived from glutamate through enzymic carboxylation (10.6), a process which requires vitamin K as a co-factor. Warfarin, by antagonising this vitamin K dependent process, results in increased decarboxylated osteocalcin, which is not incorporated into the bone matrix, but released into the circulation (10.7).

As warfarin is a commonly prescribed drug, any adverse effect on bone deserves further investigation. As previously stated, metabolic changes affect trabecular bone more rapidly than they do cortical bone. Therefore any effect of warfarin should be greatest within the trabecular component, and skeletal sites rich in trabecular bone. pQCT should therefore be valuable in assessing its effect on bone. The influence of warfarin upon BMD at the radius, was compared to that at the hip and spine in

a group of men taking longterm warfarin.

10.2 Study Population and Bone Mass Measurements

40 men taking longterm warfarin were recruited from the hospital anticoagulant clinic (WARFARIN group). The indications for anticoagulation were as follows: prosthetic heart valve replacement (HVR; n=16), atrial fibrillation (AF; n=13), bypass surgery for peripheral vascular disease (PVD; n=7), and recurrent venous thrombo-embolism (VTE; n=4). The degree of anticoagulation was determined by averaging the INR values at the anticoagulant clinic visits before and after the day of study. Controls were obtained from a search of hospital discharge summaries, clinic lists and surgical registers (CONTROL group). Each individual in the WARFARIN group was matched to a control for age (within 5 years). They were also matched for underlying disease so that individuals in the WARFARIN group with AF and PVD were matched to controls with the same condition but not requiring warfarin. Likewise those taking warfarin for HVR were matched to controls with HVR not requiring warfarin, although a small number of controls had undergone open heart coronary artery by-pass grafting rather than HVR. Those taking warfarin because of VTE were matched to controls who had undergone lower limb varicose vein surgery. All men were Caucasian and ambulatory. Individuals with underlying conditions or who were taking drugs (with the exception of thiazide diuretics) known to influence bone metabolism or bone mass were excluded. The controls for individuals in the WARFARIN group taking thiazide diuretics (n=4) were also matched for thiazide diuretic use. Thus the WARFARIN and CONTROL groups were stringently matched for factors which could influence BMD other than warfarin therapy.

All individuals attended for assessment on a single visit within a three week period. At this visit all medications,

including warfarin dose, were checked. Height, weight, smoking habit and alcohol consumption were recorded. A questionnaire about physical activity was completed which gave a composite score with a range of 5(most active) to 20 (least active). All men had BMD measurements at the radius by pQCT, and hip and spine by DXA.

10.3 Statistical Analyses

Results for continuous variables were expressed as the mean with standard deviation if the data were normally distributed, otherwise as the median with ranges. Between group comparison was performed using the unpaired t-test. Within group comparison of BMD data was performed using the Kruskal-Wallis test to examine the influence of indication for anticoagulation. In the WARFARIN group, the relationships between bone mass measurements and duration and degree of anticoagulation were examined using univariate regression analyses.

10.4 Results

Anthropometric, lifestyle and warfarin related data are shown in table 10.1. As might be expected from the matching process, there were only slight, and insignificant differences between the groups for anthropometric and lifestyle variables. One man had received warfarin therapy for 4 months, the remainder for more than 12 months. LS (1.061 ± 0.182 vs 0.95 ± 0.139 g/cm^2, p=0.003) and Qtrab (219.8 ± 37.1 vs 200 ± 39.8 g/cm^3, p=0.024) were significantly lower in the WARFARIN group. Whilst the remaining pQCT (Qtot: 398.7 ± 64.2 vs 376.7 ± 61.3 g/cm^3, Qscort: 533.3 ± 86.5 vs 509.8 ± 77.3 g/cm^3, and Qcort: 529.6 ± 70 vs 527.6 ± 61.3 g/cm^3) and DXA hip (FN: 0.817 ± 0.122 vs 0.801 ± 0.142 g/cm^2, FT: 0.794 ± 0.147 vs 0.748 ± 0.13 g/cm^2, and FW 0.587 ± 0.106 vs 0.571 ± 0.139 g/cm^2) were also lower in the WARFARIN group, the differences failed to reach statistical

significance. Figures 10.1 and 10.2 show the pQCT and DXA BMD data for both groups respectively. There were mean percentage differences of -10.4% and -9.0% for LS and Qtrab respectively. The percentage differences for all other measurements were lower: -5.5%, -4.4% and -0.4% for Qtot, Qscort and Qcort respectively; and -2%, -5.8% and -2.9% for FN, FT and FW respectively. Controlling for height, age and weight differences between groups did not significantly change the findings. There were no differences in BMD measurements within the subgroups of the WARFARIN group based upon indication for warfarinisation. Linear regression analyses of the WARFARIN group showed that there were no significant relationships between any of the BMD values and dose or duration of warfarin therapy, or with the degree of anticoagulation as indicated by the INR. These relationships with Qtrab and LS BMD are shown in figures 10.3 and 10.4 respectively. Unexpectedly, the slopes of the regression lines of duration of warfarin therapy versus LS and Qtrab BMD were both positive, but failed to reach statistical significance.

10.5 Discussion

These results show that males treated with longterm warfarin have lower BMD at the radius, spine and hip than age matched male counterparts. The greatest difference was found at the lumbar spine, where trabecular bone accounts for about 65% of the vertebral body bone mass (1.20). Trabecular BMD at the radius was affected to a similar extent, whilst there was very little difference in radial cortical BMD. This suggests that trabecular bone is preferentially affected by warfarin, no doubt due to its increased metabolic rate compared to cortical bone. This is in keeping with the effects of other drugs which have an adverse effect upon bone such as corticosteroids (10.8), and those which have a beneficial effect, such as HRT and etidronate (see chapter 9). Bearing in mind that the DXA

lumbar spine measurement is a composite measure of both trabecular and cortical bone, it is surprising that the difference at the spine was greater than that for the purely trabecular measurement at the radius. Differences in trabecular bone at the lumbar spine, which could be measured by QCT, would probably be greater than the difference detected by DXA in this thesis, and therefore also greater than that found at the radius. This suggest that bone at the radius is affected less than that at the spine. At the hip, the greatest difference was found for the femoral trochanter site which has a greater proportion of trabecular bone than the femoral neck (1.20). Whilst the femoral Ward's area is supposed to represent the most trabecular rich area within the proximal femur, poorer precision would explain why the difference at this site is less than other hip sites.

There were no significant relationships between duration or dose of warfarin, or degree of anticoagulation with BMD measurements at any site. The relationship between duration of warfarin therapy and lumbar spine and radial trabecular BMD appears to be a positive. However, the majority of men had been on warfarin for less than 160 months (range 4-302 months), with only 6 being on treatment for longer. It is possible that these 6 individuals are not representative of this population and may have skewed the data and resultant regression slope. Alternatively, the bone losing effect of warfarin may occur early in the course of treatment, as it does with corticosteroids (10.8). There are differences between the vitamin K antagonism on carboxylation in bone and liver (10.9) and it is possible that the antagonistic effect on bone occurs at doses lower than is necessary for anticoagulation. This may explain the lack of relationship between dose and INR with BMD measurements. The issues relating to duration, dose and INR would be better addressed in a prospective study with larger

numbers of subjects.

Men were chosen for the study group because the matching of individuals in the warfarin group with controls (for age, thiazide diuretic use and underlying disease) was considered to be very important. This would have been much more difficult had women been studied, as it would have been necessary to match for menopausal status and duration since the menopause as well. Matching individuals for underlying condition proved to be imperfect, as is illustrated by men taking warfarin for venous thromboembolism being matched to controls who had undergone varicose vein surgery. Such difficulties are probably of minor importance in this work, and are inevitable in cross-sectional designs.

The clinical importance of these findings are unclear at the present time, as there is no fracture incidence data available to date. However, a 10% reduction in BMD is equivalent to about 10 years of age related bone loss (8.40), and around 50% of the difference between postmenopausal and premenopausal women (10.10). It is also comparable to a fall in BMD of almost 1SD within the general population (10.11), which is associated with up to a three fold increase in fracture risk (6.10,10.12,10.13). In view of the increasing indications for anticoagulation, such as non-rheumatic atrial fibrillation and poor left ventricular function, perhaps the adverse effect on bone should also be considered when deciding to anticoagulate individuals, particularly those already at increased risk of osteoporosis, such as postmenopausal women.

Table 10.1 Anthropometric, lifestyle and warfarin related data for the WARFARIN and CONTROL groups.

	WARFARIN gp	CONTROL gp	p
Age (years)	64.2 (7.1)	64.9 (6.7)	NS
Height (m)	1.702 (0.062)	1.703 (0.081)	NS
Weight (kg)	76.5 (12.4)	77.1 (11.7)	NS
Smoking (pack-years) §	26.5 (0-108)	23 (0-130)	NS
Alcohol (units/week) §	4 (0-30)	2.5 (0-28)	NS
Physical Activity Index	9.1 (2.9)	8.4 (2.7)	NS
Warfarin dose (mg)	4.9 (1.9)	-	
INR	2.7 (0.7)	-	
Warfarin Duration (months) §	40.5 (4-302)	-	

Values are mean (SD), except § which are median (range).

p-value is for the unpaired t-test, or the Mann-Whitney U test when the median (range) is expressed.

