# THE EPIDEMIOLOGY OF OSTEOPOROSIS

# IN THE FRAIL INSTITUTIONALIZED ELDERLY

**BY**


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# STATEMENT OF ORIGINALITY

I declare that this submission is my own work. To the best of my knowledge and belief it contains no material previously published or written by another person. No part of this thesis has been used to obtain any other degree.

Jane Zochling

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# PUBLICATIONS RESULTING FROM THIS THESIS

## Peer reviewed papers

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Zochling J, Nguyen TV, March LM, Sambrook PN. Quantitative ultrasound measurements of bone: measurement error discordance, and their effects on longitudinal studies. Osteoporos Int 2004:Feb13 (online first)

## Presentations and Abstracts

Zochling J, Nguyen T, Sambrook PN. Quantitative ultrasound variance in elderly institutionalized women. Calcif Tiss Int 2003;72(4):408-9

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Sitoh YY, Zochling J, Lau TC, Schwartz JM, Brnabic AJ, March L, Cameron ID, Cumming RG, Lord S, Sambrook P. Hypovitaminosis D is common, and more severe in winter, in institutionalized older people in Sydney. Gerontology 2001;47(Suppl.1):561

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# ABSTRACT

As our population ages, the proportion of frail elderly people requiring assisted accommodation in aged care facilities is increasing. This population is at high risk of falls and fractures, which bring significant morbidity and mortality. The prevalence of osteoporosis also increases with age, but there have been few studies of bone density in residents of hostels and nursing homes. This thesis looked at the prevalence of osteoporosis and falls in elderly people in residential care, to define the size of the problem and identify risk factors for low bone density and falling, with particular reference to vitamin D levels.

Two thousand and five men and women aged between 65 and 104 years were enrolled in the Falls and Fracture Risk in the Elderly Epidemiology (FREE) study between 1999 and 2003. The key findings from analysis of this population were firstly, that quantitative ultrasound (QUS) measures were higher in men than women independent of age, and that in men there was no significant decline in either BUA or VOS, but in women BUA declined by over 3% per decade and VOS by 1% per decade. Both ultrasound machines used in the study were shown to be reliable, with precision unaffected by advanced age. QUS was found to be sensitive to longitudinal change even in this frail elderly cohort.

Vitamin D deficiency was found in the majority of elderly aged care facility residents but supplementation conferred higher serum 25-OH-vitamin D levels. Vitamin D levels were not shown to be related to BUA, VOS or the risk of falling in this

population. Serum parathyroid hormone might be important in determining future falls risk.

In summary, the results of this thesis give an important insight into the prevalence of osteoporosis and falls in the frail elderly, and how these might be predicted. Future study of prospective fracture rates in this group will then be able to assess relative risk factors for osteoporotic fracture, and identify those individuals who might benefit from directed fracture prevention strategies.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **1,25-OH-Vit D** | 1-25 dihydroxy Vitamin D |
| **25-OH-Vit D** | 25 hydroxy Vitamin D |
| **ANOVA** | Analysis of Variance |
| **bALP** | Bone-specific alkaline phosphatase isoenzyme |
| **bSD** | Between-subjects standard deviation |
| **BMC** | Bone mineral content |
| **BMD** | Bone mineral density |
| **BMI** | Body mass index |
| **BUA** | Broadband ultrasound attenuation |
| **CI** | Confidence interval |
| **CTx** | Carboxy-terminal cross linked telopeptide of type I collagen |
| **CV** | Coefficient of variance |
| **dB** | Decibel |
| **DEXA** | Dual energy X-ray absorptiometry |
| **DOES** | Dubbo Osteoporosis Epidemiology Study |
| **DPA** | Dual energy photon absorptiometry |
| **Dpy** | Deoxypyridinoline |
| **EPIDOS** | Epidemiology of Osteoporosis Study |
| **EPOS** | European Prospective Osteoporosis Study |
| **EVOS** | European Vertebral Osteoporosis Study |
| **FREE** | Falls and fracture Risk Epidemiology in the Elderly Study |
| **FRI** | Fracture Risk Index |
| **LoA** | Limit of agreement |

| | |
|---|---|
| **LSC** | Least significant criterion |
| **MHz** | Megahertz |
| **NH&MRC** | National Health and Medical Research Council (Australia) |
| **NOF** | Neck of femur |
| **NTx** | Amino-terminal cross linked telopeptide of type I collagen |
| **OC** | Osteocalcin |
| **OR** | Odds ratio |
| **PTH** | Parathyroid hormone |
| **Pyr** | Pyridinoline |
| **QCT** | Quantitative computed tomography |
| **QOL** | Quality of life |
| **QUS** | Quantitative ultrasound |
| **RCS** | Resident classification score |
| **ROI** | Region of interest |
| **RR** | Relative risk |
| **SD** | Standard deviation |
| **SE(M)** | Standard error (measurement) |
| **SMMSE** | Standard Mini-Mental Status Examination |
| **SPA** | Single energy photon absorptiometry |
| **SPSS** | Statistical package |
| **SXA** | Single energy x-ray absorptiometry |
| **VOS** | Velocity of sound |
| **wCV** | Within-subjects coefficient of variability |
| **WHO** | World Health Organization |
| **wSD** | Within-subjects standard deviation |

# CHAPTER 1

# INTRODUCTION AND BACKGROUND

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## 1.1 Introduction

Osteoporosis, a disease characterized by skeletal fragility and an ensuing increased risk of minimal trauma fracture, is a major public health problem which is growing as our population ages. The direct costs alone of treating osteoporotic fracture in Australia have been estimated at $1.9 billion in 2001 (1). Hip fractures are the most costly to treat and associated with a significant increase in mortality, but any osteoporotic fracture brings with it a significant morbidity and impairment of quality of life (2;3).

The elderly have a high incidence of both involutional osteoporosis and of falling. The combination results in a population who are at particular risk of osteoporotic fracture. The group who are likely to be at highest risk, those elderly individuals who are unable to live independently due to disease or frailty, have not been extensively studied to determine which factors in particular contribute to fracture risk. The purpose of this thesis is to measure the incidence of both osteoporosis and falling in the frail institutionalized elderly, and describe potential predictors of osteoporotic fracture in this high risk group.

## 1.2 Assessment of Bone

Bone is important as both a solid structure for support and movement, and a dynamic organ involved in calcium homeostasis. Measurement of the both the strength and the activity of bone are important in health and disease. Static measures of bone density are used in clinical practice as a surrogate for bone strength, due to the relative inaccessibility of bone in vivo. Dynamic bone turnover can be quantified by measuring serum markers of bone turnover.

### 1.2.1 Quantitative Assessment

Bone mineral density (BMD) first became measurable in the 1960s with the introduction of single photon absorptiometry (SPA) (4). Steady improvements in technology have seen the development of single x-ray absorptiometry (SXA), dual photon absorptiometry (DPA) and more recently dual-energy x-ray absorptiometry (DEXA), considered the gold-standard for BMD assessment. Alongside absorptiometry techniques, other imaging modalities used in the assessment of osteoporosis include quantitative computed tomography (QCT) which can assess volumetric BMD, and quantitative ultrasound (QUS) of bone which is thought to incorporate connectivity and porosity in addition to pure density.

#### 1.2.1.1 Dual-energy X-ray Absorptiometry (DEXA)

Dual-energy x-ray absorptiometry is the most commonly used technique for the assessment of osteoporosis. Two incident beams at different energies are passed through a tissue from an x-ray source, and resultant photon attenuation is measured. Differential absorption and scattering of the incident photons in different tissues allow differentiation between bone and soft tissue. The technique is used to measure areal

BMD in $g/cm^2$, the integral mass of bone mineral with a standard chemical composition (hydroxyapatite) in the measurement region of interest (ROI) divided by the projected area (5).

Early versions of this technique include single-energy x-ray absorptiometry (SXA), which used only one incident beam and thus required correction for the thickness of soft tissue in the ROI. Single- and dual-energy photon absorptiometry (SPA, DPA) used a radionuclide source of photon emissions, which had a lower photon flux and larger diameter source, resulting in much longer scanning times, poorer image definition and poorer precision than DEXA today.

Current precision errors for DEXA are quoted between 1 and 1.5%, and patient radiation is relatively low (10 μSV at the lumbar spine and 2 μSV at the hip) (6). Limitations of the technique include problems associated with incident beam hardening and the stability of the polyenergetic spectra, which can result in deterioration in measurement accuracy. Variation in the soft tissue composition of the ROI can also impair accuracy. As calculations are based on bone mineral being uniquely made up of hydroxyapatite ($Ca_{10}(PO_4)_6OH_2$), problems arise when this assumption is not met, for example with fluoride or more recently strontium therapy. The atomic number of strontium is 38, compared to 20 for calcium, and so when it is incorporated into the bone mineral a disproportionate rise in BMD is seen as measured by DEXA (7).

A working party of the World Health Organization (WHO) has defined osteoporosis in postmenopausal women as a BMD more than 2.5 standard deviations below the

young normal mean BMD, (8;9) based on DEXA measurements at the hip. This allows for comparison of fracture risk between different DEXA machines, and simplifies interpretation of scan results in this population. There is some controversy as to whether this classification is generalizable across other populations (10) or different methods of BMD measurement (11); nevertheless the nomenclature has been widely accepted by the clinical community as the standard method for reporting imaging of osteoporosis.

Dual-energy x-ray absorptiometry of the hip and spine has been well proven to predict osteoporotic fracture in post-menopausal women (12-14). Measurement of other sites is less predictive and not used in clinical practice (15;16). There are few studies of DEXA and fracture prediction in the very old. A large prospective study of 7598 independent women over the age of 75 years (17) showed an increase in the relative risk of hip fracture of 1.9 for each standard deviation decrease in BMD at the femoral neck. There are no studies of DEXA and fracture in the institutionalized elderly; Chandler et al (18) showed that low BMD as measured by SXA at the radius is a significant independent risk factor for osteoporotic fracture, particularly in those who were transfer independent as opposed to transfer dependent.

#### 1.2.1.2 Quantitative Ultrasound (QUS)

Quantitative ultrasound (QUS) is a more recently developed technique for assessing bone strength. It uses non-ionizing ultrasound waves at a frequency of 0.1-1MHz which are passed through tissue by means of transducers. As they pass, some of the energy is lost as the beam is attenuated causing a change in the resultant sound intensity measured at the receiving transducer. Any sound waves will lose energy

exponentially with distance, and so the waves are measured in the logarithmic scaled decibels (dB) to allow a linear relationship between dB and distance travelled. Bone ultrasound attenuation (BUA) is the measure of this energy loss across bone, and is given as dB/MHz. The interface between air and soft tissue causes pronounced attenuation, and so in practice air needs to be removed from the ROI. Early QUS machines used water baths to achieve this; dry systems use gel applied to the limb and transducers.

Velocity of sound (VOS) is measured as the speed at which ultrasound waves traverse the tissue, in metres per second (m/s). At the calcaneus, this is the average of the velocity across soft tissues and the velocity across bone, which in practice is similar to velocity across bone alone. This is dependent on transducer separation.

It is thought that QUS is more related to the so called 'quality' of the bone than just bone density, as measured by DEXA (19-22). The more bony trabeculae present in a given area, the greater the scattering of sound waves, suggesting BUA is related to bone structure. Velocity of sound also reflects the elastic modulus of the tissue. Whether these factors give an improved estimate of bone strength in clinical practice is not yet clear.

Advantages of QUS over other methods of bone assessment include its portability, ease of use, low cost and absence of ionizing radiation. This makes it an ideal tool for individuals who are less mobile, such as the institutionalized elderly. Disadvantages lie in a slightly poorer precision than DEXA, error ranging from 1-5% for BUA and 0.3-1.0% for VOS across different machines (23). Collagen diseases such as Ehlers-

Danlos syndrome and systemic sclerosis are thought to alter the relationship between bone density and ultrasound properties (24), which might limit the usefulness of the technique in certain disease states.

There are a number of QUS machines in use both in research and in clinical practice today. Most measure QUS at the calcaneus, as a surrogate for the clinically important vertebral bodies or neck of femur; the calcaneus is a weight bearing bone, has a high percentage of trabecular bone, and has a similar pattern of bone loss to the vertebral bodies. Earlier water bath systems, including the Achilles+ (Lunar), UBA575 (Walker Sonix) and DTU-one (Osteometer), have largely been superseded by more portable dry systems. The CUBA Clinical (McCue) was the primary machine used to measure bone density in the following research, and correlates well with the Lunar Achilles+ machine (25) Transducers are 19mm in diameter and spring-loaded to give constant pressure over the patient's heel, and are silicone-capped to accommodate heels of different sizes and shapes. It is easily portable at 10kg, and easy to operate. Calibration is by electronic and water-filled phantoms. Measures of BUA and VOS are calculated. Other dry systems in use include the Sahara (Hologic Inc.), which in addition to BUA and VOS calculates a quantitative ultrasound index (QUI), relating measures back to a young adult normal value of 100. QUS is also used at other sites, including the proximal phalanges, the tibia (primarily measuring cortical bone) and multi-site machines including the Omnisense (Sunlight Ultrasound Technologies).