Fig 10.1: pQCT radial BMD measurements for WARFARIN and CONTROL groups

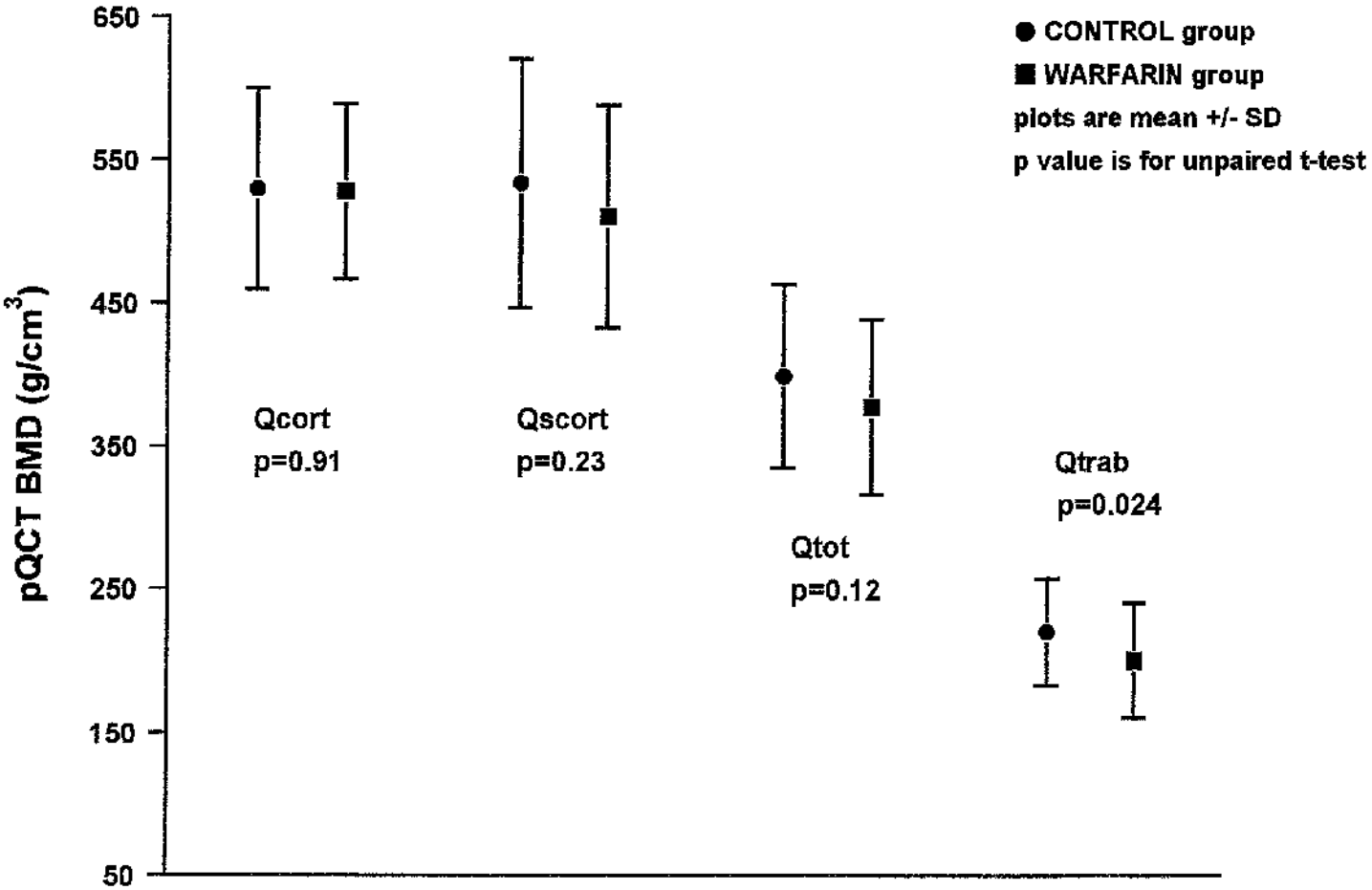


Fig 10.2: DXA hip and spine BMD measurements for WARFARIN and CONTROL groups

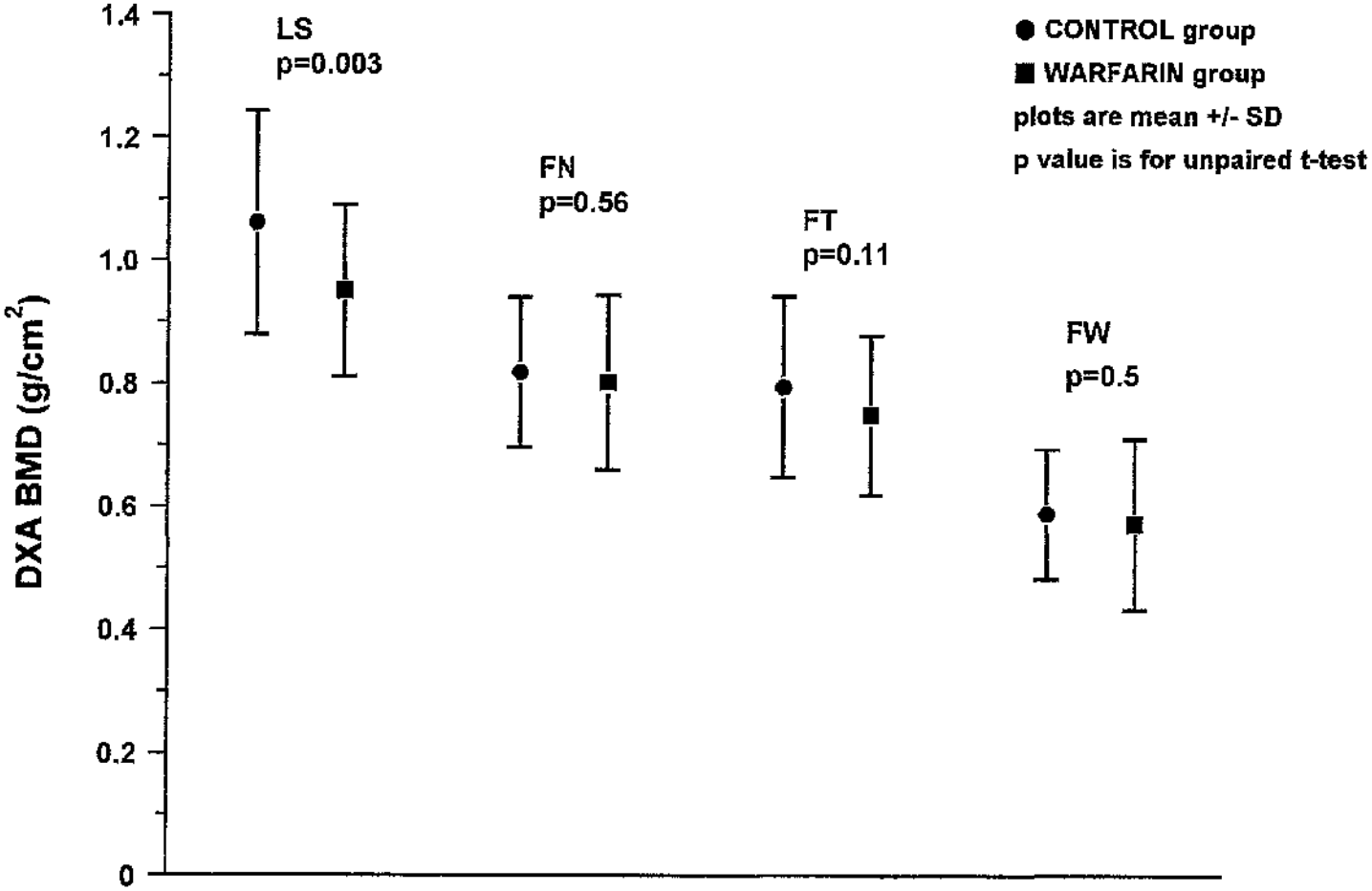
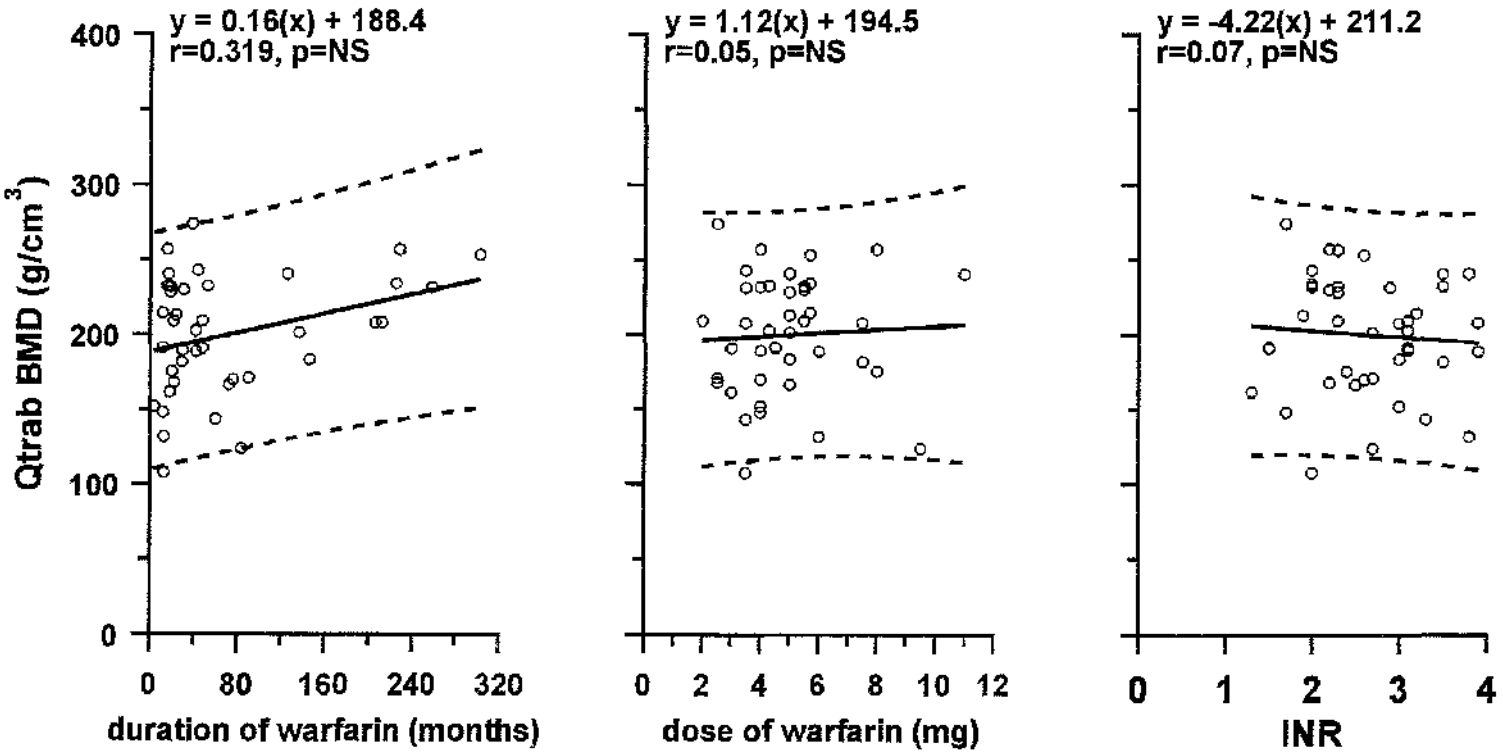
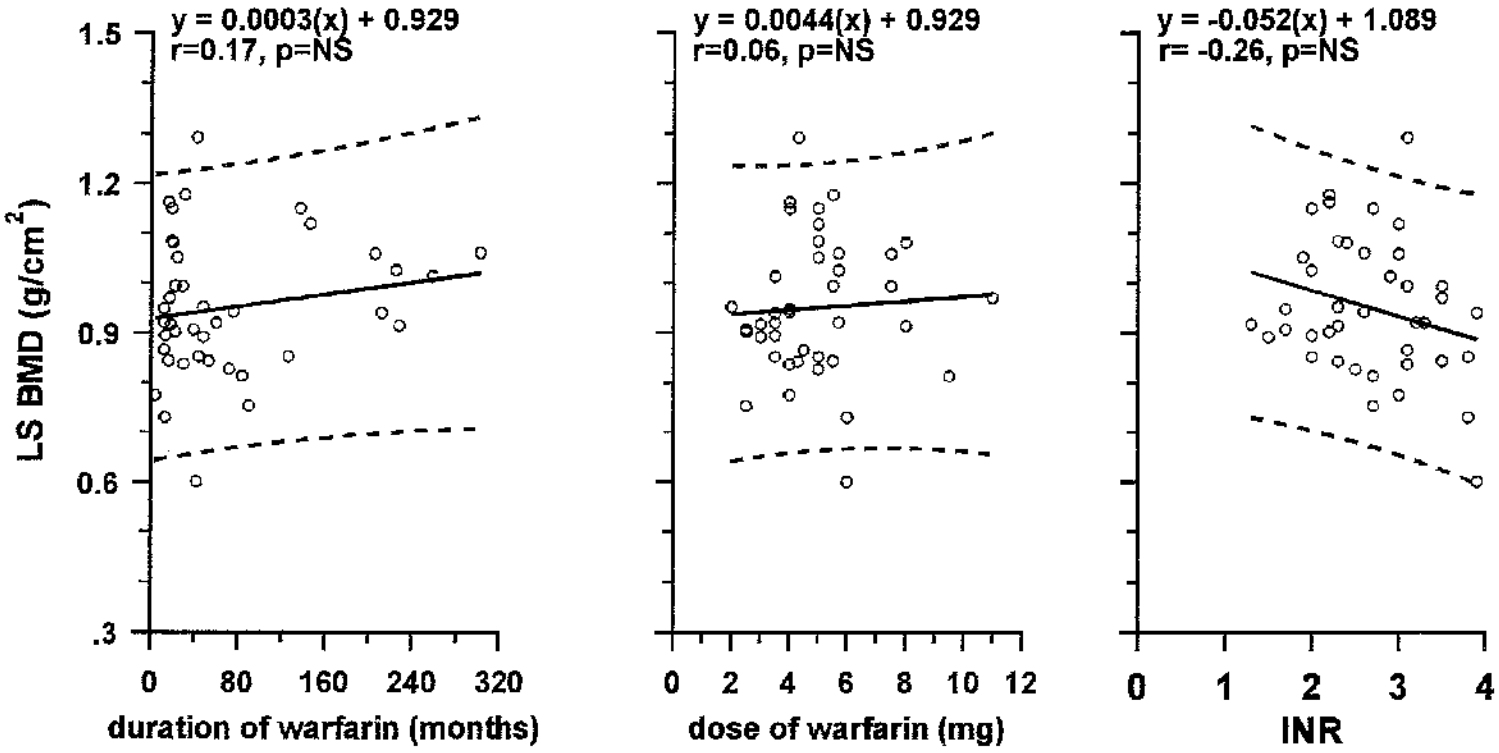


Fig 10.3: Relationships between Qtrab BMD and warfarin duration, dose and INR



95% confidence limits for regression equations shown

Fig 10.4: Relationships between LS BMD and warfarin duration, dose and INR



95% confidence limits for regression equations shown

CHAPTER 11

THE EFFECTS OF DISEASE AND CORTICOSTEROIDS ON APPENDICULAR BONE MASS IN POSTMENOPAUSAL WOMEN WITH RHEUMATOID ARTHRITIS: COMPARISON WITH AXIAL MEASUREMENTS

11.1 Introduction.

Reduced bone mass is a well recognised feature of rheumatoid arthritis (RA), with many studies showing reductions at both axial and appendicular sites (11.1). The effect of oral corticosteroid therapy on bone mass in RA is contentious especially at appendicular sites (11.2,11.3). There is evidence to support the concept of generalised bone loss (11.4,11.5), but controversy exists about the distribution and degree of bone loss, and the relative contribution of immobility, low dose corticosteroids and the systemic effects of RA (11.3-11.8).

The pQCT measurement scan occurs at the ultra-distal radius in close proximity to the carpus. As the carpus is frequently involved in RA, and periarticular bone loss is a characteristic feature, pQCT seems an ideal technique to study periarticular bone changes related to RA. Additionally, trabecular bone is metabolically more active than cortical bone, and therefore may be more responsive to stimuli such as corticosteroid therapy (11.9), which is used to treat a proportion of patients with RA. Accordingly, by quantifying trabecular bone, pQCT may be able to differentiate the effects of RA disease activity and corticosteroid therapy on bone at the radial site.

The ankle and subtalar joints are also frequently involved in RA. One might therefore expect the os calcis, which is also a trabecular rich bone (1.21), to be affected in a similar manner to the distal radius by local inflammatory processes and

corticosteroid therapy. It would of interest to determine how calcaneal ultrasound measurements are affected by RA, and how such changes relate to those found with pQCT.

The relative importance of corticosteroids, disease parameters and life style on bone mass in postmenopausal women with RA, were examined using pQCT, and compared with ultrasound, and DXA of hip and spine.

11.2 Study Population, Clinical Assessments and Bone Mass Measurements

11.2.1 Study Population

75 ambulatory, Caucasian, postmenopausal women were studied. The control group comprised of 29 previously normal postmenopausal women, the recruitment of which is discussed in chapter 5 (5.2.point 3). The remaining 46 women had suffered from RA (as defined by the American College of Rheumatology) (11.10) for at least 6 months and were recruited from out-patient clinics and a casenote review. 25 of the RA women had been on longterm low dose prednisolone therapy (≤ 10mg/day) for at least 6 months (RA+P group). The remaining 21 had never received oral corticosteroids (RA group). Patients who had received intra-articular steroid were not excluded. Subjects with abnormal renal function (serum creatinine >140 μmol/l) or other conditions known to affect bone metabolism were excluded as were individuals taking drugs such as HRT and bisphosphonates. Patients on thiazide diuretics were not excluded. Each individual had all assessments performed on the same day.

11.2.2 Clinical Data

Data collected included age, height, weight, years since

menopause, smoking history (cigarettes/day) and alcohol consumption (units/week). Dietary calcium intake (mg/day) was determined by a locally derived questionnaire, and level of physical activity by the Framingham questionnaire. All individuals underwent lateral thoracolumbar spine x-ray (T4-L5) and fractures were noted (defined as a reduction of 25% in anterior, mid or posterior vertebral body height).

RA patients completed a health assessment questionnaire (HAQ). Articular index (painful joint count only), mean grip strength of three measurements of right and left hands (mm Hg), visual analogue pain score (150mm horizontal line) and the time taken to walk 15 meters on level ground were recorded. X-rays of hands and wrists were scored using the Larsen method. Serum C-reactive protein and rheumatoid factor were measured using standard laboratory methods.

11.2.3 Bone Density Measurements

pQCT was performed at the ultra-distal radius of the non-dominant forearm. The effect of RA on in-vivo short-term precision is discussed in chapter 3. Briefly, precision measurements [expressed as the coefficient of variation (CV)] are poorer in the RA population compared to young normals (1.24% vs 1.6%, 1.33% vs 4%, 1.58% vs 1.84% and 1.88% vs 2.8% for Qtot, Qtrab, Qscort and Qcort respectively). pQCT was not possible in one RA subject due to bilateral wrist surgery. Ultrasound of the non-dominant os calcis was performed, but due to machine servicing, ultrasound data is missing from 7 controls and 1 RA subject. DXA hip and spine measurements were performed using a single scanner. Hip measurements were not possible on one RA+P subject due to bilateral hip replacements. Fractured vertebrae within the DXA spinal region of interest were excluded from the analysis. The effect of RA upon precision values of ultrasound and DXA hip and spine

measurements was not studied.

11.3 Statistical Analyses

Results for continuous variables were expressed as the mean with standard deviation if the data were normally distributed, otherwise as the median with ranges. Categorical data were examined using the Chi squared (χ^2) test. Variables common to all three groups were compared using the oneway analysis of variance (ANOVA) or Kruskal-Wallis where appropriate. Subsequent comparisons among groups were performed through the use of Scheffe's multiple comparison test. Variables relevant only to the RA groups were compared using the unpaired t-test or Mann-Whitney U test. Bone measurements across groups were examined having corrected for the influence of age, height, weight and years postmenopause by analysis of covariance with subsequent multiple comparison testing among groups. The independent relationships between corticosteroid use, RA variables, life-style variables and bone mass measurements were examined using Pearson correlation co-efficients and stepwise multiple regression analysis.

11.4 Results

Detailed clinical data for the three groups are given in Table 11.1. There were no significant differences in age, years postmenopause, height, weight, smoking habit or dietary calcium among groups, although the RA+P group was slightly heavier and more years postmenopause than the others. A greater proportion of the control group consumed alcohol than either RA group, although the amount consumed was not significantly different ($p=0.16$; Kruskal-Wallis). The physical activity index was significantly higher in the control group compared to either RA group, but not significantly different between RA groups. Thiazide diuretic use was similar for the combined RA groups and control group. 17 (81%) of the RA group and 19 (76%) of the

RA+P group were taking disease modifying agents (sulphasalazine, auranofin, hydroxychloroquine, penicillamine, myocrisin, methotrexate or azathioprine). The median disease duration was 4 years greater in the RA+P group (p=0.24, Mann-Whitney U test) and although there was a trend toward worse disease parameters in the RA+P group, significance was reached only for the HAQ. There were more vertebral fractures in the RA groups than controls, although the difference was not significant.

Bone mass measurements are shown in figures 11.1 - 11.3. There were significant reductions in both RA groups compared to the control group for all measurements except the lumbar spine and forearm subcortical and cortical BMD. Although Qscort was lower in both RA groups compared to the control group, this reached significance only for the RA+P group. pQCT BMD measurements were (control vs RA vs RA+P; overall ANOVA p value: Qtot: 340.6 +/- 67.1 vs 289 +/- 67 vs 285.9 +/- 89.7 g/cm^3; p=0.016, Qtrab: 174.2 +/- 40 vs 111.8 +/- 52.6 vs 111 +/- 63 g/cm^3; p=0.001, Qscort: 466.9 +/- 92.8 vs 413.4 +/- 72.6 vs 393 +/- 102.3 g/cm^3; p=0.009, Qcort: 495.2 +/- 89.3 vs 518.6 +/- 66.8 vs 498 +/- 97.2 g/cm^3; p=NS). Ultrasound measurements were (control vs RA vs RA+P; overall ANOVA p value: BUA: 68.7 +/- 13 vs 49.5 +/- 17 vs 44.6 +/- 20.5 dB/MHz; p=0.001, VOS: 1517 +/- 51.2 vs 1428 +/- 36.9 vs 1408 +/- 40.8 m/s; p=0.001). DXA BMD measurements were (control vs RA vs RA+P; overall ANOVA p value: LS: 0.89 +/- 0.16 vs 0.85 +/- 0.21 vs 0.82 +/- 0.18 g/cm^2; p=NS, FN: 0.78 +/- 0.14 vs 0.68 +/- 0.15 vs 0.65 +/- 0.11 g/cm^2; p=0.002, FT: 0.61 +/- 0.12 vs 0.55 +/- 0.15 vs 0.52 +/- 0.11 g/cm^2; p=0.012, FW: 0.56 +/- 0.14 vs 0.45 +/- 0.14 vs 0.47 +/- 0.08 g/cm^2; p=0.007). Differences persisted after adjustment for the influence of age, height, weight and years postmenopause. There were no significant differences between the RA groups for any bone mass measurement. Combining the RA groups, the percentage

difference in bone mass compared to controls was -36.1%, -15.6%, -8.4% and +2.4% for forearm trabecular, total, subcortical and cortical measurements respectively, -31.7% and -6.6% for calcaneal BUA and VOS respectively, -15.4%, -13.1% and -17.9% for femoral neck, trochanter and Ward's area respectively, and -6.7% for the lumbar spine.

Stepwise multiple linear regression analyses on the whole population are shown in table 11.2. Weight was positively correlated with lumbar spine and hip BMD, radial trabecular BMD and ultrasound measurements. Physical activity was positively correlated with lumbar spine and hip BMD. The independent variable RA (coded 0=no, 1=yes) was negatively correlated to radial total, trabecular and subcortical BMD, calcaneal ultrasound measurements and femoral neck and trochanter BMD. Years postmenopause was negatively correlated with radial total, subcortical and cortical BMD. Age was negatively correlated with femoral trochanter BMD. Introducing RA disease variables into the regression analyses for the combined RA group showed that the Larsen score (LARS) was negatively correlated with BUA [BUA = 86.25 - 1.04(LARS); R^2=0.485, F Sig <0.0001], VOS [VOS = 1472.1 - 1.45(LARS); R^2=0.185, F Sig = 0.0037], Qtot [Qtot = 347.2 - 1.852(LARS); R^2=0.093, F Sig =0.0348] and Qtrab [Qtrab = 205.6 - 2.21(LARS) - 0.06(RhF), R^2=0.503, F Sig <0.0001], with rheumatoid factor titre (RhF) being negatively correlated with Qtrab. Table 11.3 shows the correlation coefficients of individual RA disease variables with pQCT and ultrasound measurements for the combined RA groups. The Larsen score for the non-dominant wrist and whole hand (wrist + MCP's + PIP's) was negatively correlated with Qtrab, BUA and VOS, whilst the Larsen score of the non-dominant wrist was positively correlated with Qcort. Rheumatoid factor titre was negatively correlated with Qtrab, BUA and VOS, whilst grip strength was positively correlated with Qtrab and BUA. The

significant linear regression relationships of Qtrab, BUA and VOS with RA disease variables are shown in figures 11.4 - 11.6 respectively.