The DEXA-derived T-score is not necessarily applicable for other methods of assessing bone strength. When the principle of expressing raw data as standard deviations from the young normal mean is extended into QUS measurements,

classifying patients as being ‘osteoporotic’ with a T-score less than -2.5 results in vastly different proportions of disease as is seen with DEXA (11). Faulkner et al showed that in 60 year old postmenopausal women, the prevalence of T-score-defined osteoporosis ranges from 3% when measured by QUS at the heel to 50% as measured by spinal QCT, suggesting that the use of WHO T-score thresholds to define fracture risk should be limited to the DEXA measures they were derived from.

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Quantitative ultrasound of the calcaneus has been shown to predict fracture-defined (26;27) and DEXA-defined (28;29) osteoporosis. A number of studies have shown that BUA is significantly higher in men than age-matched women (29-31), although this relationship is not seen as clearly with VOS (31). A cross-sectional study of healthy Japanese shows lower rates of bone density loss as measured by QUS compared to DEXA (32), decreasing by 0.6% per year in both males and females over the age of 20. In women, DEXA at the hip and spine was better than QUS at discriminating between subjects with and without vertebral fractures (33).

Quantitative ultrasound has been well demonstrated to correlate with DEXA measures of BMD at the calcaneus (34;35). It has also been to correlate well with BMD at the spine and hip (35-37), and is associated with similar risk factors for osteoporosis (38;39). Normative data in different populations has confirmed that BUA and VOS decrease with age (40-42), although there were few individuals included over the age of 85 years. The clinical importance of QUS however lies in its ability to predict osteoporotic fracture.

Case control and cross-sectional studies have shown that QUS of the calcaneus is able to differentiate between fractured and non-fractured populations in women (43-45) and in men (27;46). The relationship exists for wrist (47;48), hip (49;50) and vertebral (51-53) fractures. There are fewer prospective studies. Huang et al (54) showed that low QUS was significantly associated with increased risk for hip, for non-spine and for any fracture in 590 post-menopausal healthy women over an average follow-up period of 2.7 years.

The best prospective studies have been done in elderly populations, as there is a higher incidence of fracture allowing shorter follow-up periods. A large prospective study of 5662 independently-living elderly French women, mean age 80.4 years (55), showed that both BUA and VOS were significantly associated with incident hip fractures over 2 years, independent of femoral neck BMD as measured by DEXA. Similar results were seen in a 2-year prospective study of 6189 healthy women over the age of 65 years in the United States (56). QUS also appears useful in the frail elderly; Porter et al (57) showed in an elderly, institutionalised population that BUA was lower in those suffering hip fracture than those who did not fracture. More recently, a study of 710 residents of nursing homes or apartments for the elderly (58) showed QUS to be significantly associated with the risk of incident hip fracture over one year follow-up.

With good prospective evidence for the utility of QUS for predicting hip fracture in the institutionalized elderly, this portable and safe method of assessing fracture risk is ideal for studies such as the FREE study presented here.

#### 1.2.1.3 Quantitative computed tomography (QCT)

Conventional computed tomography techniques can also be used to quantify BMD using appropriate software. The cross-sectional tomographic image allows a true volumetric BMD to be calculated in $g/cm^3$, as opposed to the areal value given by DEXA, giving a conceptually more meaningful density measure. The technique has the highest diagnostic sensitivity of available assessment methods for disease and age-related bone loss (59), and has been shown to be an independent predictor of prevalent vertebral fracture in cross-sectional studies (60). However relatively high patient exposure to radiation (6), a precision error at the lumbar spine of 2-4% (5) and high installation and running costs prohibit the use of QCT clinically. Peripheral QCT of the wrist is still used frequently in research, as radiation is much lower, it selectively measures trabecular bone and allows visualization of the bone micro-architecture.

### 1.2.2 Biochemical markers

Bone is a living tissue, which is constantly modeling and remodeling both to maximize its function as a supportive structure and to contribute to calcium homeostasis. Biochemical measures of calcium metabolism are generally normal in osteopenia and osteoporosis, available assays being not sufficiently sensitive to detect the small changes which may theoretically be present. Serum calcium, phosphate and intact parathyroid hormone must nevertheless be measured in osteoporosis to exclude the presence of other disease states which may be impacting on bone, such as hyperparathyroidism, myeloma, metastatic disease, malnutrition, osteomalacia or phosphate wasting diseases. Vitamin D levels are the exception; as well as indicating malabsorption, nutritional deficiency and osteomalacia, 25-OH-vitamin D is

important to incorporate calcium into the bone matrix. Hypovitaminosis D leads to loss of bone mineral and osteoporosis.

Bone formation and resorption markers, shown in Table 1.1, give a picture of what is happening in bone at the cellular level.

**Table 1.1:** Markers of bone turnover

| | |
|---|---|
| ***Bone Formation Markers (serum)*** | |
| Bone-specific alkaline phosphatase (bALP) | Osteoblast membrane enzyme |
| Osteocalcin (OC) | Bone matrix protein |
| Collagen type 1 propeptides (pro-N, pro-C) | Collagen precursors |
| ***Bone Resorption Markers (serum and urine)*** | |
| Collagen cross-links: | Collagen breakdown products |
| Total or free pyridinolines (Pyr, Dpy) | |
| Telopeptides (NTx, CTx) | |
| Hydroxyproline, Hydroxylysine glycosides | Collagen breakdown products |
| Tartrate-resistant acid phosphatase (TRAP) | Osteoclast enzyme |

Alkaline phosphatase (ALP) is a cell membrane-associated enzyme expressed by liver, bone, kidney and placenta. The bone-specific isoenzyme (bALP) forms approximately 40% of the total serum ALP, and is derived from osteoblasts and osteoblast precursors. Immunoassays are specific, with an intra-individual coefficient of variance (CV) of less than 10%. There remains a small cross-reactivity with other isoforms of ALP (liver, placenta and intestine).

Osteocalcin is a polypeptide expressed by osteoblasts as they actively deposit bone, and is under 1,25-OH-vitamin D control. Serum levels represent a spillover of osteoblastic synthetic activity. It is measured by immunoassay.

The most commonly measured markers of bone resorption are the collagen cross-links. These are formed in fibrils, and have no means of metabolism once collagen is degraded and so can be measured unaltered in the urine by high-performance liquid chromatography (HPLC). The two forms are pyridinoline (Pyr) and deoxypyridinoline (Dpy). As bone is the largest reservoir for type 1 collagen in the body and turns over more rapidly than other sources, the majority of the cross-links found in the urine are from bone. There is a higher proportion of Dpy in bone than in other tissues, making it logically more specific for bone degradation.

Collagen telopeptide assays are also useful, targeting the two intermolecular sites of Pyr cross-linking in type 1 collagen: amino-terminal (NTx) and carboxy-terminal (CTx) telopeptides. The remaining markers listed in Table 1 will not be discussed, as they are less bone specific and their role in research and clinical practice is less well defined (61).

There is some biological variation in bone turnover markers. There is a distinct circadian rhythm, with levels being lowest in the morning. There are seasonal differences, which may be related to seasonal variation in 25-OH-vitamin D levels.

Changes in bone markers are strongly associated with BMD changes (62-66). A relationship to fracture is also emerging. Garnero et al (67) showed in the large EPIDOS study that elevated CTx and free Dpy levels were associated with a doubling in the risk of hip fracture, but formation markers bALP and OC were not predictive of fracture. Vertebral fracture has also been associated with higher bone turnover markers (CTx and OC) (68). It has been suggested that markers should be interpreted in conjunction with BMD measures rather than in isolation (69), and although bone turnover markers are at present largely a research tool, there may be a role for their use in clinical practice (70).

## 1.3 Bone and Gender

It is interesting that in most walks of life society is pushing toward gender equality, in the workplace, in opportunity and in basic human rights. However, when it comes to bone disease, osteoporosis in men and women is often treated as the same disease entity, with the same outcomes and many of the same treatment options. The WHO guidelines for grading osteoporosis are based on normative data from women; there are no corresponding well validated measurement scales for men. Gender differences are evident in bone acquisition in childhood, growth and morphometry, peak bone mass, bone loss with age and fracture rates, and so bone disease in the two sexes must be considered in light of these differences.

### 1.3.1 Bone in childhood

In infancy (age 0 – 18 months), absolute bone mineral content (BMC) has been shown to be the same in males and females (71), but once weight and age are taken into account, males have statistically higher bone mineral density (BMD) and BMC ($p=0.02$). Total body BMC has also been shown to be significantly higher in pre-pubertal males than females (72). Nguyen et al measured BMD and BMC in 94 males and 92 females ranging in age from 6 to 36 years, and found no difference between measures at any site before puberty (73). A Tasmanian cohort of 8-year-old children observed boys to have significantly higher hip BMD, and girls higher lumbar spine BMD, once body size had been taken into account (74). At puberty, girls had higher BMD measures at the pelvis, and higher BMD and BMC at the lumbar spine. After puberty, males generally had higher measures at all sites than their age-matched counterparts (73;75). Rates of BMD increase at the lumbar spine are fastest in early childhood (age 0-3 years) and adolescence (76). Changes in cortical bone BMD and

BMC at the radius show a similar relationship to age and sexual development with females reaching their maximum rate of bone increase earlier than males, generally within 12 months of the onset of menarche (77;78). By the age of 17, females had reached 93% of their expected peak BMC and BMD, whereas males had reached 86% (77;79). Proximal radius BMD measures in a group of 362 children and young adults aged 6 – 23 years by QCT showed no gender differences pre-puberty (78), but after reaching Tanner stage 3 of development, girls had higher BMD at this site.

Peak bone mass, measured both by DEXA and QUS, have been shown to have a strong genetic influence (80), which is independent of gender. Nevertheless, environmental factors still play a major role in determining both peak bone mass in humans and subsequent bone loss with age. Bone acquisition in 8-year-old boys has been shown to be related to participation in sports and muscle strength, whereas in 8-year-old girls BMD is related to winter sunlight exposure (74). An interventional study of physical activity in 12-16 year old children confirmed a beneficial effect on BMC, areal and volumetric BMD at the femoral neck in boys but not in girls (81). Retrospective studies of exercise in older age groups confirm an effect of moderate to high physical activity on bone density at the lumbar spine and femoral neck in men (82;83).

### 1.3.2 Age-related changes in bone

From such a gender-defined baseline, BMD measured at the hip is subsequently seen to decrease with age in both men and women (84-86). Cross-sectional data suggests a small bone density loss at the hip in pre-menopausal women, and higher rates of loss in women after the menopause and in men (86). When this cohort was re-examined 2

years later, again a low rate of BMD loss was seen in pre-menopausal women, which tripled at the menopause before decreasing to pre-menopausal rates in the elderly. In men, the longitudinal study showed a small constant BMD loss at the hip with age (86).

BMD changes differently dependent on the site of measurement (87). The picture is not so straightforward at the spine, with BMD showing little change with age in men in cross-sectional or longitudinal studies (86;88), probably due to osteoarthritis. Bone mineral density changes in women closely followed those described at the hip in one study (86), decreasing to zero (no significant change) in the elderly, whereas Krall et al (89) showed both sexes to increase BMD at the lumbar spine after the age of 65. Relatively few studies have compared the loss of cancellous bone histomorphometrically with age between genders (90). Age-related changes in micro-architecture, as seen in iliac crest biopsies, include thinning of the trabeculae in men more so than women, and loss of trabecular connectivity more marked in women (91-94).

Cortical bone changes with age, as measured at the radius with QCT, suggest the BMD remains stable in women aged 22-40 years, then declines slowly with a more rapid drop around the age of 55 years (95). Males show a higher peak BMD which occurs in the 20s, then a rapid decline until the gender difference disappears by the age of approximately 60 years. A large, population-based study in Tromsø, Norway (96) looked at BMD at the distal and ultra-distal radius in 3062 men and 4558 women using single-energy x-ray absorptiometry. Bone mineral density decreased by 0.1% per 1 year age increase in both sexes. Over the age of 50, the rate of BMD loss in

males increased to 0.6% per year, and by a greater extent to 1.3%-1.5% in females. There is little available data on the changes in bone density in the very old.

Cross-sectional studies show that QUS parameters decrease with increasing age (97-104), although changes in the frail elderly with age have not been as extensively documented (57). Longitudinal age-related bone changes over one year can be detectable by VOS and stiffness (101) but the decrease seen in BUA did not reach statistical significance. Such longitudinal studies must be interpreted in light of the precision of the instrument used. Schott et al (105) measured QUS in 88 healthy post-menopausal women at baseline and again after 2 years. The study showed a small, statistically significant decrease in all parameters, but the decrease in BUA approximated the long-term reproducibility precision error for BUA. Velocity of sound and stiffness performed better, decreasing by 0.8% and 1.85% respectively over 2 years, at 2.5 to 5 times their precision errors. Studies using QUS to assess bone after treatment for osteoporosis have shown the instrument to be sensitive to change over 2 to 4 years (106-110) but requires a longer time period for sequential measures than DEXA due to higher precision error.