11.5 Discussion

This study has demonstrated marked reductions in appendicular bone mass measurements in patients with RA using both pQCT and ultrasound. Some appendicular measurement changes were more marked than those noted at the femoral neck and lumbar spine, with the changes at the latter site being insignificant in this small study.

pQCT measurements were difficult in a small number of patients with RA, and the precision of pQCT is poorer in this population. There are several reasons for this, which are discussed in chapter 3 - namely a lower mean BMD value in RA patients, and difficulty visualising the radio-carpal joint during the scout scan in patients with more severe RA where the normal anatomical landmarks are distorted. However, unless there is severe destruction and resorption of the distal radius and ulnar, measurement scans in the RA population should be in a position similar to those of the control group. In this study, pQCT trabecular and total BMD measurements were marked reduced in the RA groups (36.1% and -15.6% respectively) compared with controls, with very little difference between the RA groups. These data are in keeping with previous studies examining radial bone loss in patients with non-steroid treated RA using pQCT (11.11,11.12). There are however some important differences between the studies. The previous longitudinal studies examined premenopausal and postmenopausal women with early (< 3 years) RA, whilst the cross-sectional study population reported in this thesis is purely postmenopausal with longer and variable disease duration. The pQCT scanners used also differed. An ^{125}I rather than x-ray radiation source

was used previously, trabecular BMD was measured at the 8-10%, and cortical BMD at the distal 1/3 site (rather than the 4% site here). As the proportion of trabecular and cortical bone changes dramatically over short distances at the distal radius (1.17,1.19), these are important differences. Nevertheless, annual rates of loss up to 25% were recorded for trabecular BMD, whilst cortical BMD changes were similar to the control group (11.11), results similar in distribution and magnitude to ours. Rapid trabecular bone loss at the radius occurs early in the disease process with subsequent slowing (11.12). In view of the substantially lower trabecular BMD found in the RA groups, the data presented here would suggest that there is considerable ongoing bone loss beyond this initial period of rapid loss, although this would be better addressed by a longterm longitudinal study. The strong correlation of whole hand and wrist Larsen scores with trabecular BMD suggests that local inflammatory mechanisms responsible for joint damage, and resultant wrist immobility have important adverse effects on ultra-distal radial bone mass, as found previously (11.13). An increasing rheumatoid factor titre was negatively correlated to trabecular bone, which may be related to more aggressive local disease in such individuals. The correlation of grip strength with trabecular BMD supports the concept that mechanical loading and stimulation has a beneficial effect upon local bone mass (4.2). In this case, it is detectable within the trabecular component, which being more metabolically active, is more responsive to such stimuli.

As corticosteroid induced bone loss preferentially affects trabecular bone, one might expect pQCT to be a sensitive technique for detecting such an effect. However, it is apparent that there is no significant corticosteroid effect on any of the forearm BMD measurements, even within the trabecular component. The subcortical measurement was significantly lower

in the steroid treated RA group, but not the non-steroid treated RA group compared to controls, but there was no significant difference between the RA groups. The lack of corticosteroid effect is almost certainly due to the juxta-articular, inflammatory driven bone loss (11.14) overwhelming other mechanisms affecting trabecular bone at this site. The radial measurement site is therefore an important consideration. That for SPA is more proximal than pQCT, and as such is further removed from the inflammatory process occurring at the wrist. The effect of corticosteroid could therefore be more pronounced at a more proximal site, which might explain why some have found significantly lower radial bone mass in patients with corticosteroid treated RA (11.2). In keeping with the results reported above, others found no significant corticosteroid effect at the radius (11.3,11.15).

Similarly, immediate postmenopausal bone loss preferentially affects trabecular rather than cortical bone, yet the duration since menopause was negatively correlated with total, subcortical and cortical, but not trabecular BMD. Presumably this is also due to the periarticular inflammatory process overwhelming menopausal effects on trabecular bone, but having much less effect upon cortical bone, which is metabolically less active. Cortical bone comprises 55% of the pQCT total BMD measurement which explains the relationship of duration since the menopause with the latter BMD. Cortical bone is also known to undergo postmenopausal as well as age related change (1.51), as is the pQCT subcortical measurement as discussed in chapter 7.

There were no difficulties in performing ultrasound of the os calcis in these RA patients as the foot recess was wide enough to accommodate broad feet, and application of the transducers was not impaired by the degree of subtalar deformity. There

were reductions in ultrasound attenuation and velocity of -31.7% and -6.6% respectively in the combined RA group, again with no additional significant steroid effect. Weight was an important determinant of ultrasound measurements as was the Larsen index in the RA groups. The latter finding is particularly intriguing as the Larsen index was measured at the hand and wrist. The same inflammatory mechanisms causing bone loss at the wrist may well effect the trabecular rich os calcis, explaining the correlation between the Larsen index at the wrist and the ultrasound measurements at the os calcis. As for radial trabecular BMD, and presumably for the same reason, both calcaneal ultrasound measurements were negatively correlated with a rising titre of rheumatoid factor. It is difficult to explain the correlation between grip strength and BUA, but this may well reflect similar long-term disease activity in the hands and feet in this group of patients.

There have been many previous studies addressing axial BMD in RA, and these have been reviewed recently (11.1). DXA measurements were included here to allow comparison with pQCT and ultrasound within the same population. A significant reduction in femoral neck BMD of 12.8% (0.71 SD) and 15.4% (0.93 SD) in the RA and RA+P groups respectively, with no significant corticosteroid effect is in keeping with most of the present literature (11.6,11.7,11.8,11.15,11.16). Such reductions are associated with an increased risk of future hip fracture (1.192), which has been recently demonstrated in the RA population (11.17). Weight and physical activity were important determinants of hip BMD in keeping with previous work (11.7,11.8), suggesting that patient mobility helps maintain hip BMD.

The 4.5% and 7.9% reductions in lumbar spine BMD for the RA and RA+P groups respectively failed to reach significance and are

smaller than those recorded at the hip, radius and calcaneus. Although the groups were well matched for age, we cannot exclude age and fracture related spinal osteoarthrosis influencing our spinal BMD results (1.171-1.177). Interpretation of the lumbar spine results in the light of previous work has to be cautious because of differences in measurement techniques, study populations and dose of corticosteroid. In those studies which examined postmenopausal women, Hall et al studied larger numbers and found a larger and significant difference of 7.5% between control and non-steroid treated RA groups (11.8). Although a significant difference of 6.5% was found between steroid and non-steroid treated RA groups, the difference was smaller (4.3%), and non-significant when a subgroup with a lower cumulative dose of corticosteroid was examined. Verstraetaen et al studied the effect of higher dose prednisolone in women with much longer disease duration than their non-steroid treated counterparts (11.3). Also, rather unusually, lumbar spine BMD was much higher in the non-steroid RA group compared to control group, suggesting that either the RA or control group was non-representative. Using QCT, Laan et al found a reduction of 34.7% in lumbar spine trabecular BMD in a low dose steroid-treated RA group compared to a non-steroid treated group (11.18), which is much greater than that reported here. However, QCT measures purely trabecular bone, whereas DXA measures a composite of cortical and trabecular bone, and as such, the techniques are clearly not comparable. In patients with RA, one would not expect differences in radial trabecular BMD (as measured by pQCT) to be comparable to differences in spinal trabecular BMD (as measured by QCT), as the spine is far removed from the periarticular inflammatory process which profoundly influences radial trabecular BMD. Also, there is poor correlation between radial and axial BMD in the general population (11.19, see chapter 6). Compared to controls, Lane et al (11.15) found DXA

lumbar spine BMD 8.4% lower in non-steroid treated RA patients, but a non-significant difference for steroid treated patients, although the steroid treated group was small (n=13 for LS BMD measurements). The greater difference in lumbar spine BMD for the non-steroid treated group in comparison to the results presented here, can be explained by the longer duration of RA (mean: 24.5 yrs) in the group studied by Lane et al. Others have examined populations which differed in gender and menopausal status (1.131,11.6,11.7,11.16), or studied the effect of higher dose corticosteroid (11.3,11.7,11.8,11.16) which makes direct comparison with the results reported here difficult. An increased prevalence of vertebral fracture has been demonstrated in steroid treated postmenopausal women with RA (11.20), although there was no non-steroid treated RA group for comparison. The increased prevalence was greater than expected from DXA spinal BMD differences, suggesting a steroid effect on bone architecture as well as mass.

This study has highlighted important changes in appendicular bone mass in RA. There is now good evidence that bone loss occurs early in RA at the radius (11.11,11.12), hip and spine (11.4), with axial bone loss being related to disease and physical activity (11.4). Recently there has been interest expressed in measuring appendicular BMD as a method of monitoring disease activity in RA (11.1,11.21). pQCT and calcaneal ultrasound, by quantifying trabecular bone adjacent to the carpus and ankle respectively, offer novel and unique opportunities to study the effect of RA on periarticular bone, and may be valuable methods of monitoring response to treatments such as disease modifying anti-rheumatic drugs and corticosteroid. Further work is necessary to examine the clinical use of pQCT and ultrasound in RA.

Table 11.1. Characteristics of the control, rheumatoid arthritis (RA) and steroid treated rheumatoid arthritis (RA+P) groups.

	RA + P (n = 25)	RA (n = 21)	Controls (n = 29)	Overall p-value
Age (years)	65.1 (6.3)	64.1 (6.4)	63.8 (6.3)	n.s.
Height (m)	1.59 (0.07)	1.58 (0.05)	1.57 (0.06)	n.s.
Weight (kg)	66.2 (12.2)	63.5 (11.2)	62.6 (10.2)	n.s.
Years since menopause	18.0 (8.3)	17.5 (7.2)	14.9 (9.2)	n.s.
Physical activity index	28.7 (2.7) **	29.2 (2.5) *	31.2 (1.5)	0.0002
Dietary calcium intake (mg/day)	706.5 (369.1)	835 (165.6)	836 (232.8)	n.s.
Number (%) of smokers	8 (32)	6 (28.6)	5 (17.2)	n.s.
Number (%) who drink alcohol	5 (20)	2 (9.5)	19 (65.5)	0.01
Number (%) on thiazide diuretics	2 (8)	1 (4.8)	3 (10.3)	n.s.[1]
Number (%) with vertebral fractures	5 (20)	5 (23.8)	1 (3.4)	n.s.
Disease duration, years §	12 (2-30)	8 (2-35)		n.s.
Health assessment questionnaire	1.95 (0.69)#	1.4 (0.77)		0.014
15m Walking time, secs	16.9 (6.6)	16.8 (13.2)		n.s.
Ritchie articular index	11.0 (8.3)	9.6 (8.1)		n.s.

Table 11.1 (cont). Characteristics of the control, rheumatoid arthritis (RA) and steroid treated rheumatoid arthritis (RA+P) groups.

	RA + P (n = 25)	RA (n = 21)	Controls (n = 29)	Overall p-value
Mean grip strength, mmHg	90.5 (41.4)	111.3 (44.4)		n.s.
Visual analogue pain score, mm	54.0 (32.3)	55.4 (43.4)		n.s.
Mean Larsen score	41.4 (13.8)	34.1 (13.5)		n.s.
Number (%) Rheumatoid Factor +ve	21 (84)	10 (47.6)		0.006
C-reactive protein, mg/dl	1.94 (1.83)	1.41 (1.79)		n.s.
Daily prednisolone dose, mg §	6.5 (2.5-10)			
Cumulative prednisolone dose, grams §	8.21 (1.8-65.2)			
Prednisolone duration, years §	4.0 (1-21)			

Unless otherwise stated, values are mean (SD) and § median (range) .
Continuous variables compared by ANOVA (* $p<0.05$, ** $p<0.001$ versus controls: Scheffe's multiple comparison test) and unpaired t-test (# $p<0.05$ versus RA group).
Categorical variables compared by χ^2 test ($^{(1)}$ = Fisher exact χ^2 test after compression of (RA) & (RA+P) groups into a single group).

Table 11.2. Important determinants for bone mass measurements at the ultra-distal radius, os calcis, lumbar spine and hip as determined by stepwise multiple linear regression of data from all subjects.

Qtot BMD	= -48.48(RA) - 2.123(PMYR) + 372.2	(R^2=0.145, Sig F =0.0017)
Qtrab BMD	= 1.098(wt) - 63.83(RA) + 105.5	(R^2=0.283, Sig F <0.0001)
Qscort BMD	= -57.88 (RA) - 3.36 (PMYR) + 516.9	(R^2=0.190, Sig F =0.0002)
Qcort BMD	= -4.96(PMYR) - 10.44(PAQ) + 894.59	(R^2=0.184, Sig F =0.0003)
BUA	= 0.748(wt) - 24.55(RA) + 22.99	(R^2=0.403, Sig F <0.0001)
VOS	= 1.316(wt) - 106.03(RA) + 1436	(R^2=0.571, Sig F <0.0001)
LS BMD	= 0.007(wt) + 0.015(PAQ) - 0.05	(R^2=0.228, Sig F <0.0001)
FN BMD	= 0.003(wt) + 0.022(PAQ) - 0.073(RA) - 0.157	(R^2=0.385, Sig F <0.0001)
FT BMD	= 0.005(wt) + 0.018(PAQ) - 0.057(RA) - 0.264	(R^2=0.387, Sig F<0.0001)
FW BMD	= 0.024 (PAQ) - 0.21	(R^2=0.178, Sig F=0.0001)

wt = weight, PAQ = physical activity, RA = Rheumatoid Arthritis (coded 0=no, 1=yes)

PMYR = years postmenopause,

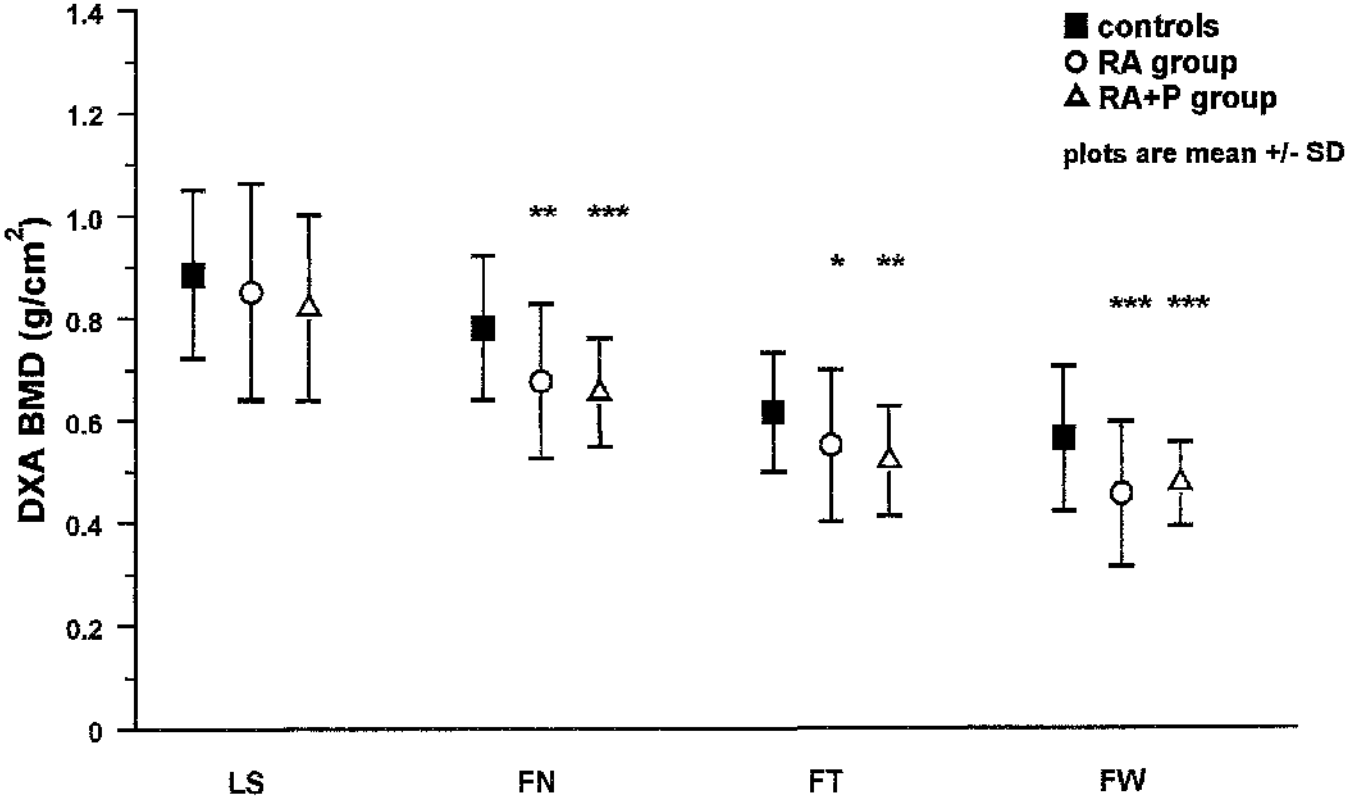
R^2 = adjusted R^2, Sig F = significance of regression equation

Table 11.3. Pearson correlation co-efficients for RA disease parameters and radial pQCT total (Qtot), trabecular (Qtrab), subcortical (Qscort) and cortical (Qcort) BMD measurements and calcaneal ultrasound attenuation (BUA) and velocity (VOS) for the combined steroid (RA+P) and non-steroid (RA) treated RA groups.

	Qtot	Qtrab	Qscort	Qcort	BUA	VOS
Years with RA	-0.06	-0.18	0.01	0.07	-0.09	-0.14
Years on prednisolone	0.01	0.06	-0.11	-0.13	-0.01	-0.23
Daily prednisolone dose	-0.08	-0.12	-0.13	-0.08	-0.2	-0.28
Cumulative prednisolone dose	-0.08	-0.02	-0.17	-0.15	-0.05	-0.21
Ritchie tenderness score	0	0.05	-0.02	-0.1	0.14	0.02
Grip strength (non-dominant hand)	0.1	0.35*	-0.08	0.02	0.33*	0.22
Visual analogue pain score	0.13	-0.11	0.21	0.22	-0.14	-0.08
Health assessment score	0.11	-0.19	0.15	0.23	-0.29	-0.23
Physical activity score	-0.04	0.19	-0.07	-0.19	0.29	0.19
C reactive protein	0.01	-0.18	0.02	0.06	-0.27	-0.12
Rheumatoid factor	-0.11	-0.44**	0.03	0.24	-0.45**	-0.36*
Larsen score (non-dominant hand)	-0.18	-0.63***	-0.07	0.25	-0.66***	-0.39*
Larsen score (non-dominant wrist)	-0.08	-0.55***	0.02	0.33*	-0.59***	-0.4**

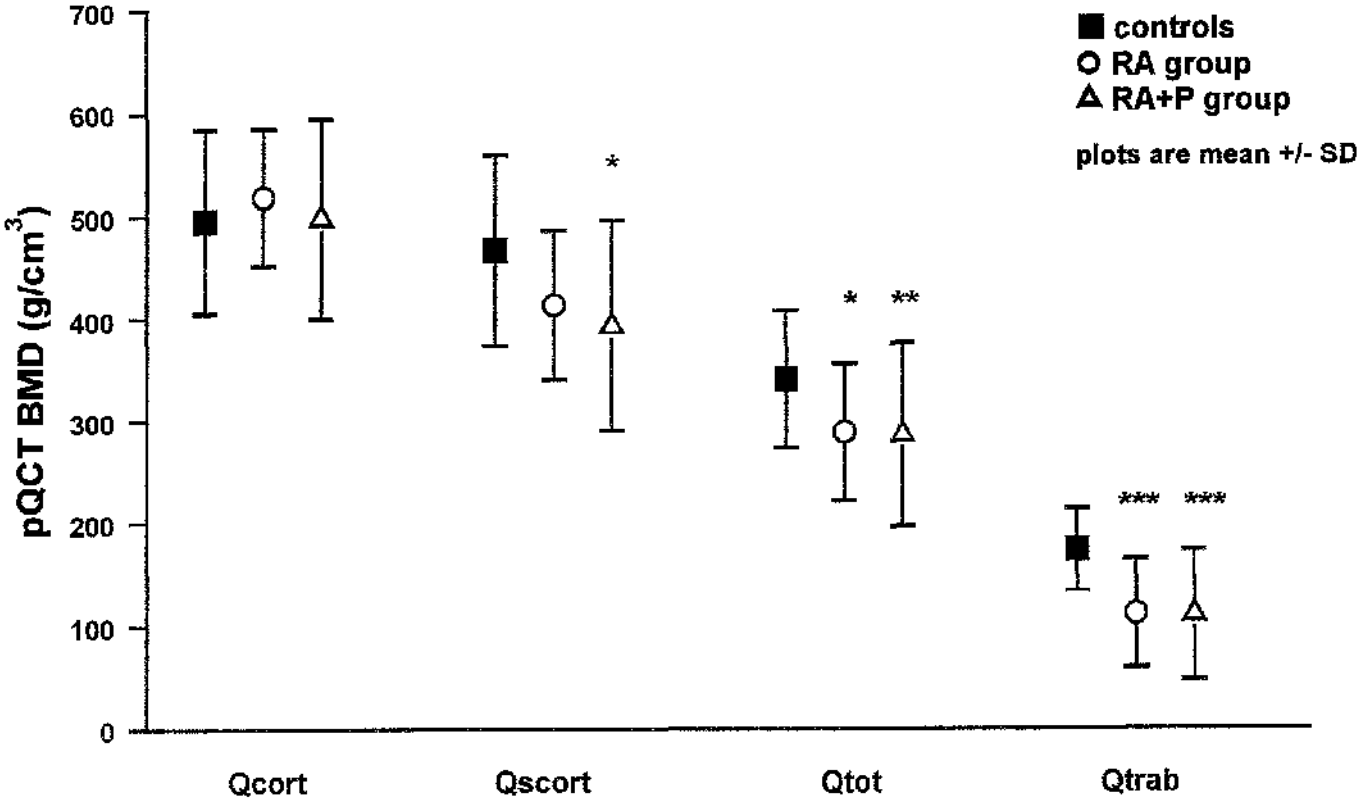
Significance values are: * 0.05>p>0.01, **0.01>p>0.001, ***p<0.001, otherwise not significant.