### 1.3.3 Anatomy and bone strength

It would be nonsensical to assume that bone size is the same between genders. Males have wider bones, seen as a larger cross-sectional area for matched vertebral bodies (111-113), independent of body size (114). This becomes important when the forces imposed on the vertebral bodies are considered; being in general taller and heavier, males impose greater forces on any one vertebral body compared to females. However, the greater male vertebral cross-sectional area results in the load per unit

area being similar between males and females as young adults (112). As the skeleton ages, the increase in vertebral cross-sectional area due to periosteal bone growth is more marked in males, whereas age-related endosteal resorption of bone is more marked in women (111;115). This differential change leads to female vertebral bodies supporting a greater relative stress on a smaller relative area of bone (116).

Volumetric BMD measures allow comparison of bone density between genders allowing for skeletal size. A recent study of opposite-sex twins confirmed that there are only small bone density differences between the sexes (117) measured at the L3 vertebra, femoral neck and distal third of the radius, when bone volume, age, genetic and environmental effects are taken into account. Ebbesen et al (118) examined the L3 vertebral body in 51 female and 50 male cadavers, aged from 18-96, and found that although BMD as measured by DEXA and QCT did not vary in absolute value or rate of decline with age between the sexes, the ash weight of L3 (vertebral body bone mass), vertebral body volume and cross-sectional area were significantly lower in females at any age. Vertebral compressive strength decreased at twice the rate of BMD with age. There was no significant gender difference detected in maximal compressive stress (defined as load divided by cross-sectional area), however no corrections were made for body size.

Duan et al (112) use the term ‘Fracture Risk Index (FRI)’ to quantify the ratio of vertebral body compression load to vertebral body strength, with unity (or less) equating to appropriate biomechanics. Using this definition, they found male FRI increased by 21% with ageing, in contrast to 102% in women, and 9% of elderly men compared to 26% of older women had an FRI greater than unity. This is further

supported by the cadaveric study by Oyster et al (119), who measured vertebral body and phalangeal strength as the force required to crush the bone. It was shown that a significantly higher force was required to fracture the vertebral bodies of men despite no differences in vertebral BMD (measured by DEXA) by gender. Cortical bone was also stronger in men, with twice the force required for fracture than the age-matched female counterparts.

Hip geometry is related to the risk of hip fracture independent of BMD (120;121). The large European Prospective Osteoporosis Study (EPOS) (122) describes the epidemiology of the different measures of hip strength in Europeans over the age of 50 years. A subset of 1617 individuals underwent femoral DEXA, and scans were analyzed for both bone density and geometry. Men have higher cross-sectional moment of inertia (CSMI) and femoral neck cross-sectional area compared to women, but lower compressive and tensile strength measures which together indicate stronger bone. After adjusting for age, weight and height, males required higher forces at the femoral neck to sustain a fracture.

Other physical attributes of bone have been examined to explain the gender differences in fracture rates. Elastic modulus and hardness of the extra-cellular matrix are not different between genders (123). Macintyre et al (124) examined the non-dominant radius of 57 males and 88 females, and reported males to have higher connectivity index, lower mean hole size and higher BMD, all reaching statistically significance. The connectivity index decreased with age in both genders, but the rate of change was higher in females ($p<0.001$). An age-related increase in hole size

reached statistical significance in women but not men. All of these differences support an increased fragility in female bones when compared to men.

### 1.3.4 Bone turnover

Serum levels of bone-related alkaline phosphatase (bALP), N-terminal osteocalcin (OC), and C-terminal type 1 collagen products are tools used primarily in research to assess bone turnover. A cross-sectional study of 20-40 year old men and women (75) showed serum bALP, OC, Dpy and urinary NTx to be statistically higher in males, however all significant differences were lost after correcting for total body BMC, suggesting that bone size is important to consider when assessing gender differences in bone markers in young adults. In females, markers are seen to increase with age after the $4^{th}$ decade, and more sharply after the $6^{th}$ decade, corresponding to menopause (125-129), whereas in males most markers are seen to decrease. Thus bone loss in females is related to a biochemical increase in bone turnover, whereas in men the opposite would seem to be true (127). Parathyroid hormone, important in maintaining calcium homeostasis and acting directly on bone, increases with age but has no differential gender effects (130).

### 1.3.5 Associations with BMD

Bone mineral content and BMD of the calcaneus, measured by a $^{125}I$ photon absorption method, were significantly higher in men than women (131), but similar relationships are seen with smoking, body mass and early physical activity. Body mass index and weight are associated with BMD at all sites in women, but only at weight bearing sites in men (132-134). Lower fat content is related to lower BMD at the femoral neck in women (135;136), although being moderately overweight is seen

to be associated with a higher femoral neck BMD in both genders (133). Lean muscle mass is associated with BMD and total body BMC throughout life, similarly in prepubescent males and females, but more important in females after menarche; Ferretti et al (137) showed women to have higher BMD for a given lean body mass. Ratios of total BMC to lean body mass tended to equalize between genders after the menopause. In Japanese subjects, lean body mass is more highly correlated with BMC as measured by DEXA in males, whereas the correlation between BMC and fat content is more marked in females (138)

### 1.3.6 Fractures

Knowing that female bones are smaller, less dense and more fragile, it is hardly surprising that age-adjusted incidence of any limb fracture is almost 3 times greater in women (139;140) than men. The incidence of most fractures increases with age in men, except for forearm fractures. Sanders et al (140) found fracture rates were highest for hip, then spine, distal forearm and humerus in decreasing order, similarly in men and women. Overall, fracture incidence was 3-4 times higher in women. In the age group 35-55 years, incidence was 65/10,000 person years in women, and 35/10,000 person years in men, and increased significantly with age independent of gender. Hip fracture rates in Oslo over 50 years were 118/10,000 person years in women and 44/10,000 person years in men (141). A large cross-sectional study showed vertebral fractures to be more common in men than women aged 50-59 years, but a slower increase in incidence is seen with age in men and by over 80 years, females predominate (142). This study however had some methodological inconsistencies in fracture ascertainment, the reporting of some traumatic fractures or osteoarthritic change as osteoporotic fracture introducing a spuriously large vertebral

fracture incidence in men. A large 2 year prospective study of 7428 men and 7865 women showed the incidence of any fracture in men aged 15-49 was 2.3 times that in women (143), whereas over 60 years of age women had 2.3 times the number of fractures as men. Peak fracture rates in men occurred in young adult males, the elderly of both genders, and in 40 year old women, particularly with respect to wrist fracture. Mortality after fracture is also higher in men (144;145).

Just as there are differential risk factors for BMD between sexes, there are also differences in fracture associations. BMD is an important risk for vertebral fracture in both sexes (146), however a case-control study of individuals with vertebral fracture did not reveal a significant difference in vertebral body morphometry between men and women (146). Men have been shown to have a higher prevalence of morphometric vertebral fracture (147), but they fracture at a higher BMD than women, such that at any given spinal BMD, men are 3 times more likely to have morphometric fracture. Men also show a higher risk of multiple (>2) vertebral fractures (148) than women. These observed differences are likely to be in part due to the higher incidence of old traumatic fractures in men. Selby et al (149) replicated this gender difference in BMD fracture threshold, with a 50% risk in fracture occurring at a significantly higher BMD in men (0.908 $g/cm^3$) than women (0.844 $g/cm^3$) (150). Heavy exercise has been shown to be related to vertebral fracture in men alone, OR 1.5-1.7 (151), but again there is some question of whether the crush fractures recorded were indeed true osteoporotic fractures or the result of earlier trauma, which might have resulted from such heavy exercise.

A cross-sectional study comparing individuals with hip fracture to age-matched controls confirms that men with hip fracture have significantly lower BMD at the femoral neck than their male non-fractured counterparts (152), and women with fracture have significantly less cancellous bone at the fracture site, less cortical bone at impact and significantly larger proximal femur dimensions than female controls. The large Mediterranean Osteoporosis Study (MEDOS) (151;153;154) looked at gender differences in hip fracture and quantified the contribution of various risk factors to this difference. Five percent of the gender difference was attributable to sun exposure, 3% to past history of fracture, 4% to body mass index (BMI), 4% to work-related exercise and 14% to recreational exercise. The effect of calcium did not show a gender predisposition. The effect of alcohol consumption also shows a gender bias, with a smaller ethanol intake being related to hip fracture risk in women than in men (155). In women, 14 – 27 alcoholic beverages per week inferred a relative risk (RR) of hip fracture of 1.44 (1.03-2.03), whereas in men the risk of hip fracture increases at an alcohol intake of over 28 drinks per week, RR 1.75 (1.06-2.89). Current smoking is associated with an increase in the risk of hip fracture in women only, but a significant interaction is not seen between smoking and gender (156). After 5 years, male ex-smokers show a 25% reduction in fracture risk compared to their smoking counterparts, but this protective effect of smoking cessation is not seen in women.

Genetic influences on hip fracture risk are similar in men and women (157;158). Peak height in women and magnitude of height loss with age in men are independent predictors for hip fracture (151). Bone morphometry does not contribute significantly to the difference in risk of hip fracture between the sexes (159).

Similar to other sites, distal forearm fracture is more common in women. Population-based studies have found an incidence of 18 wrist fractures per 10,000/year in women aged over 35 years, compared to 7/10,000/year in men (140); a similar discrepancy is seen in an older cohort of Europeans (incidence 7.3/1000 patient years in women, 1.7/1000 patient years in men) (139). Forearm fracture increases progressively with age in women in this group (139;160-162), whereas the incidence of wrist fracture in men does not increase until a much older age (161-163). History of diabetes mellitus (odds ratio (OR) 0.34, 95% confidence interval (CI) 0.15-0.75) and a history of prior osteoporotic fracture (OR 2.72, 95% CI 1.20 – 6.19) were independently associated with fracture risk in women but not men (164).

## 1.4 Falls in the Elderly

Falling and the subsequent problems of injury, loss of mobility and loss of independence is a significant public health issue in the elderly. One in every three to four people over the age of 65 years and up to two-fifths of those over 80 will experience a fall in the next year (165-167), and many will suffer multiple falls. Falling in the community significantly increases the risk of requiring institutionalized care (168). Physiological changes of aging including loss of muscle bulk and strength (169), deteriorating peripheral sensation (169), balance (169;170) and vision (169;171) combine with disease states, drug-related effects and environmental hazards to impede stable posture and gait. Risk factors for falling in independent-living elderly people have been well characterized (Table 1.2). Intuitively, it is likely that the institutionalized elderly are at an even higher risk of falling due to poorer general health, increased frailty and increased age.

Rates of falling in institutions for elderly care are significantly higher than amongst community-dwelling elders (167). An early review of falls literature in nursing homes (172) revealed an overall mean incidence of falls of 1.5 falls per bed per year (range, 0.2 to 3.6). Studies of falls risks in the institutionalized elderly largely identify the same factors as those identified in their community-based compatriots, in addition to risks peculiar to institutionalized care.

Fall history remains the strongest risk factor for falling (173), those residents who have previously fallen having more than 3 times the risk for subsequent falls. The very old (aged over 87 years) are significantly more likely to fall than their younger counterparts.

**Table 1.2:** Risk factors for falling in community-dwelling elderly persons.

***Demographic Factors***:

- Advanced age (166;174)
- History of previous falls (174-179)
- Limitations in activities of daily living (180)

***Balance and Mobility:***

- Poor standing balance (177;178;181-183),
- Impaired gait and mobility (175;184)

***Sensory and Neuromuscular Factors:***

- Altered proprioception (185)
- Altered muscle strength (178;179;182;185)
- Vision problems (acuity, depth perception) (171;184)
- Poor reaction time (169)

***Medical Factors:***

- Parkinson's Disease (175)
- Arthritis (175)
- Cognitive function (177;186)
- Foot problems (177)
- Depression (187;188)
- Stroke (166;167)
- Urinary incontinence (189;190)

***Medications:***

- Central nervous system-acting (177;191;192)
- Cardiac drugs (193)
- Analgesics (193)
- Use of four or more medications (194;195)

***Environmental factors:***

- Home hazards (196;197)
- Use of walking aids (177)

Muscle strength, in particular lower limb strength, is important for postural stability. Most studies in nursing homes have assessed qualitative muscle strength and its relationship with falls. A case-control study of two distinct populations of elderly people found fallers had poorer lower limb strength than non-fallers (167). 'Weak hip strength', assessed on physical examination (not described further), was associated with being a faller in nursing home residents, mean age 88 years (OR 8.36, 95% confidence interval 2.71-25.79) and in community dwelling elders, mean age 69 years (OR 10.33, 95% confidence interval 2.64-40.36). 'Weak knee strength' was only significantly associated with falling in the community (OR 9.90, 95% confidence interval 2.03-48.44). Tinetti et al. (198) evaluated muscle strength by standard physical examination in 79 nursing home residents, and then followed the group prospectively for 3 months. Reduced muscle strength was recorded as 'decreased knee strength' or 'decreased lower extremity strength', but not quantified. The primary outcome measure was 'multiple (2 or more) falls'. Recurrent fallers were more likely to have reduced muscle strength in either category, compared to residents who fell once or not at all ($p<0.0005$).