Figure 11.1: DXA hip and spine measurements for control, non-steroid (RA) and steroid treated (RA+P) RA groups



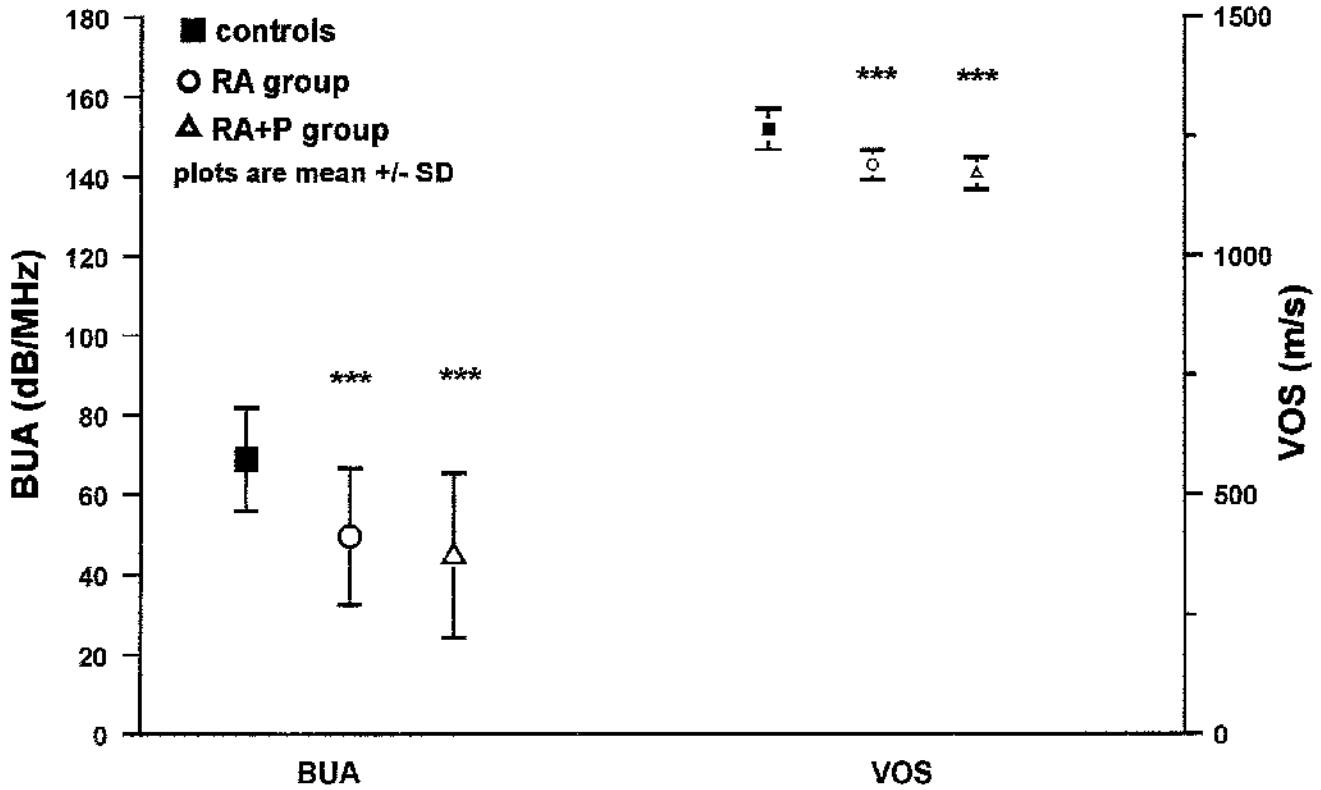
analysis of covariance multiple comparison test adjusting for age, height, weight and years postmenopause
* p<0.05, ** p<0.01, *** p<0.001 versus control group

Figure 11.2: pQCT measurements for control, non-steroid (RA) and steroid treated (RA+P) RA groups



analysis of covariance multiple comparison test adjusting for age, height, weight and years postmenopause
* p<0.05, ** p<0.01, *** p<0.001 versus control group

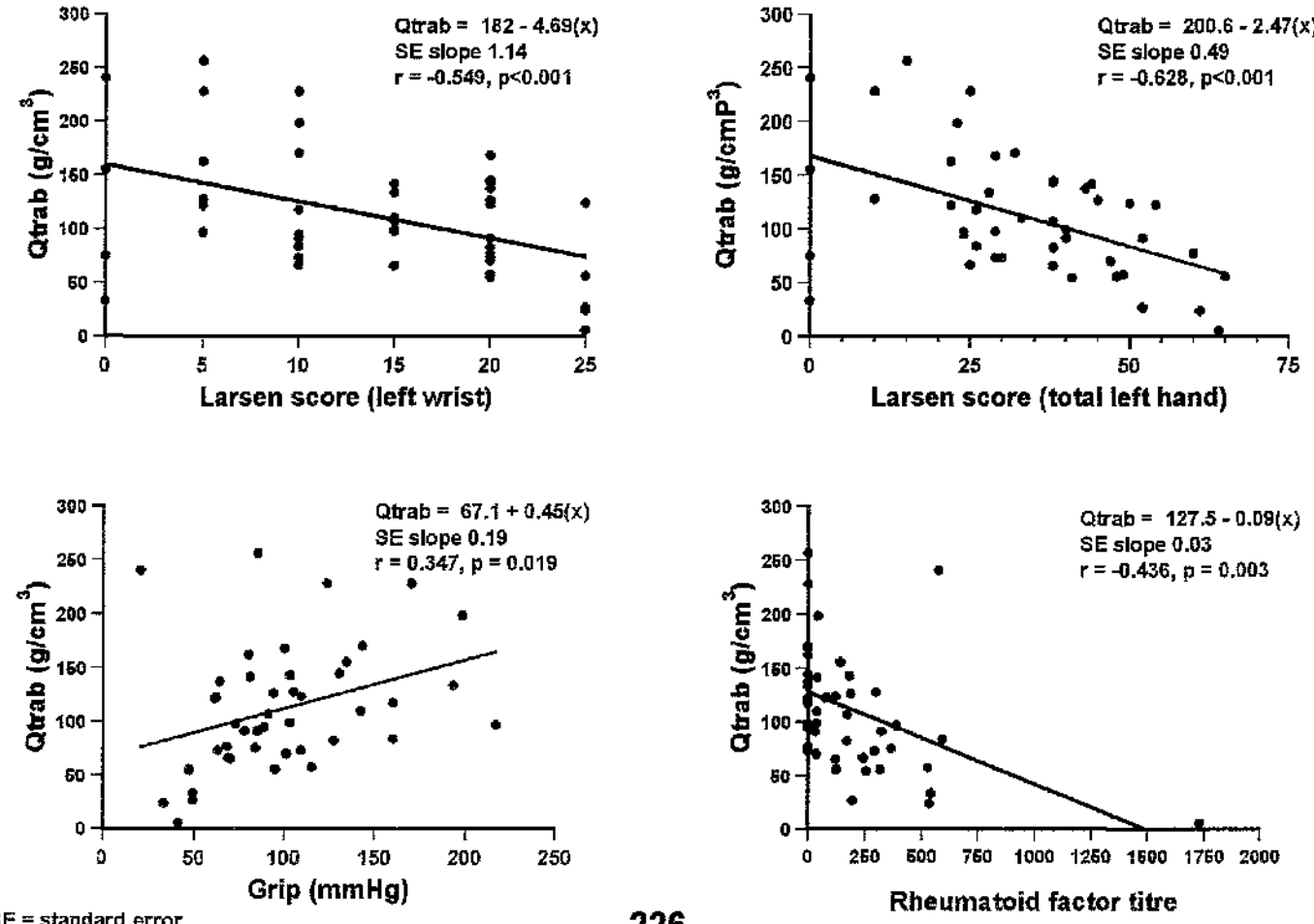
Figure 11.3: Ultrasound measurements for control, non-steroid (RA) and steroid treated (RA+P) RA groups



analysis of covariance multiple comparison test adjusting for age, height, weight and years postmenopause

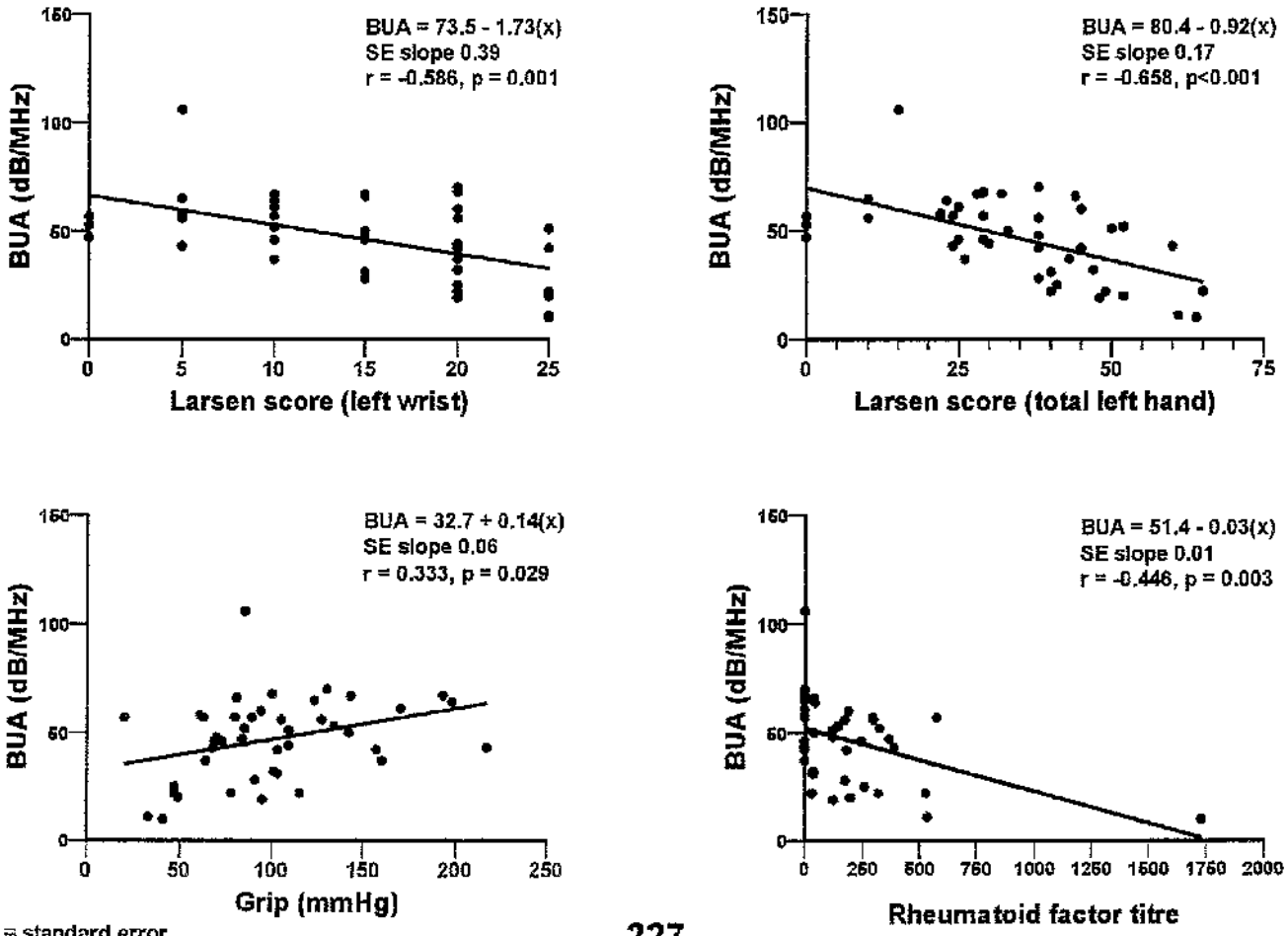
* p<0.05, ** p<0.01, *** p<0.001 versus control group

Figure 11.4: Relationships between Qtrab and disease variables for combined RA groups



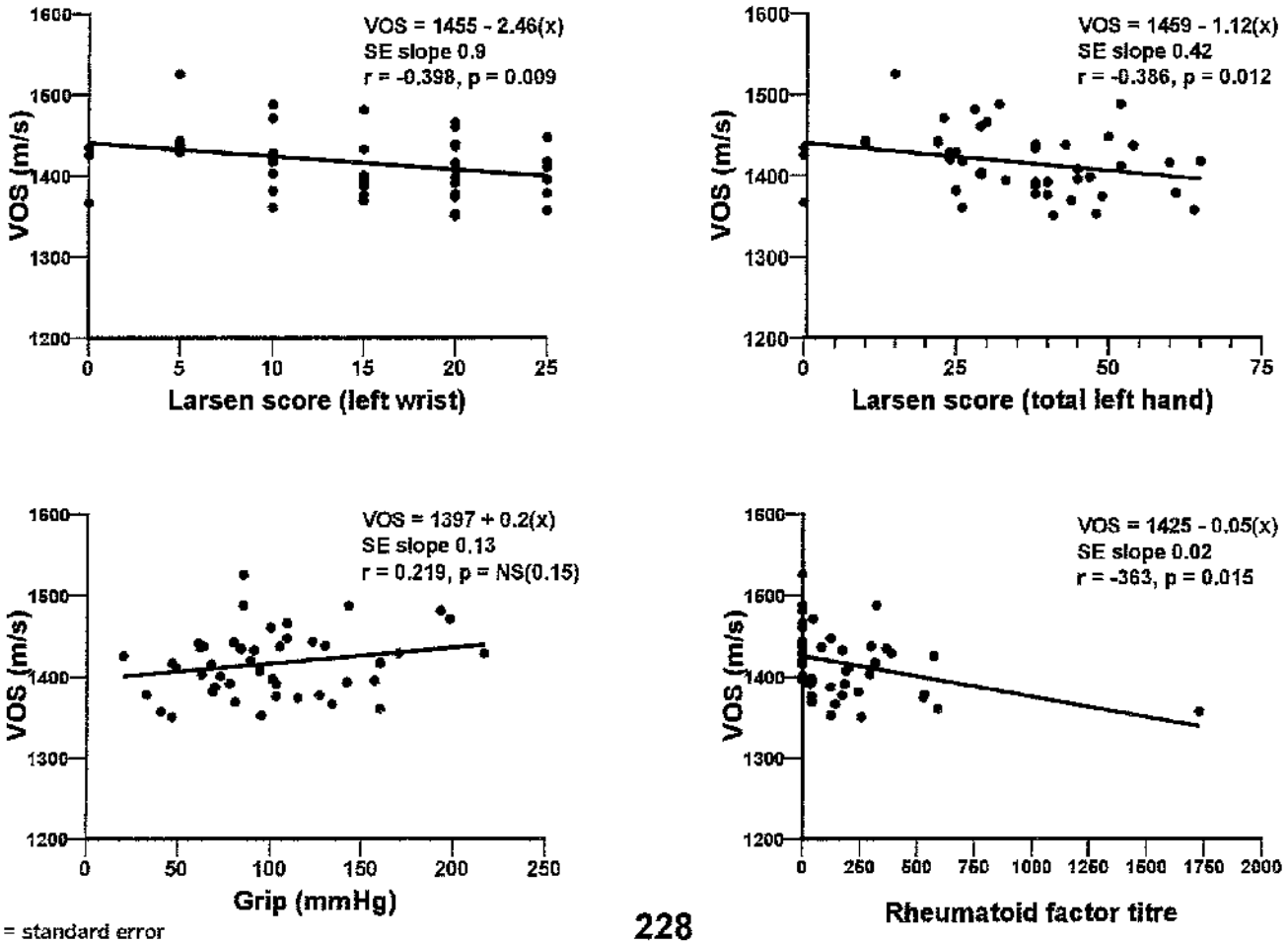
SE = standard error

Figure 11.5: Relationships between BUA and disease variables for combined RA groups



SE = standard error

Figure 11.6: Relationships between VOS and disease variables for combined RA groups



SE = standard error

CHAPTER 12

OVERALL CONCLUSIONS AND DISCUSSION.

Briefly, the aims of this thesis were to examine the use of pQCT in the field of osteoporosis. The precision of pQCT was studied in different populations. The effect upon precision of minimising the difference between scan voxel numbers in follow-up scans was also investigated. The effect of dominance in individuals of normal day-to-day activity was studied. Normative data from the local female population was obtained, from which, important anthropometric determinants were determined, and estimated rates of change derived. pQCT was variably compared to DXA measurements and calcaneal ultrasound in a number of different situations. These were: perimenopausal changes in BMD; the relationships with other bone mass measurements and the implications for screening; discrimination of vertebral and hip fracture populations from non-fracture controls; the effect of HRT and etidronate therapy upon BMD and the implications for monitoring treatment; the effect of warfarin upon BMD; and the effect of disease and low dose corticosteroid in postmenopausal women with rheumatoid arthritis.

The precision of the Stratec XCT 960 pQCT scanner was comparable to other scanning modalities such as DXA with precision values of 1-2%. Although less precise than the multi-slice pQCT technique, it is cheaper and more ubiquitous. The precision was found to be poorer in older postmenopausal women with vertebral fracture, and in women with rheumatoid arthritis It is likely that the precision of the Stratec XCT 960 pQCT system could be improved by increasing the number of scan slices, thus increasing the measurement sample size. However, this would result in a longer scan time, and consequently a greater chance of movement artifact. The local radiation dose

would also be increased, although this is unlikely to be a problem, as the radiation dose associated with the present system is so low.

Precision was shown to be influenced by the difference between voxel numbers of repeat scans, suggesting that scan voxel numbers can be used as a surrogate marker of cross-sectional area, and an aid to positioning during repeat scanning. This is an important consideration in repeat scanning of the ultra-distal radius, as absolute BMD, and the proportion of cortical and trabecular bone change significantly over short distances (1.16-1.19). With the present Stratec system, beyond standardization of the scanning technique, further improvement in precision is possible by limiting the difference in voxel numbers between repeat scans. At the present time, a difference of 30 voxels or less is recommended from the work presented in chapter 3. However, this should be further validated, for example, by an in-vitro cadaveric study. Dominance influenced radial BMD by only 1-2% in individuals of normal physical activity. Although not statistically significant, it does have important clinical implications. A lack of consistency with respect to which forearm is scanned, would introduce a further 1-2% variance in BMD measurements. It was our policy therefore, to always scan the non-dominant forearm unless there had been a previous Colles fracture, and to always scan the same forearm in longitudinal studies.

The importance of acquiring a normal range based upon the local population was shown in chapter 5. BMD values of the normal range derived from the Grampian region of Scotland were greater than those of the manufacturers and a previously reported German population (1.50). The population sample was somewhat lacking in numbers in the 30-39 years age group, which unfortunately negates any meaningful attempt to address the

issue of timing of peak bone mass. Not surprisingly, age was negatively correlated with all pQCT BMD measurements in multiple regression analyses. Weight was found to be positively correlated, inspite of the radius being a non-weight bearing site. The negative correlation for height with total and trabecular BMD measurements is surprising, but may indicate that taller women have thinner radii.

The cross-sectional pQCT data presented in this thesis indicates that radial BMD was stable from the age of 18 years until the menopause, which is inkeeping with almost all of the previous literature(1.50,1.51,1.63,1.68,1.69,1.70,1.78,1.79). However, the longitudinal data from 23 normal premenopausal women (mean age 47.2 year, range 46-54 years) showed a significant decrease in total and subcortical BMD (-1.04% and -1.35% respectively) after follow up for one year, inspite of ongoing regular menses. The differences in results between estimated and observed rates of change illustrate that population variability hides small changes in BMD in cross-sectional data, which can be better determined in precise, longitudinal studies. Premenopausal changes in radial BMD should be clarified with more long term, prospective studies involving greater numbers of participants.

The menopause is considered to induce profound bone loss. The pQCT data in chapter 7 of this thesis, derived from the cross-sectional studies supports this finding in part. When all postmenopausal women were considered as a single group, estimated rates of bone loss up to -1.39%/yr were found. Surprisingly however, the rate of trabecular BMD loss for postmenopausal women was generally lower than that of other pQCT BMD measurements. It also gradually increased with the duration since the menopause, which is contrary to the accepted theory that trabecular bone is preferentially affected

immediately following the menopause (1.49,1.64,1.66,1.67,1.74-1.77), at least at the radius. In contrast, the work in chapter 7 showed that subcortical bone was preferentially affected in the early postmenopausal years. This supports the recent observation that during this period, remodelling results in trabecularization of endosteal cortical bone and expansion of the intramedullary radial cavity at the expense of the cortical shell, whilst there is little change in trabecular BMD (6.6). This was confirmed when changes in pQCT BMD around the menopause were examined further by comparing early postmenopausal and late premenopausal women in a cross-sectional study, where a greater difference was found in subcortical than trabecular BMD. In this perimenopausal group, it was also apparent that difference in radial BMD measurements were less than those found at the hip and spine as measured by DXA.

It is appreciated that bone mass at one skeletal site does not necessarily reflect that of another. This was borne out in the work presented in chapter 6, where there was at best, only moderate correlation between radial pQCT BMD measurements, calcaneal ultrasound and axial hip and spine measurements. Additionally, the longitudinal studies which examined annualized rates of change in premenopausal and postmenopausal women in chapter 7, albeit in small numbers, and only after 12-18 months of follow-up, showed that there was no relationship between changes at the radius and those at either the hip or spine. Further study of these relationships involving a greater number of individuals followed for a longer duration are required. Pending these studies and prospective studies addressing fracture prediction using pQCT, these preliminary findings suggest that pQCT has little role as either a screening or pre-screening tool (eg. for axial DXA assessment), should population based screening for osteoporosis risk ever

become a reality. Essentially a single radial measurement did not adequately predict axial BMD, and serial measurements did not reflect changes in axial BMD in the short-term.

At the present time, fracture prediction is best achieved by BMD assessment. In chapter 8, a retrospective study comparing axial DXA with radial pQCT measurements showed that radial trabecular BMD was superior to all other measurements in discriminating vertebral fracture from non-fracture populations. In contrast, the discriminatory power of all pQCT measurements was poor in a retrospective study of hip fractures, and significantly worse than DXA femoral neck BMD. This suggest that pQCT may be useful in the prediction of vertebral fractures, but less so for hip fractures. Prospective studies are now required to confirm this suggestion.

Monitoring response to drug therapy is an established indication for BMD assessment (1.145,1.146,1.153,1.154,9.1). Preliminary work presented in chapter 9 compared changes in radial pQCT BMD measurements with DXA hip and spine measurements in response to HRT and cyclical etidronate during the first year of treatment. The results showed that the response to both drugs follows a similar pattern, with a significant increase in spinal BMD evident within 4 months and further increase thereafter. In contrast, there was a more gradual increase in hip BMD, while radial BMD, including the trabecular measurement, remained virtually unchanged. This suggests that in the majority of cases, response to these therapies is best assessed at the lumbar spine. This needs to be confirmed by larger studies with longer follow-up. It should be borne in mind however, that as lumbar spine DXA measurements can be influenced by severe spondylosis (1.171-1.177), multiple fractures and overlying aortic calcification (1.168,1.169,1.170), it is not always the best measurement for

monitoring purposes. Based upon the data presented here, there is no suggestion that pQCT could be used as an alternative, although further work, as suggested above, is necessary before its use in this area can be completely discounted.