Quantitative measures of quadriceps strength were used in a prospective cohort study comparing falling and muscle strength between ambulatory residents of aged care facilities in Japan and the United States (199). Strength was measured as maximum kilograms lifted at the ankle for a single knee extension, and the average measure for each quadriceps used for calculations. There was a four-fold higher fall incidence in the US compared to the Japanese group. Within the US cohort, increasing muscle strength was shown to be related to lower risk of falling ($p=0.04$), and in both cohorts the most falls occurred in residents within the lowest quartile of muscle strength. This

study adds quantitative evidence to the observation that reduced quadriceps muscle strength contributes to the risk of falling in the elderly.

Of recent interest has been the role of vitamin D, parathyroid hormone (PTH) and calcium homeostasis in balance, muscle strength and falls. It is known that vitamin D deficiency brings with it muscle weakness and abnormal gait (200-202) but most studies of the effect of vitamin D on muscle do not consider associated PTH status. It has been suggested that PTH itself has an effect on muscle strength, with muscle weakness and fatigue being a feature of primary hyperparathyroidism (203;204), and improvements being seen in patients after treatment (205-207). A study of the effect of both vitamin D and PTH levels and their relation to falls in long-term care facilities for the aged addressed this issue (208). Eighty-three hostel residents were recruited. Vitamin D levels were universally low (median 25-hydroxyvitamin D level was 27 mnol/L, interquartile range 18-37 nmol/L), and inversely related to PTH levels. Fallers (ascertained retrospectively, but after biochemical analysis) had a significantly lower 25-OH-vitamin D and higher PTH level than non-fallers. Logistic regression showed PTH levels to be predictive of having a history of falls, but 25-OH-vitamin D levels became non-significant. This was the first study to link PTH and falling, but was limited by small numbers and a retrospective study design.

Anti-depressant use in nursing home patients has been shown to be associated with a higher risk of falling (209-212) which is not dependent on the type of anti-depressant therapy (tricyclic anti-depressants, selective serotonin-reuptake inhibitors or trazodone) (213). This large retrospective study by Thapa et al. reviewed 2428 nursing home residents in Tennessee between 1993 and 1996 and identified new users

of each of the three anti-depressant types at inception. These residents and a group of randomly-selected non-user controls were then followed for a variable period of time, until leaving that institution or ceasing medication for 14 days, whichever occurred first. Falls were recorded as the primary outcome, and a total of 3524 falls were experienced over 1460 person-years of follow-up. Adjusted rate ratio for tricyclic anti-depressant use compared to no anti-depressant was 2.0 (95% confidence interval 1.8-2.2), for SSRI use was 1.8 (1.6-2.0) and for the triazolopyridine derivative trazodone 1.2 (1.0-1.4). The higher fall rates persisted through the first 180 days of drug therapy. The half-life of benzodiazepines had an impact on falls risk within this cohort (214), drugs with a longer elimination half-life (>= 24 hours) incurring a higher risk of falling, adjusted rate ratio 1.73 (95% confidence interval 1.40-2.14) compared to 1.12 (0.94-1.40) for drugs with a half life <12 hours. Shorter half-life drugs did however bring an increased risk of nocturnal falls, consistent with their peak period of action, adjusted rate ratio 2.82 (2.02-3.94). There is no conclusive evidence of a different effect of oxidative versus non-oxidative benzodiazepines on femoral fracture rate (215).

The same group identified the different range of falls risk factors between those residents who were able to ambulate independently and those who are non-ambulatory (216). Male residents who were not able to transfer independently were twice as likely to sustain an injurious fall, and those residents within the non-ambulatory group who were more mobile had a higher risk of falling. In contrast, the ambulatory group showed a strong association between the use of psychotropic agents and falls, and female residents were twice as likely to fall as their male counterparts. Nevertheless, residents who were able to transfer independently remain at a higher

risk of falling than the less mobile (173), odds ratio 1.64 (95% confidence interval 1.52-1.75).

It is not clear if the increased risk of falling in males seen in some studies is a real effect (217), with the only well-controlled study of proposed gender differences showing similar falls rates (218). Lord et al. (219) showed that community-dwelling men perform better than women at tests of muscle strength, visual field dependence, body sway and dynamic balance, all of which could be considered protective against falling. Campbell et al. (178) showed there were different risk factors for falling between the genders, men with stroke, arthritis, impaired gait or greater body sway being at high risk of falling, while women are at higher risk if they are on polypharmacy, psychotropic drugs, have muscle weakness or low systolic blood pressure. It may be that the differential distribution of risk factors does not enable reliable comparisons to be made.

The use of physical restraints in nursing home residents has been a widespread practice in the past, until it was discovered that their use was associated with a higher occurrence of fall-related injury (220). An increased rate of falls and recurrent falls with the use of physical restraints has been described in confused elderly nursing home residents (221;222). An interventional study looking at the effect of a restraint reduction program found that non-serious falls were higher after implementation of the program, but there was no significant effect on injurious falls (221). More recently, a large 2 year prospective study of education for restraint reduction in the nursing home environment has shown a 90% reduction in the use of physical restraint

use brought with it a significant decrease in the number of moderate and serious injuries, rate ratio 1.58 (p=0.003) (223).

So is there a difference between a non-serious fall and a fall that causes injury? Tinetti (224) suggests this is the case, finding in a study of 79 nursing home residents with chronic disabilities that injured fallers were over three times more likely to have bilateral lower extremity weakness, were more independent in ambulation and fell less often than uninjured fallers. In a study of risk factors for falling in the community, Lord et al. (225) showed multiple fallers to have weaker quadriceps muscles, poorer tactile sensation, more dependence on visual fields and higher body sway. More research needs to be done to define types of fallers, and who are at the higher risk of injury; this will be addressed further in Section 1.6. Vitamin D replacement alone has not been shown to have a significant effect on the risk of falling (226;227), with the exception of one study of 86 community-dwelling Japanese elders suffering from Parkinson's disease (228). Even in this group, there was a reduction in falls resulting in fracture, but not a significant reduction in falls overall. Two randomized controlled trials have looked at the effect of vitamin D replacement in conjunction with calcium supplementation. Dawson-Hughes et al. (229) reported no effect on any fall parameters with 500mg of elemental calcium and 700IU of vitamin D over 3 years compared to placebo in independently living older people; a more recent short-term randomized controlled trial (230) in long-stay geriatric care however has shown a beneficial effect on of 1200mg of calcium and 800IU of vitamin D the total number of falls over 12 weeks, compared to calcium supplementation alone. It is interesting to note that the institutionalized group was largely vitamin D deficient, 50% of all participants being profoundly deficient and

90% with 25-OH-vitamin D levels below 30 ng/ml (lower limit of normal). This is not surprising as the group was frail, elderly and relatively immobile with reduced exposure to sunlight. Baseline 25-OH-vitamin D levels in the independently-living study were within the normal range. Taken together, these studies would suggest that the effect of vitamin D supplementation on falling is dependent on the recipients being deficient in vitamin D to be significant.

## 1.5 Fractures in the Elderly

Osteoporotic fracture is well recognized as an increasing public health problem, conferring significant cost both to the individual and the community. The problem is only growing larger as the population ages, due to the increased incidence of fracture with increasing age (231): 50-60% of all women over the age of 65 are predicted to have a fragility fracture in their lifetime, and up to one third of men (232).

Over the age of 60, women fracture about 2.3 times as often as men, with the incidence of all fracture types increasing with age for both genders (143). Hip fracture incidence for women aged 85-89 years is 2.8%, and for men in this age group 1.4%. Vertebral fracture is under-reported, but prospective studies using radiological fracture as the outcome estimate the incidence to be 1.1% in women and 0.6% in men (233). Using data from the EVOS study (234), the prevalence of morphometric vertebral deformity ranges from 7.3% to 19.2% in men, and 3.5% to 16.6% in women depending on the stringency of the criteria used in reading the films.

Nursing home residents are not immune to sustaining fractures, with an incidence of hip fracture in institutionalized care of 1.9% (235), and a 7.8% incidence of any fracture (236), translating into 30% of all admissions to hospital for hip fracture (237).

There are multiple documented risk factors for sustaining a fracture in the elderly population, including medications (238), body mass (239-241) and loss of weight (242), falls (243) and low bone mineral density measured by DEXA (14;17;244;245) or by QUS (18;55;56;246), but few studies compare the relative contributions of these factors.

The burden of disease is seen as increased morbidity and mortality at an individual level, and increased health resource utilization and health expenditure on a population level. There is significant morbidity associated with vertebral fracture (247), causing pain and disability. Hip fracture increases the risk of subsequent fracture (248) and of requiring institutionalized care (237). It frequently results in loss of mobility and independence; even those individuals who return to living in the community have significantly impaired mobility and self-reported quality of life (249). A time trade-off study of the utility associated with hip fracture revealed that maintaining independence in daily life was of utmost importance to elderly women (250), and the loss of this independence was perceived to impact greatly on quality of life. Even wrist fracture has been shown to have an associated loss of physical function (251) Both vertebral (144;252-254) and hip fracture (144;237) are associated with a significant increase in mortality. The hazards ratio for 10-year mortality is 2.3-2.4 in both women and men with prevalent vertebral fracture (253). Mortality following hip fracture is much higher, ranging from 25 to 30% in the first year (255).

Loss of independence also contributes to the community costs of osteoporotic fracture. A one-year longitudinal study of the costs arising from hip fracture in Canada showed that the mean 1-year cost of hip fracture for an individual who is transferred or readmitted to institutionalized care is over double that of a patient who returns to independent living (256), acute hospitalization costs only contributing to 27% of the overall incurred costs. Vertebral fracture is associated with significant hospitalization costs, estimated to account for over 400,000 bed-days and US$500 million over one year (257).

Thus with a high incidence of fracture in the frail elderly translating into significant morbidity, mortality and health-related expenses, it is important that those at highest risk can be identified to allow cost-effective, directed interventions.

# CHAPTER 2

# STUDY DESIGN AND DESCRIPTION OF ELDERLY POPULATION

## 2.1 Aims

The Fracture Risk Epidemiology in the Elderly (FREE) study was designed to test the following hypotheses:

1: That quantitative ultrasound (QUS) parameters combined with clinical risk factors for osteoporosis and for falling are useful tools to predict osteoporotic fractures in a high risk population, the frail older person.

2: That vitamin D deficiency contributes to hip fracture risk through an increased risk of falling.

The study was supported by a project grant from the National Health and Medical Research Council of Australia (NH&MRC), and employed the equivalent of two full time research assistants who were responsible for data collection and maintenance of the study database. Ethics approval was obtained from the Royal North Shore Hospital Ethics Committee.

## 2.2 Study Design

The FREE study was set up as a large population-based prospective study of risk factors for falls and fractures, including quantitative ultrasound (QUS) measures to assess osteoporosis. Falls and fractures were then recorded prospectively for a period of 2 years. The study was carried out in the Northern Sydney Health Services area, which covers a geographical area of 1301.8 square kilometres and has a population of 47 275 men and 67 817 women aged 65 years and over (at 2001 Census, http://www.ausstats.abs.gov.au).

Recruitment of aged care facilities to participate in the FREE study began in March 1999. A database of all hostels and nursing homes for aged care in the Northern Sydney Health Services Area was compiled from a list provided by the Department of Health and Aged Care, and institutions were randomly assigned to blocks of 10 nursing homes and 5 hostels. Facilities were then approached block by block (approaching equal numbers of nursing home and hostel blocks) to maintain randomization. Initial contact was made by letter, with a follow up phone call to arrange a preliminary visit.

At each participating facility, all eligible residents were visited and invited to participate. Individuals who were totally non-weight bearing (bed bound, bilateral amputees), non-English speaking or under the age of 65 years were not included in the study. Residents gave informed, signed consent or if unable, their next of kin was approached by letter to give proxy consent. Information on past medical history, falls and fracture risks and a proxy quality of life questionnaire was also obtained from

carers when a resident's cognitive impairment precluded accurate history taking. These individuals were identified by facility staff. If a resident gave independent consent but was subsequently found to be cognitively impaired (defined as a Mini Mental Score of less than 18), the appropriate carer was then approached prior to further participation in the study. This method of obtaining proxy consent has been shown to be valid in other populations (258), and will be further evaluated in this study. Copies of each signed consent form were provided for each patient's file, along with an information sheet about the FREE study and contact details for study personnel. Examples of these forms are given in Appendix 1.

Recruitment of aged care facilities was completed in February 2003, when the target of more than 2000 enrolled residents was reached. Population data from Dubbo, New South Wales, Australia identified a fracture rate of 5 to 10% per year for any fracture in independently-living elderly men and women, and a hip fracture rate of 3 to 5% (232). Estimates from published trials in nursing homes suggest a hip fracture rate of up to 6% per year (259;260). Over the 2 year follow up period, the cohort would be expected to experience approximately 60 (3% per annum) to 120 (6% per annum) hip fractures (allowing for some attrition due to death in this elderly group).

## 2.3 Measurements

Clinical risk factors for both falls and for osteoporosis and fractures were assessed in all subjects at interview. Basic demographics including age, sex, country of birth, activities of daily living status (Barthel Index) (261) and co-morbidities (by Resident Classification Scale graded 1 (lowest care) to 8 (highest level of care required)) (262) were recorded. The RCS is assigned by an aged care assessment team (independent of this research study) and is linked to government funding for ongoing aged care. It incorporates assessments of communication, mobility, ability to eat and drink, hygiene, bladder and bowel management, cognition, aggression or emotional instability, danger to self or others, social needs, medications and technical nursing care requirements (Appendix 2), and as such is a tool to define the degree of nursing care and supervision an individual requires on a daily basis.

The following parameters previously shown to be related to falls (Chapter 1.5) were assessed: use of a walking aid, medications (ascertained by medical record review), history of falls in the previous year, history of stroke, Parkinson's disease, continence, joint replacement, and osteoarthritis of the hip or knee. Knee pain (263) and osteoarthritis of the knee (264) have been associated with objective impairment of balance.

Cognitive function was assessed using the Standardised Mini Mental Status Examination (SMMSE) (265). When one or more (up to 7) of the 30 items were not completed due to visual or hearing impairment, a correction calculation was made (as per personal communication, Dr A. Jorm, NHMRC Psychiatric Epidemiology Research Centre):

$$\frac{\text{(total score possible * total number of items completed satisfactorily)}}{\text{(total score possible – total number of items not attempted).}}$$

When 8 or more items were missing, the total score was recorded as missing as a refusal is most likely due to inability to respond correctly (266). A score of less than 18 was interpreted as the most appropriate cut-off to define insufficient cognitive function to give informed consent for the purposes of this study (267).

Quality of life (QOL) was measured using the EQ-5D (268), a categorized scoring model of the generic EuroQol instrument (269) (which uses visual analogue scale assessments). The form used for data collection is shown in Appendix 1. The EQ-5D has been shown to be valid and reliable for measuring health-related QOL in a number of different healthy (270-273) and disease populations (274-277), including postmenopausal osteoporosis (278). Choice of health-related quality of life instrument is largely a function of the population to be studied (279). The EQ-5D has been shown to be completed more reliably than the other commonly used QOL instrument, the SF-36, in elderly patients after a stroke (258), and experience with other projects in Northern Sydney has shown the EQ-5D is more easily completed by frail older people than either the Sickness Impact Profile or the Medical Outcome Study Short Form 12 (personal communication, Prof. Ian Cameron). Analyses were conducted both with and without proxy quality of life data in light of systematic differences between individual and proxy reporting (280;281). A disease-specific instrument was not incorporated into the study due to the high number of confounding variables and comorbidities in this frail population.

A validated implicit reviewer assigned severity score was given for each resident (282), rated at the time of the baseline assessment, where scores are given as:

- 1 - no symptoms or medical complications
- 2 - mild symptoms
- 3 - moderate symptoms
- 4 - severe symptoms that severely alter or immediately threaten life or prognosis

according to predefined definitions (Appendix 3).

Information relating to osteoporosis and fracture risk was also collected. This included a history of past corticosteroid and hormone replacement therapy (quantified where possible), current or past smoking and history of previous low trauma fracture (after age $\geq$ 50). Self-report of medical conditions (283-285), in particular of previous fracture (286-288), has been shown to be reliable in elderly persons.

Falls risk was tested by assessments of quadriceps strength and static balance, reaction time, visual contrast sensitivity and proprioception according to published methods proven to predict falls and fractures in the elderly (169;245). Quadriceps muscle strength was measured in the sitting position from a standardized chair in the subject's dominant leg using a strain gauge, measured in kilograms. Quadriceps muscle strength, the ability to stand from a seated position and visual contrast discrimination were measured, but will not be discussed further for the purposes of this thesis.

Static balance was measured as the ability of subjects to maintain balance while standing on a firm and a compliant surface, comprising a 150 x 150 x 10 cm foam mat. Subjects were classified into 5 grades

- 1 - unable to maintain balance for any period without support on a firm surface
- 2 - able to stand for less than but not equal to 30 seconds unsupported
- 3 - able to stand for 30 seconds unsupported on firm ground but not on a compliant surface
- 4 - able to stand for 30 seconds unsupported on firm ground but less than 30 seconds on a compliant surface, and
- 5 - capable of maintaining balance whilst standing on a firm or compliant surface for 30 second periods without difficulty.

Weight was measured using the same set of scales in those residents able to stand unsupported. For those who were not sufficiently mobile to use the scales, the scales were calibrated to measure '0 kg' with a ramp and empty wheelchair, and then the resident was weighed whilst sitting in that wheelchair to give a net resident weight. If neither of these methods was possible, the most recent weight in the patient's medical notes was recorded. In order to estimate height, the lower leg length from floor to knee (bent at 90 degrees) was measured for subsequent calculations (289).

An assessment of bone mass was made using two quantitative ultrasound (QUS) machines. Broadband ultrasound attenuation (BUA) and velocity of sound (VOS) were measured at the left calcaneus in all participants using the same McCue CUBA Mark II ultrasound machine. In the event of foot deformity, unilateral foot amputation or injury to the left foot, a measurement was made at the right calcaneus and the reason documented. BUA was also measured using a Metra QUS-2 ultrasound machine in a smaller sample of subjects, as this machine only became

available after study commencement. The coefficient of variation from duplicate measurements for BUA in our laboratory is 2.9% for the CUBA machine and 1.3% for the QUS-2. Each QUS measurement was repeated twice in the study population, repositioning the foot between measurements; a third measurement was taken when the difference between the first two BUA measures was greater than 5 dB/MHz. Each machine was calibrated daily using standard operating phantoms for each machine.

Blood was taken for vitamin D and biochemistry analysis in all consenting participants. Due to the 'invasive' nature of venesection, any resident was permitted to refuse blood being drawn without being excluded from the remainder of the study. Biochemistry was analyzed on a Hitachi 917 analyzer in a single laboratory. Serum 25-hydroxyvitamin D (25OHD) was measured using the Diasorin 25-OH-D radioimmunoassay (RIA) kit. Sensitivity was measured at 4 nmol/L, intra-assay precision 7.6% and inter-assay precision 9.0%, with a 'normal' laboratory range of 39 – 140 nmol/L.

Baseline serum levels of intact parathyroid hormone (PTH) were determined by a two-site chemiluminescent enzyme-linked immunometric assay on a DPC Immulite 1000 analyser. The assay procedure measures the intact PTH molecule. The assay has a typical intra-assay precision of 5.5%, an inter-assay precision of 7.9% and the laboratory reference range is 23.7 – 66.2 pg/mL (2.5 – 7.0 pmol/L).

Serum albumin was measured by BCG colorimetric assay (Roche), with a normal range of 40-50 g/L. The within-run precision (coefficient of variance, CV) given by

the manufacturer was 0.4% and the between-run CV was 1.7%. Inter-assay precision in this laboratory has been calculated as 2.0%. Serum calcium was measured by colorimetric assay (Roche) using p-cresolphthalein and adjusted for circulating albumin levels, with a normal range 2.15-2.55 mmol/ L, manufacturer's within-run CV 0.9% and between-run CV 1.5%, and measured inter-assay CV in this laboratory 2.1%. A modified Jaffé (picric acid) kinetic colorimetric assay was used to measure serum creatinine with a normal range in males of 70-110 μmol/L and in females 50-90 μmol/L, manufacturer's precision of 0.7% intra-assay and 2.3% inter-assay and a measured inter-assay CV of 3.0%. Inorganic phosphorus levels were measured by an endpoint method with sample blanking, based on the formation of ammonium phosphomolybdate complex. The normal range in this laboratory is 0.6-1.3 mmol/L and inter-assay precision of 2.5%; manufacturer's within-run CV is 0.9% and between-run CV is 1.4%.

## 2.4 Follow Up

Once enrolled in the FREE study, residents were followed up on a regular basis to record the number of falls, injuries and fractures that had occurred since recruitment. A fall was defined as 'unintentionally coming to rest on the ground, floor or other lower level, whether or not an injury occurred'. An injury was recorded if it required treatment, medical consultation, investigation or observation or pain relief. Any fracture was confirmed by x-ray, x-ray report or hospital discharge summary. Where a clinical diagnosis of a fracture was made without radiological evidence, it was recorded as 'unconfirmed' and not included in subsequent analyses.

Incident reports were examined at each facility to confirm falls, and radiology reports obtained to confirm each fracture and its site. Residents' medical progress notes were also reviewed to confirm incident reports, to assess any injury that might have been sustained at the time of the fall and to identify any falls that were not captured on incident report. X-ray reports are recognized as being superior to medical record review for ascertainment of fracture incidence (290). All deaths were recorded. Residents who moved facilities were tracked in order to minimize follow up losses.

The first follow up visit took place about 6 weeks after all baseline assessments had been completed for that aged care facility. Visits continued approximately every 2-3 months for 2 years or until death. After 2 years, only hip fractures and deaths were recorded at follow up.

Previous studies have shown osteoporotic fractures to be associated with a decline in QOL (144;168;291) and an increase in overall mortality (144). To assess whether

fractures in frail elderly residents of aged care facilities lead to a decrease in cognitive function, quality of life and increased mortality, each resident sustaining a fracture during the study period was reassessed four months after fracturing, using the SMMSE and EQ-5D instruments. A control subject, matched for age, gender, institution and broad SMMSE function, was also reassessed at that time.

## 2.5 Population Characteristics

Thirty hostels and 52 nursing homes were included in the study. A further 2 hostels were due to be approached but had closed between randomization and study participation. Four nursing homes were approached but refused to participate, 2 were undergoing rebuilding and unable to participate at the time they were approached, and 5 had closed since randomization. Numbers of residents available for recruitment and the subsequent participation rates are given in Table 2.1.

**Table 2.1:** Participation of residents from hostels and nursing homes

| | | Hostel | Nursing home |
|---|---|---|---|
| Number of residents (total) | | 1751 | 2685 |
| Excluded | Age < 65 years | 33 | 59 |
| | Bed bound | 0 | 458 |
| | Non-English speaking | 23 | 89 |
| | Other | 3 | 3 |
| | Total | 59 | 701 |
| Total possible | | 1692 | 1984 |
| Self consent | Total | 1232 | 562 |
| | Included (% response) | 958 (77.8%) | 428 (76.2%) |
| Carers consent | Total | 460 | 1432 |
| | Included (% response) | 149 (32.4%) | 470 (32.8%) |
| Participants | Total (% response) | 1107 (65.4%) | 898 (45.3%) |

A total of 2005 residents were recruited for the study and completed the baseline assessments. Of these, 67% (n=1386) had been self-consents, and the remaining 33% (n=619) had proxy consents completed. As anticipated, carer consent was more difficult to obtain due to a number of reasons, including inability to locate the appropriate carer, introduction of privacy laws that restricted access to information about carers, non-response to multiple mail-outs, mistrust of clinical trials and a desire that a relative be not inconvenienced.

Simple demographic details were collected on non-participants for the first year of the study. Those individuals who refused to participate in the study, either personally or through carer advice, were of a similar age to participants (mean age of non-participants 85.5 years compared to mean age of participants 85.2 years, t=0.79, p=0.4). Non-participants had been residing in aged care facilities for slightly less time than participants (mean difference 3.8 months, 95% confidence interval for the difference 0.15 to 7.4 months, t=-2.04, p=0.04). More non-participants fell into RCS categories 1 and 2 and less into 6-8 than participants ($\chi^2$=116, df 7, p<0.0001) suggesting a lower level of dependency on nursing care.

Baseline demographic characteristics of the study group are given in Tables 2.2 and 2.3. There was no significant difference in the distribution of RCS scores between men and women ($\chi^2$ =11.08, df=7, p=0.14), suggesting that the range of disability was the same for men as for women.