Monitoring the effect of drugs with an adverse effect upon bone is equally important. Such an effect is epitomised by corticosteroid therapy. Unfortunately, it was not possible to examine the role of pQCT in monitoring steroid induced bone loss per se, but this area is undoubtedly deserving of future study. It was however possible to examine the potential adverse effect of warfarin upon bone, a side-effect seldom considered. In a case control study of males presented in chapter 10, lumbar spine and radial trabecular BMD were almost one standard deviation lower at each site in those men on longterm warfarin compared to the control group. Bearing in mind the increasing use of warfarin, this is an important adverse effect to be aware of. In considering the effect of HRT, etidronate and warfarin on radial BMD, there appears to be disparity in the results. It seems strange that radial trabecular BMD was unchanged with both HRT and etidronate, yet significantly decreased by warfarin. The study designs must be borne in mind however. The HRT/etidronate effects were studied for only one year in a longitudinal study, whereas the warfarin effect was examined in a cross-sectional design where the drug had been given for a median duration of 40.5 months (range 4-302). The disparity in results could be related to the duration of drug therapy, warfarin having had a much longer time to exert its effect upon radial bone, than HRT or etidronate. With longer follow up, a significant increase in radial BMD may have been found with HRT and etidronate.

Rheumatoid arthritis (RA) is one of the many conditions which is known to induce bone loss and cause osteoporosis (11.1,11.4-

11.8,11.11,11.12,11.15-11.17,11.20). The pathogenesis is multifactorial, and the effect of low dose prednisolone at all sites controversial. In chapter 11, the effect of A and low dose prednisolone upon radial pQCT BMD measurements was investigated in a case control study, with comparison of BMD at other skeletal sites. Trabecular BMD was reduced by more than 30% in patients with A compared to controls, with very little additional corticosteroid effect. In contrast cortical BMD was unaffected. A similar significant difference was detected at the os calcis, a smaller but significant difference at the hip, and an insignificant difference at the lumbar spine. This study supports the growing body of evidence suggesting that the use of low dose corticosteroid in patients with A does not have a deleterious effect upon BMD. The effect upon periarticular trabecular BMD at the wrist in this study (as measured by pQCT) was dependent upon articular damage, which is the longterm consequence of uncontrolled inflammatory joint disease. Previous work by others has shown loss of radial trabecular BMD (as measured by pQCT) early in the natural history of the disease (11.11,11.12), and the data presented here suggests further loss in the longer term. This begs the question, could assessment of trabecular BMD by pQCT be used to monitor disease progression, and possibly response to therapy? Further work, preferably in interventional, prospective studies of early A are needed to address this issue.

It is apparent from the work presented here that radial BMD behaves differently from that at the hip and spine. There was poor correlation between radial and axial measurements. There was no correlation between the rate of change at the radius and that at the hip or spine. The response to drugs such as HRT and etidronate differed between sites. Although pQCT has the advantage of assessing trabecular and cortical BMD independently, radial bone seems less active, and responds

differently and more slowly than does axial bone. This may well be due to differences in remodelling at the radius as discussed above in this chapter, and in differences in the bone marrow present between sites. Yellow marrow is present in the radial medullary cavity throughout adulthood, whereas haematopoietic marrow predominates at the spine and proximal femur. Osteoclasts and osteoblasts are derived from haematopoietic marrow. The signalling and control of osteoclasts/osteoblasts and remodelling is extremely complex and not fully characterised, but thought to involve numerous cytokines, hormones and matrix factors (1.2,1.3,1.8,12.1). The close proximity to, and interaction with haemopoietic rather than yellow marrow may well explain some of the different behaviour of axial and radial bone which was apparent from the work presented in this thesis.

Osteo-densitometry is a relatively new concept and significant advances have been made in this field in recent years. Although present day osteo-densitometers are the best method of assessing "osteoporosis" in its broadest context, research into pQCT and other modalities, both established and novel, must continue to ensure future progress. Two and three dimensional QCT systems have been developed (1.149,1.150,8.35,12.2-12.8) which allow structural analysis of trabecular bone, providing in effect, a non-invasive bone biopsy. This structural information along with BMD may further improve the performance of pQCT (12.7). Scanners with a higher spatial resolution than that of the Stratec XCT-960 system have largely been used for this, although an attempt at structural analysis by enhancing the Stratec system has been reported to show an increased number of perforations in early postmenopausal compared to late premenopausal women inspite of an insignificant difference in BMD (7.5).

The work for this thesis evaluating the role of pQCT in osteoporosis was done within a limited timescale. Consequently it has its limitations and is far from being all inclusive. However, it has addressed some of the important issues which must be covered in the development of an osteo-densitometer, and has highlighted areas where pQCT may, and may not have a role in the management of patients with osteoporosis. Further work is necessary to confirm some of these findings, and address areas not covered by this work. Like most research, issues hitherto not realised, or poorly documented, have been raised which are worthy of future investigation. The most likely fruitful areas for further research and development into pQCT would be:

- The use of scan voxel numbers to improve precision, and aid repositioning in repeat scanning.
- The use of pQCT to study age related changes in BMD and bone remodelling.
- The use of pQCT in fracture prediction, more especially vertebral fracture. It may have additive predictive value in conjunction with axial DXA, as has calcaneal ultrasound in hip fracture prediction (8.19).
- The use of pQCT in determining BMD changes in response to corticosteroid therapy
- The use of pQCT as an assessment tool for monitoring disease progression and response to therapeutic intervention in rheumatoid arthritis, and possibly other inflammatory arthritides.
- Further assessment of structural considerations, both radial geometric indices, and trabecular microstructure.

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APPENDIX 1 Glossary of Abbreviations

ACTH	Adrenocorticotrophic Hormone
AF	Atrial Fibrillation
ANOVA	Analysis of Variance
AP	Antero-posterior
AUC	Area Under the Curve
BMD	Bone Mineral Density
BMU	Basic Multicellular Unit
BUA	Broadband Ultrasound Attenuation (calcaneal site)
χ^2	Chi square
cAMP	Cyclic Adenosine-3',5'-monophosphate
CM	centi-meter
CT	Computed Tomography
CV	Co-efficient of Variation
dB/MHz	Decibel / Mega Hertz
DHEA	Dehydroepiandrosterone
DPA	Dual Photon Absorptiometry
DXA	Dual Energy X-Ray Absorptiometry
ETD	Etidronate
FN	DXA Femoral Neck BMD
FSH	Follicle Stimulating Hormone
FT	DXA Femoral Trochanter BMD
FW	DXA Femoral Ward's Area BMD
g	grammes
HRT	Hormone Replacement Therapy
HVR	Heart Valve Replacement
kg	Kilogram
LARS	Larsen Score
L2-L4	2nd to 4th lumbar vertebrea
LH	Luteinizing Hormone
LHRH	Luteinizing Hormone Releasing Hormone
LS	DXA Lumbar Spine BMD

m	Meter
m/s	Meter / Second
MCP	Metacarpo-Phalangeal Joint
MXA	Morphometric X-ray Absorptiometry
NS	Statistically Non-Significant
1-CTP	Cross-linked Carboxyterminal Telopeptide of Type 1 Collagen
1-NTP	Cross-linked Aminoterminal Telopeptide of Type 1 Collagen
PBM	Peak Bone Mass
P1CP	Carboxyterminal Propeptide of Type 1 Collagen
P1NP	Aminoterminal Propeptide of Type 1 Collagen
PIP	Proximal Inter-Phalangeal Joint
POST	Postmenopausal Women
PRE	Premenopausal Women
pQCT	Peripheral Quantitative Computed Tomography (ultra-distal radial site)
PVD	Peripheral Vascular Disease
Qcort	pQCT Cortical BMD
QCT	Quantitative Computed Tomography
Qscort	pQCT Subcortical BMD
Qtot	pQCT Total BMD
Qtrab	pQCT Trabecular BMD
RA	Rheumatoid Arthritis
RA+P	Steroid Treated RA group
RhF	Rheumatoid Factor
ROC	Receiver Operator Curve
ROI	Region of Interest
SD	Standard Deviation
SPA	Single Photon Absorptiometry
T4-L5	4th thoracic to 5th lumbar vertebrae
T-Score	The number of standard deviations above or below the mean value of young normals

VN	Voxel Number
VN-diff	Difference in voxel numbers
VOS	Ultrasonic Velocity (calcaneal site)
VTE	Recurrent Venous Thrombo-embolism
WB	DXA Whole Body
WB-ARM	DXA Arm BMD (derived from the whole body DXA scan image)
WB-BMD	DXA Whole Body BMD
YPM	Years Postmenopause
yr	Year
Z-Score	The number of standard deviations above or below the sex and age related normal mean

APPENDIX 2 Papers Published from the Thesis Work

1. Philip WJU, Martin JC, Richardson JM, Webster J, Reid DM, Douglas AS. Decreased axial and peripheral bone mineral density in patients taking long term warfarin.
Quarterly Journal of Medicine 1995;88:635-40

2. Martin JC, Reid DM.
Appendicular measurements in screening women for low axial bone mineral density.
British Journal of Radiology 1996;69:234-40

3. Martin JC, Munro R, Campbell MK, Reid DM.
Effects of disease and corticosteroids on appendicular bone mass in postmenopausal women with rheumatoid arthritis: comparison with axial measurements.
British Journal of Rheumatology 1997;36:43-50

APPENDIX 3 Abstracts Published from the Thesis Work

1. Martin JC, Munro R, Reid DM.
   Comparison of peripheral and axial bone mineral density (BMD) with bone ultrasound in postmenopausal women with rheumatoid arthritis on longterm corticosteroids.
   British Journal of Rheumatology 1992;32(Abst Suppl):40

2. Martin JC, Reid DM.
   Comparison of dual energy x-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT) and ultrasound of the os calcis (CUBA) in screening perimenopausal women for osteopenia. Bone & Tooth Society, London, Dec 1993.
   Bone 1994

3. Martin JC, Philip W, Richardson J, Webster J, Reid DM, Douglas AS.
   Effects of longterm warfarin therapy on bone mineral density (BMD) at peripheral and axial sites.
   Scottish Medical Journal 1994;39:153

4. Martin JC, Munro R, Reid DM.
   Bone mass at multiple bone sites in Rheumatoid Arthritis (RA): Effects of disease and corticosteroid therapy.
   British Journal of Rheumatology 1994;33(Abst Suppl 1):83

5. Martin JC, Reid DM. Comparison of axial and peripheral bone loss in perimenopausal women.
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6. Martin JC, Reid DM.
The use of scan voxel numbers to improve the precision of peripheral quantitative computed tomography (pQCT).
Current Research in Osteoporosis and bone Mineral Measurement III 1994: p53

7. Martin JC, A England, DM Reid.
Can changes in appendicular bone predict axial bone mineral density (BMD) during treatment with hormone replacement therapy (HRT) and cyclical etidronate?.
British Journal of Rheumatology 1995;34(Abst Suppl 2):S72

8. Reid DM, Stewart A, Martin JC.
Does quantitative ultrasound have utility in predicting fractures and monitoring therapy in osteoporosis: comparison with dual enery X-ray absorptiometry (DXA).
Current Research in Osteoporosis and bone Mineral Measurement IV 1996: p57

9. Martin JC, A Stewart, DM Reid
Discrimination of hip fractures by peripheral quantitative computed tomography (pQCT): comparison with dual energy x-ray absorptiometry (DXA) of the hip and calcaneal ultrasound measurements.
British Journal of Rheumatology 1996;35(Abst Suppl 2):p6.

APPENDIX 4 Presentations from the Thesis to Learned Societies

1. Effects of longterm warfarin therapy on bone mineral density (BMD) at peripheral and axial sites.
   Scottish Society for Experimental Medicine, Dundee, December 1993.

2. Bone mass at multiple bone sites in Rheumatoid Arthritis (RA): Effects of disease and corticosteroid therapy.
   British Society for Rheumatology General Meeting, Brighton April 1994.

3. Comparison of axial and peripheral bone loss in perimenopausal women.
   The 10th International Bone Densitometry Workshop, Venice, April 1994.

4. The use of scan voxel numbers to improve the precision of peripheral quantitative computed tomography (pQCT).
   The 4th Bath Conference on Osteoporosis and Bone Mineral Measurement, June 1994.