**Table 2.2:** Resident classification scores (RCS) for men and women

| RCS | Male (n=473) | Female (n=1532) |
|---|---|---|
| 1 (least care required) | 37 (7.8%) | 163 (10.6%) |
| 2 | 99 (20.9%) | 304 (19.8%) |
| 3 | 68 (14.4%) | 240 (15.7%) |
| 4 | 21 (4.4%) | 52 (3.4%) |
| 5 | 26 (5.5%) | 119 (7.8%) |
| 6 | 63 (13.3%) | 184 (12.0%) |
| 7 | 37 (7.8%) | 163 (10.6%) |
| 8 (most care required) | 99 (20.9%) | 304 (19.8%) |

**Table 2.3:** Baseline characteristics of the FREE cohort

| | | Male | | | Female | | |
|---|---|---|---|---|---|---|---|
| | | Hostel | NH* | Total | Hostel | NH | Total |
| Number | | 263 | 210 | 473 | 844 | 688 | 1532 |
| Age (years), mean (sd) | | 82.3 (7.42) | 83.4 (6.36) | 82.8 (7.81) | 86.6 (8.24) | 86.7 (6.86) | 86.6 (6.59) |
| Implicit review | 1 (no symptoms) | 20 (7.5%) | 1 (0.5%) | 21 (4.4%) | 44 (5.2%) | 2 (0.3%) | 46 (3.0%) |
| | 2 (mild symptoms) | 102 (38.8%) | 28 (13.3%) | 130 (27.5%) | 313 (37.1%) | 83 (12.1%) | 396 (25.8%) |
| | 3 (moderate symptoms) | 133 (50.6%) | 165 (78.6%) | 298 (63.0%) | 471 (55.8%) | 552 (80.2%) | 1023 (66.8%) |
| | 4 (severe symptoms) | 7 (2.7%) | 14 (6.7%) | 21 (4.4%) | 10 1.2%) | 38 (5.5%) | 48 (3.1%) |
| | Not yet determined | 1 (0.4%) | 2 (0.9%) | 3 (0.7%) | 6 (0.7%) | 13 (1.9%) | 19 (1.3%) |
| Number of fallers in past 12 months (%) | | 118 (44.9%) | 123 (58.6) | 241 (51.0%) | 381 (45.1%) | 411 (59.7) | 792 (51.7%) |
| Number sustaining a low-trauma fracture since the age of 50 (%) | Any fracture | 56 (21.3%) | 61 (29.0%) | 117 (24.7%) | 409 (48.5%) | 372 (54.1%) | 781 (51.0%) |
| | Hip | 12 (4.6%) | 25 (11.9%) | 37 (7.8%) | 108 (12.8%) | 184 (26.7%) | 292 (19.1%) |
| | Spine | 7 (2.7%) | 7 (3.3%) | 14 (3.0%) | 80 (9.5%) | 145 (21.1%) | 125 (8.2%) |
| | Wrist | 5 (1.9%) | 8 (3.8%) | 13 (2.7%) | 138 (16.4%) | 85 (12.4%) | 223 (14.6%) |
| Smoker (current) | | 46 (17.5%) | 8 (3.8%) | 54 (11.4%) | 30 (3.6%) | 19 (2.8%) | 49 (3.2%) |
| OA knee | | 78 (30.0%) | 46 (21.9%) | 124 (26.2%) | 332 (39.3%) | 196 (28.5%) | 528 (34.5%) |
| Hip replacement | | 14 (5.3%) | 18 (8.6%) | 32 (6.8%) | 84 (10.0%) | 74 (10.8%) | 158 (10.3%) |
| Knee replacement | | 21 (8.0%) | 13 (6.2%) | 34 (7.2%) | 56 (6.6%) | 34 (4.9%) | 90 (5.9%) |
| Incontinence | Day | 76 28.9%) | 99 (47.1%) | 175 (37.0%) | 291 (34.5%) | 371 (53.9%) | 662 (43.2%) |
| | Nght | 110 (41.8%) | 119 (56.7%) | 229 (48.4%) | 336 (39.8%) | 429 (62.4%) | 765 (47.5%) |
| HRT | | N/A | N/A | N/A | 55 (6.5%) | 23 (3.3%) | 78 (5.1%) |
| Corticosteroids | | 28 (10.6%) | 10 (4.8%) | 38 (8.0%) | 81 (9.6%) | 59 (8.6%) | 140 (9.1%) |
| Parkinson's disease | | 23 (8.7%) | 32 (15.2%) | 55 (11.6%) | 17 (2.0%) | 44 (6.4%) | 61 (4.0%) |
| History of CVA | | 69 (26.2%) | 62 (29.5%) | 131 (27.7%) | 151 (17.9%) | 153 (22.2%) | 304 (19.8% |

Women were an average of 3.8 years older than their male counterparts (95% confidence interval for the difference 2.99 to 4.55, t=9.51, p<0.0001). Women were more three times more likely than men to have a history of minimal trauma fracture since the age of 50 years, independent of fracture type (Table 2.4). There was no significant difference in the reporting of falling in the previous 12 months between men and women.

**Table 2.4:** Odds ratios (OR) for demographic measures for females compared to males.

| | OR | 95% CI | $\chi^2$ statistic | p |
|---|---|---|---|---|
| Nursing home accommodation | 0.98 | 0.80 – 1.21 | 0.038 | 0.9 |
| History of falls | 1.02 | 0.89 – 1.09 | 0.116 | 0.75 |
| History of any fracture | 3.18 | 2.52 – 4.02 | 101.144 | <0.0001* |
| - hip fracture | 2.80 | 1.96 – 4.01 | 33.051 | <0.0001* |
| - wrist fracture | 6.09 | 3.45 – 10.76 | 49.24 | <0.0001* |
| - spine fracture | 2.91 | 1.66 – 5.11 | 15.143 | <0.0001* |
| Smoking | 0.26 | 0.17 – 0.39 | 49.69 | <0.0001* |
| Incontinence - day | 1.36 | 1.07 – 1.64 | 6.46 | 0.01* |
| Incontinence - night | 1.09 | 0.89 – 1.34 | 0.605 | 0.4 |
| Parkinson's disease | 0.32 | 0.22 – 0.46 | 38.29 | <0.0001* |
| History of CVA | 0.65 | 0.52 – 0.83 | 12.32 | <0.0001* |

*statistically significant p<0.05)

Elderly persons in Australia who require assisted accommodation are assigned places in hostels or nursing homes according to the perceived level of care required,

measured by RCS. It would therefore be expected that nursing home residents, requiring a higher level of day to day care, would have significantly more comorbidity and poorer levels of function. When compared to hostel residents, individuals living in nursing homes were seen to have approximately a two-fold increase risk of being fallers (OR 1.9, $p<0.0001$), were more likely to have sustained a hip fracture (OR 2.5, $p<0.0001$) and more likely to be incontinent of urine or have a history of stroke (Table 2.5). Nursing home residents were significantly less likely to be current smokers, most probably related to immobility (smoking now rendered an outdoor activity in Australian aged care facilities).

**Table 2.5**: Odds ratios (OR) for demographic measures for nursing home residents compared to hostel residents.

| | OR | 95% CI | $\chi^2$ statistic | p |
|---|---|---|---|---|
| Female gender | 1.02 | 0.83 – 1.26 | 0.04 | 0.9 |
| History of falls | 1.93 | 1.61 – 2.31 | 50.23 | <0.0001* |
| History of any fracture | 1.32 | 1.11 – 1.58 | 9.44 | 0.002* |
| - hip fracture | 2.49 | 1.95 – 3.18 | 55.80 | <0.0001* |
| - wrist fracture | 0.77 | 0.58 – 1.01 | 3.31 | 0.07 |
| - spine fracture | 0.72 | 0.51 – 1.03 | 2.97 | 0.09 |
| Smoking | 0.42 | 0.27 – 0.66 | 15.16 | <0.0001* |
| Incontinence - day | 2.34 | 1.95 – 2.81 | 83.97 | <0.0001* |
| Incontinence - night | 2.50 | 2.08 – 3.01 | 98.00 | <0.0001* |
| Parkinson's disease | 2.54 | 1.71 – 3.77 | 22.88 | <0.0001* |
| History of CVA | 1.38 | 1.11 – 1.71 | 8.63 | 0.002* |

*statistically significant, $p<0.05$)

The FREE cohort has been shown to be a heterogeneous population, with wide ranges of comorbidity. Their commonality lies in their advanced age, and a requirement for assisted living which renders them unable to live independently. This thesis examines the health of the frail elderly with respect to bone, specifically their risk of falls and fractures which incur significant morbidity and mortality to an already impaired population.

## 2.6 Discussion

The major strengths of this study lie in its size, randomization and prospective follow up. To our knowledge this is one of the largest prospective studies of falls and fracture risk that has been undertaken in frail institutionalized elderly population, with previous studies recruiting in the low hundreds (176;292-295). In particular, this is the largest cohort of elderly men studied in aged care facilities for any of the falls or fracture parameters. The study is population-based, with rigorous prospective data collection over a minimum of 2 years. Aged care facilities were randomized at the outset and this randomization was maintained throughout the study with negligible facility refusal or drop-out. Large numbers of both men and women have been recruited. The response rate from residents able to give self-consent was reasonable, and once recruited all participants completed the study with minimal 'missing' data.

The population was comparable in age and gender to previous published studies in the elderly who live in assisted care facilities (58;173;176), allowing generalizability to other groups around the world. This supports the applicability of our results to other frail elderly populations. Non-participants were of a similar age to participants and had lower RCS classifications, so that we can be confident in the assumption that the study includes the more frail population. This does introduce a potential bias in the study group, which must be considered when relating the results of the FREE study in healthier, more independent populations.

All major outcome measures had been previously validated in published studies, to allow meaningful conclusions to be drawn.

Quantitative ultrasound of the calcaneus has been shown to be a predictor of fracture rate in younger, independently living populations (54-56) and in smaller studies of the frail elderly (57;58). This study has measured BUA and VOS in a much larger population, which has not been carried out on such a large scale previously. It is anticipated that this will provide a greater power to predict fracture in a population of elderly persons living in aged care facilities. This is important from a practical viewpoint, as QUS is much more easily performed in a frail immobile population than the 'gold standard' DEXA measurement.

One of the problems encountered in the recruitment of participants for the FREE study was a poor carers' response, resulting in a smaller proportion of cognitively impaired residents (compared to those with adequate cognition to give self-consent) being included in the study. This skews the population towards a higher cognitive function than truly exists in hostel and nursing home accommodations. Such a recruitment bias must be considered when interpreting results, particularly if poor cognitive function contributes to falls and fracture risk (176;296). This systematic bias would result in an underestimate of the true falls and/or fracture risk in assisted care facilities, and reduce the power of the study to detect possible relationships between cognitive function, falls and fractures.

Those individuals who were non-English speaking, bed-bound or bilateral amputees were not included in the analysis, which might impact on the generalizability of our results. There were a total of 112 (2.5%) non-English speaking residents who were not approached for the study; care must be taken in applying the findings of the FREE study to recent immigrants to Australia. Nevertheless, 83 (4.1%) of residents included

in the study were born in non-English speaking countries, allowing a degree of generalizability of results to elderly individuals of different ethnic backgrounds who have lived in Australia for some years.

There were 458 residents (10.3%) in the nursing homes participating in the study who were bed bound and therefore not included; this is unlikely to have affected outcomes as it is deemed that if a resident does not mobilize in any way, the only factor important in future risk of falling is nursing care, which is not the purpose of this study. The remaining 6 exclusions form only 0.1% of the aged care facility population, and so even if they fell in the highest or lowest risk categories, their exclusion would not impact the final results.

Loss to follow up is a major difficulty in this elderly population, due to the high mortality rate in the frail elderly. Cox regression has been carried out to maximize the information collected during the study, allowing all residents who completed baseline assessment to be included in the analyses up until the time of death. The large number of residents recruited for the study will in part offset the expected losses to mortality from all causes.

In summary, this is a large well-constructed population-based prospective study of falls and fracture risks in the frail elderly living in aged care facilities which is expected to yield valuable information to ultimately assist in formulating preventative strategies for this high-risk population.

# CHAPTER 3

# VARIANCE OF QUANTITATIVE ULTRASOUND MEASUREMENT IN THE FRAIL ELDERLY

# VARIANCE OF QUANTITATIVE ULTRASOUND MEASUREMENT IN THE FRAIL ELDERLY

## 3.1 Introduction

Osteoporosis is an increasing community health problem, particularly as the population ages. Bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DEXA) is the current gold standard for the diagnosis of osteoporosis. BMD has been shown to predict fracture risk, with each standard deviation reduction in femoral neck BMD increasing the age-adjusted risk of hip fracture by about two fold (range 2.0 to 3.5) as well as the risk of any atraumatic fracture by two (range 1.7 to 2.4) (14;17;244;245). DEXA is however not always feasible, for example in large population 'screening' and in elderly, less mobile groups. Calcaneal ultrasound is a portable, easy to use and non-invasive method of assessing trabecular bone and has been recently shown to predict risk of osteoporotic fracture in community-dwelling postmenopausal women (55;56). Little is known of the reliability or reproducibility of heel ultrasound techniques in the very elderly and how this may vary with increasing age.

This study aimed to investigate the reliability and reproducibility of two calcaneal ultrasound machines in a population of frail elderly institutionalized subjects, exploring the variability of broadband ultrasound attenuation (BUA) and velocity of sound (VOS) in the very elderly and to assess sensitivity to change with extreme ageing.

## 3.2 Methods

As this analysis was carried out prior to the completion of patient recruitment, only the first 1587 subjects recruited into the FREE study who had calcaneal ultrasound measurements were included in this analysis, of which 1210 (76.2%) were female.

### 3.2.1 Measurements

Broadband ultrasound attenuation (BUA) and velocity of sound (VOS) were measured in all participants using the same CUBA Mark II ultrasound instrument (McCue Ultrasonics, London, UK). BUA was also measured using the QUS-2 ultrasound machine (Quidel Corporation, San Diego, USA) in 684 (509 females) of the participants. BUA measurements were taken in a lesser number of subjects with the QUS-2 machine, as the machine only became available for use after study commencement. Assessments were made at the left calcaneus, unless foot deformity or oedema precluded measurement and then the right heel measurement was taken. Two consecutive measurements were made, repositioning the foot for each measurement. Fifty-six consecutively recruited residents of hostels were remeasured using the same technique on the CUBA after an average period of 2.2 years. T-scores were calculated using machine-defined normal ranges.

Patient details including age and medication history were collected, and weight was measured in all participants, using a wheelchair ramp for those patients unable to stand unsupported on the scales. Height was not measured in this population.

Ambient temperature has been shown to affect QUS accuracy and precision of the Achilles (Lunar) water bath machine, giving higher values at lower temperatures

(297), but it is not known if this is applicable to dry systems. Air conditioning in hostels and nursing homes kept relatively stable room temperatures throughout our study. Moreover, follow-up measures were taken in the same season as the original measurements to avoid temperature measurement errors longitudinally.

### 3.2.2 Statistical methods

*Analysis of reproducibility*

Three sample statistics were computed to assess the reproducibility of each measure: (a) the standard error measurement (SEM, within-subject standard deviation) which was calculated as the square root of the average variance from individual subjects, (b) this SEM was then expressed in relation to the overall mean as the coefficient of variation, and (c) the limit of agreement (LoA) as described by Bland and Altman (298).

*Analysis of concordance between CUBA and QUS-2 machines*

The concordance between the CUBA and QUS-2 instruments for BUA was addressed by calculating the coefficient of concordance (299) as

$C = \frac{2Cov\left(BUA_c, BUA_q\right)}{s_c^2 + s_q^2 + \left(BUA_c - BUA_q\right)^2}$. $Cov(BUA_c, BUA_q)$ is the covariance between the measurement of BUA by CUBA, and BUA by QUS-2 instrument, $s_c^2$ and $s_q^2$ are the between-subjects variance of BUA measurements by the CUBA and QUS-2, respectively, and $BUA_c$ and $BUA_q$ are the respective means of BUA measured by the two instruments. The coefficient $C$ is an index of agreement of measurements between two instruments, i.e. the degree to which pairs of measurements fall on the line of identity. Thus, even with a high correlation between the two methods, if their

means are different, the value of *C* is still small, e.g. poor agreement. Limits of agreement between machines were calculated using repeated BUA measures for each of the two instruments (12). The weighted Kappa statistic was used to assess the degree of agreement between the two instruments in various T-score-based classifications.

*Longitudinal analysis*

Statistical analysis was carried out following the method of Nguyen and Eisman (300). For subjects with two visits, the rates of change in BUA and VOS (CUBA) were expressed in actual units and in percentage terms. In the latter, the difference between the mean measurement at the follow-up visit and the mean baseline measurement was calculated, then divided by the mean baseline measurement, and expressed as a percentage change. Because each measurement (either at baseline or follow-up visit) was subjected to random measurement error, a change was considered "significant" if it exceeds the change that may be expected from random fluctuation with a certain probability. In traditional analysis, the variance of difference between two successive measurements, $x_0$ and $x_1$ is equal to the sum of individual variances, i.e., $\text{var}(x_0 - x_1) = 2s^2$, where *s* is an estimate of SEM as mentioned above. Under the assumption of the Normal distribution, $1.96 \times \sqrt{2}s$ (also known as the least significant criterion (*LSC*)) covers 95% of the random variability of within-subject differences. However, the above formulation is based on the assumption that successive measurements within an individual are independent. This is unlikely to be true, as measurements within an individual are correlated, although the correlation decreases with increasing intervals between measurements. Therefore, a more logical formulation must take this correlation into account. Assuming a simple

autoregressive model, the variance of difference between successive measurements can be shown to be equal to: $\text{var}(x_0 - x_1) = 2s^2\left[(1-\rho_i) + \rho_i s_a^2 / s^2\right]$, where $\rho_i$ is the serial correlation between two consecutive measurements; and $\sigma_a^2$, the analytical variance (e.g. its square root, $\sigma_a$, is referred to as measurement error) included in the within-subject variance, $s^2$. As the analytical variance is small relative to the within-subject variance, the formula can be reduced to: $\text{var}(x_0 - x_1) = 2s^2(1-\rho_i)$. Therefore, in this study, we used two criteria to assess the longitudinal change in each ultrasound measure

## 3.3 Results

### 3.3.1 Demographics

The characteristics of the study population are shown in Table 3.1. Females were on average of 3.94 years older than their male counterparts (95% confidence interval 3.13 to 4.74 years, p <0.001) and weighed 14.4kg less (95% CI 12.8 - 15.9, p <0.001).

**Table 3.1:** Descriptive statistics of the study population and duplicate ultrasound measures, given as mean and standard deviation.

| | | Female | Male |
|---|---|---|---|
| Number | | 1210 | 377 |
| Age (years) | | 86.26 (6.68) | 82.32 (7.78) |
| Weight (kg) | | 56.76 (12.52) | 71.14 (13.47) |
| CUBA BUA (dB/MHz) | Measure 1 | 45.70 (18.13) | 71.83 (23.00) |
| | Measure 2 | 45.44 (18.31) | 71.88 (23.02) |
| CUBA VOS (m/s) | Measure 1 | 1558.73 (42.83) | 1596.46 (47.60) |
| | Measure 2 | 1558.45 (43.52 | 1596.26 (47.97 |
| QUS-2 BUA (dB/MHz) | Number | 509 | 175 |
| | Measure 1 | 53.52 (14.88) | 73.50 (21.19) |
| | Measure 2 | 53.43 (14.81) | 73.46 (21.96) |

The mean difference between repeated BUA measures on the CUBA machine for the entire cohort was 0.315 dB/MHz, standard deviation 2.388 (t=5.2, p<0.0001). This is not a clinically meaningful difference, but statistically significant due to the large sample size. Similarly the mean difference between repeated BUA measures on the

QUS-2 machine (for the entire cohort) was -0.014 dB/MHz, standard deviation 2.885 (t=-0.1, p=0.9).

### 3.3.2 Reproducibility

Reproducibility statistics are given in Tables 3.2 and 3.3. Mean CUBA BUA (F=10.93, p<0.0001), mean CUBA VOS (F= 21.14, p<0.0001) and mean QUS BUA (11.92, p<0.0001) all decreased significantly with increasing age. The within-subject SEM for BUA was 1.6 dB/MHz in the CUBA and 2.0 dB/MHz in the QUS-2 and the within-subject coefficient of variation (wCV) for BUA was 3.1% for CUBA and 3.4% for QUS-2, neither value being significantly different between machines. Variation in SEM was independent of mean BUA and of age ($r$ = -0.01, p = 0.78) as seen in figure 3.1. Limits of agreement between duplicate measurements of BUA ranged from –4.4 to 5.0 dB/MHz with the CUBA, and from –5.7 to 5.6 dB/MHz with the QUS-2.

For VOS (CUBA), the within-subject SEM was 5.0 m/s and the CV 0.3%. The within-subject SEM significantly increased as the mean VOS increased ($r$ = 0.11, p < 0.001), but there was no significant correlation between SEM and age ($r$ = 0.01; p = 0.89). The limits of agreement between two measurements ranged from -15 to 16 m/s.

**Table 3.2.** Analysis of reproducibility of CUBA BUA, CUBA VOS, and QUS-2 BUA in an elderly institutionalized population.

| | CUBA | | QUS-2 |
|---|---|---|---|
| Statistic and parameter | BUA (dB/MHz) | VOS (m/s) | BUA (dB/M |
| Mean ± SD | 51.8 ± 22.4 | 1567.5 ± 46.9 | 58.6 ± 18.9 |
| Error variance | 2.6 | 25.2 | 4.2 |
| "True" variance | 378.7 | 1975.4 | 354.3 |
| Coefficient of reliability | 0.993 | 0.987 | 0.988 |
| Coefficient of reliability (T scores) | 0.10 | 0.12 | 0.16 |
| Within-subject SD (SEM) | 1.6 | 5.0 | 2.0 |
| Coefficient of variation | 3.1% | 0.3% | 3.4% |
| Limits of agreement | -4.4 to 5.0 | -14.8 to 15.8 | -5.7 to 5.6 |
| LSC ($1.96 \times \sqrt{2}\sigma_i$) | 4.5 (8.6%) | 13.9 (0.9%) | 5.7 (9.7%) |
| $LSC = 1.96 \times \sigma_i \sqrt{2(1-\rho_i)}$ [a] | 1.3 (2.4%) | 5.4 (0.3%) | 1.6 (2.7%) |

[a]: The correlation between two consecutive measurements was estimated to be 0.92 for BUA measurement and 0.88 for VOS.

LSC – least signfigicant change

**Table 3.3.** Mean, between-subjects standard deviation (bSD), within-subjects standard deviation (wSD) and within-subject coefficient of variation (wCV) stratified by age group.

| Variable | | <80 | 80-89 | 90+ | All Ages |
|---|---|---|---|---|---|
| CUBA BUA | Mean* | 59.6 | 52.2 | 46.3 | 51.9 |
| | wSD | 1.7 | 1.8 | 1.6 | 1.7 |
| | wCV | 2.8 | 3.4 | 3.4 | 3.3 |
| | bSD | 22.4 | 22.0 | 21.6 | 22.4 |
| | bCV (%) | 37.6 | 42.1 | 46.7 | |
| | | | | | |
| CUBA VOS | Mean* | 1579.8 | 1569.1 | 1557.4 | 1567.7 |
| | wSD | 5.0 | 5.9 | 5.2 | 5.5 |
| | wCV | 0.3 | 0.4 | 0.3 | 0.4 |
| | bSD | 46.7 | 47.6 | 43.8 | 46.9 |
| | bCV (%) | 3.0 | 3.0 | 2.8 | |
| | | | | | |
| QUS-2 BUA | Mean* | 65.2 | 57.2 | 55.6 | 58.5 |
| | wSD | 2.0 | 1.8 | 2.4 | 2.0 |
| | wCV | 3.1 | 3.2 | 4.3 | 3.5 |
| | bSD | 19.3 | 18.5 | 18.3 | 1.5 |
| | bCV (%) | 29.6 | 32.3 | 32.9 | |
| | | | | | |

*statistically significant, $p<0.0001$).

**Figure 3.1a:** Difference between duplicate measures for BUA in women measured by CUBA

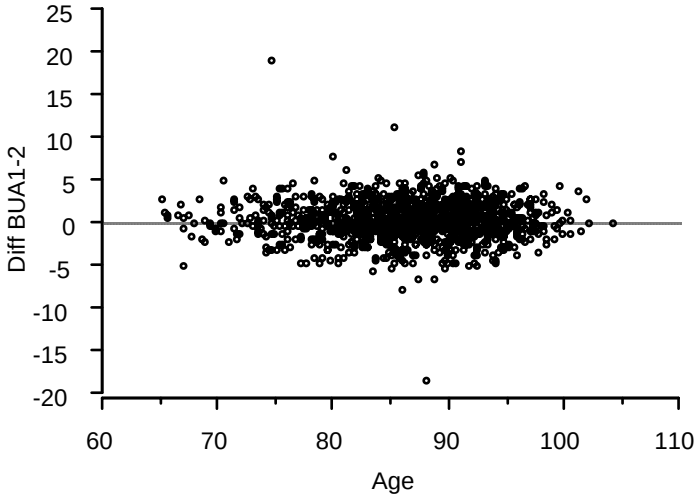
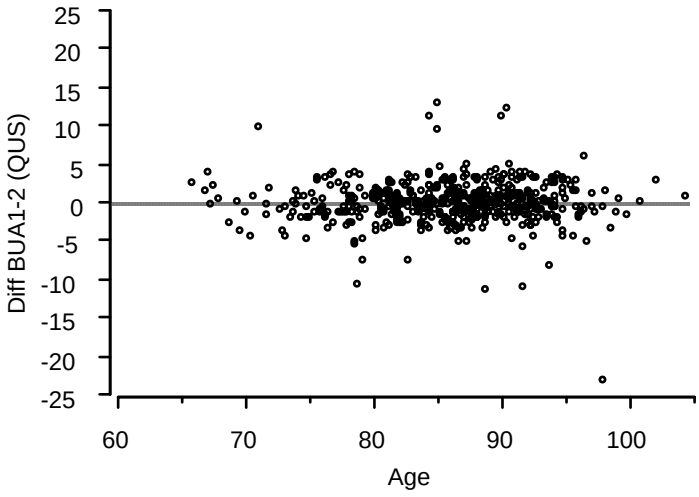



**Figure 3.1b:** Difference between duplicate measures for BUA in women measured by QUS-2



### 3.3.3 Concordance between CUBA and QUS-2

BUA was measured using both machines in 684 subjects (Table 3.4). The correlation coefficient for BUA between the two instruments was 0.87 ($p < 0.001$). On average, BUA measured by the QUS-2 was significantly higher ($p < 0.0001$) than that measured by the CUBA by approximately 1.9 dB/MHz (standard deviation of the differences corrected for repeated measures 9.547 dB/MHz). QUS-2 BUA measures may range from 16.5 dB/MHz below CUBA BUA measurement to 20.3 dB/MHz above CUBA BUA (95% confidence interval).

**Table 3.4.** Comparison of BUA (dB/MHz) and T-scores measured by CUBA and QUS-2 instruments

| | CUBA | QUS-2 | Difference (95% CI) |
|---|---|---|---|
| **Males** | | | |
| Number of subjects | 175 | 175 | |
| BUA (dB/MHz) | 73.1± 20.7 | 73.7 ± 21.4 | 0.6 (-1.0 to 2.2) |
| T-scores | -2.1 ± 1.2 | -1.2 ± 1.6 | 0.9 (0.8 to 1.0) |
| **Females** | | | |
| Number of subjects | 509 | 509 | |
| BUA (dB/MHz) | 51.1 ± 15.6 | 53.4 ± 14.8 | 2.3 (1.2 to 3.4) |
| T-scores | -2.3 ± 0.9 | -2.8 ± 1.1 | -0.4 (-0.38 to -0.50) |

When stratified by gender, the difference remains significant in females (average difference 2.3 dB/MHz, 95% LoA –15 to 19 dB/MHz) but not seen in males (average difference 0.6 dB/MHz, 95% LoA –21 to 23dB/MHz). Nonetheless, when BUA is expressed relative to the young normal mean, the QUS-2 T-scores were significantly higher than the CUBA T-scores in males; the reverse was observed in females (Table 3.4). As a result, there was a poor agreement between the two instruments in the classification of subjects based on T-scores (Table 3.5).

**Table 3.5.** T-score classifications from BUA by CUBA and QUS-2 instruments

| | Males | Females |
|---|---|---|
| Cuba BUA T-scores | | |
| Less than -2.5 | 74 (42.3%) | 269 (52.9%) |
| Between -1 and -2.5 | 74 (42.3%) | 184 (36.2%) |
| More than or equal to -1 | 27 (15.4%) | 55 (10.8%) |
| QUS-2 BUA T-scores | | |
| Less than -2.5 | 47 (26.9%) | 331 (65.0%) |
| Between -1 and -2.5 | 49 (28.0%) | 130 (25.5%) |
| More than or equal to -1 | 79 (45.1%) | 48 (9.5%) |
| Agreement between two instruments (Kappa) | 0.44 ± 0.04 | 0.62 ± 0.03 |

Product-moment correlation coefficient for BUA: 0.88 ($p < 0.0001$), and T-score BUA: 0.76 ($p < 0.0001$).

For example, in males, 42% had CUBA T-scores less than -2.5, while the same classification was found in 27% by QUS-2 T-scores. In contrast, more females are seen with QUS-2 T-scores less than -2.5 (65%) than with CUBA T-scores (53%). The Kappa coefficients for males and females were 0.44 ± 0.04 and 0.62 ± 0.03, respectively.

### 3.3.4 Longitudinal Measurements

There were 56 residents with longitudinal measurements. During the 2.2 years (range: 2.0 to 2.3 yrs) of follow-up, the mean ± SD change in BUA (measured by CUBA) was -1.9 ± 8.3 dB/MHz ($p = 0.09$, not statistically significant), but percentage change from baseline was statistically significant at -5.2 ± 16.5 % ($p = 0.02$). For VOS, the change was not statistically significant either in absolute units (0.8 ± 21.5 m/s; $p = 0.79$) or in percentage terms (0.1 ± 1.3 %; $p = 0.76$). Changes in QUS measures were not related to calcium, vitamin D supplementation or to bisphosphonate use in this small study. Eight of the 10 residents measured at 2 years who were on bone preserving medications or commenced these over the study period decreased in BUA (range -1.33 to -17.73 dB/MHz), one resident being maintained on calcium and vitamin D increased BUA by 5.46 dB/MHz and one resident commenced on calcium and vitamin D during the study increased by 29.92 dB/MHz.

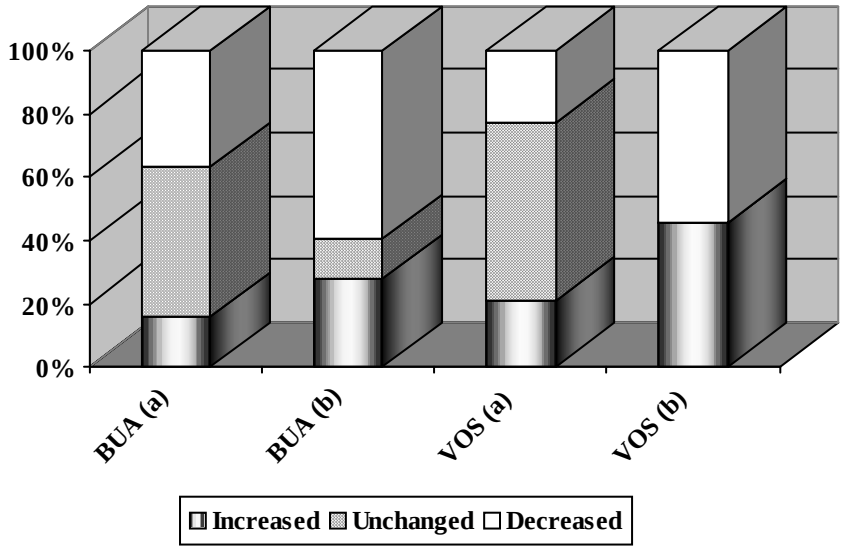
As expected, the correlation between baseline and follow-up measurements was statistically significant for both BUA ($r = 0.92$; $p < 0.001$) and VOS ($r = 0.85$; $p < 0.001$). Using the criteria of least significant change with the serial correlation being

taken into account ( $LSC = 1.96 \times \sigma_i \sqrt{2(1-\rho_i)}$ ), any change in BUA of more than 1.3 dB/MHz and in VOS of more than 5.8 m/s, in either direction, can be considered statistically significant. Accordingly, 28% and approximately 60% of the changes in BUA were classified as "decreased" and "increased", respectively, while the remainder (12%) were classified as "unchanged". Similarly, 46% of the changes in VOS were regarded as a "significant increase" and 54% were regarded as "significant decrease" (table 3.6). Approximately 39% of subjects had significant decrease in *both* BUA and VOS, while 18% had significant increase in both measurements (Figure 3.2).

**Table 3.6:** Changes in BUA and VOS (N=56), measured by CUBA.

| | **Increased** | **Decreased** | **Unchanged** |
|---|---|---|---|
| *Using* $LSC = 1.96 \times \sigma_i \sqrt{2(1-\rho_i)}$ *as criteria* | | | |
| BUA (n; %) | 16 | 34 | 7 |
| | (28.1) | (59.7) | (12.3) |
| VOS (n; %) | 26 | 31 | 0 |
| | (45.6) | (54.4) | (0) |
| *Using* $LSC = 1.96 \times \sqrt{2}\sigma_i$ *as criteria* | | | |
| BUA (n; %) | 9 | 21 | 27 |
| | (15.8) | (36.8) | (47.7) |
| VOS (n; %) | 12 | 13 | 32 |
| | (21.1) | (22.8) | (56.1) |

**Figure 3.2:** Percentage of individuals with significant change in BUA and VOS over 2.2 years using CUBA (N=56)




a: Using ($LSC = 1.96 \times \sqrt{2}\sigma_i$) as criteria for significant change

b: Using ( $LSC = 1.96 \times \sigma_i \sqrt{2(1-\rho_i)}$ ) as criteria for significant change

## 3.4 Discussion

The interpretation of any diagnostic tool requires a good understanding of the accuracy and reliability inherent in that test. This study has described the precision and reproducibility of two calcaneal ultrasound instruments in an elderly population, in order to estimate the prevalence of osteoporosis (Chapter 4) and assess bone loss over time in this group. Coefficients of variation for BUA for the CUBA ultrasound instrument (3.1%) and the QUS-2 instrument (3.4%) compare well with other machines which measure BUA, but are higher than for VOS or for BMD measured by DEXA (301). VOS appeared more sensitive to change than BUA with the LSC for BUA being 2.4% compared to 0.3% for VOS measurement, but longitudinally VOS was not seen to change in our population, with equivalent numbers of patients increasing as decreasing VOS. This has important implications for study design; choice of sample size and the most appropriate bone measurement will depend on the magnitude of change expected for each parameter measured and the power required in addition to machine precision. Our data suggests age has little influence on the precision and within subject variance of calcaneal ultrasound even in the very elderly, making it a useful tool for epidemiological studies of bone loss in an older population.

Statistically, the correlation in BUA between CUBA and QUS-2 instruments was high ($r = 0.87$, $p<0.0001$), however, there was a poor concordance between the two instruments. It is interesting to observe that BUA measured by CUBA was significantly higher than that measured by QUS-2, although the difference was found in women but not in men, probably due to the smaller sample size in the latter group. It is not clear why there was a systematic difference in BUA between the instruments, given the fact that they have virtually identical degree of precision. Nevertheless, the

discordance between the instruments raises the question of accuracy of BUA measurement.

Results of the present study also suggest that if QUS is used for the diagnosis of osteoporosis (or low bone mass) then standardisation across instruments must be addressed first. Between the two instruments evaluated in this study, there was a high discordance in the diagnosis of low bone mass. If the criteria of T-scores < -2.5 was used as a definition of "low bone mass" then QUS-2 was more likely to classify a women as "low bone mass" (65%) compared to CUBA (53%). On the other hand, in men, the prevalence of low bone mass was significantly higher in CUBA T-scores (42%) than in QUS-2 (27%). This suggests that the two instruments use systematically different referent databases, or different algorithms to compute the T-scores. Each instrument is programmed with its own specific normal range, the CUBA using a British normal population and the QUS-2 a US population; inherent differences between these groups may contribute to the different T-score classifications seen. It would seem from our comparative data for two quantitative ultrasound instruments, and the variable precision, reproducibility and sensitivity to change reported by other investigators using other machines, that the use of QUS for the assessment of osteoporosis is instrument specific and should not be generalised between models. Thuy et al (302) recently showed poor agreement between data-based and machine-based T-score classifications ($\kappa$=0.65) in a large Vietnamese population-based study using the QUS-2 instrument. The use of T-scores as a means of classifying osteoporosis was initially described in post-menopausal women using DEXA BMD values at the hip (8) and is not necessarily generalizable to other measurement modalities. Machine-derived

T-scores for QUS must certainly be interpreted with caution, and can be a trap for the unwary when QUS is used in the clinical setting.

Over 2 yrs of follow-up more than 50% of subjects had significant changes in BUA. This change appears quite sensitive, because with BMD one might expect that almost 50% would experience no change. Individual changes could not be attributed to the use of bone preserving medications. Despite being a more precise and reproducible measure, VOS was not shown to change significantly over 2 years in this population, limiting its use in this setting. Although the sample size was small compared to the cross-sectional study, it should be sufficient to detect a difference in VOS which was more precise and reproducible than BUA. It is possible that VOS is measuring a different property of bone to BUA, which changes at a different rate with time in the elderly. This does not explain the discrepancies between the FREE longitudinal study of QUS and previous studies showing significant longitudinal changes in VOS. It should be noted that a different ultrasound method (the Achilles system) was used in the Schott study (105), and we have shown in our correlation analysis between the CUBA and QUS-2 methods there are quite large differences in absolute terms between different ultrasound machines. Moreover the sample size of both studies is modest. Importantly, although VOS or SOS is quite precise, it is acknowledged to be much less sensitive to change than BUA and the % differences in change between the two studies (0.1% vs 0.8%) are not large. The only identifiable selection bias in this sub-sample of 56 residents was the institution; as sequential patients who were enrolled in the FREE study were followed up at 2 years, all had lived in one of only 3 hostels at enrolment. Their baseline QUS values however did not differ from the FREE cohort as a whole. The FREE study is older and frailer than previous studies, and we see in

Chapter 4 that QUS does not change rapidly in the very old; it is possible that there is a differential rate of change between BUA and VOS in very old age. Certainly BUA is more informative for longitudinal studies in this population.

It is difficult to determine whether the statistically significant change in BUA of 5% from baseline is clinically important without prospective fracture data. Changes in DEXA measurements at both hip and spine of 5% confer a clinically important change in fracture risk, but this is not generalizable to other modes of bone density assessment. It does not fulfill the 'one standard deviation' drop in BUA which Bauer et al showed to correspond to a doubling in fracture risk (56). The effect was diluted by some residents increasing BUA over time. There was no identifiable factor which may have caused this effect, and it is likely that it is an example of regression to the mean.

Only a few previous studies have examined changes in QUS longitudinally. Schott et al (105) followed 88 post-menopausal women (mean age 63 years) over 2 years, showing a decrease in BUA of 1% ($p=0.02$) and a decrease in VOS of 0.8% ($p=0.0001$). This change in BUA approximated the long-term precision value, while the change in VOS was more meaningful at 5 times the precision for BUA. The derived parameter of stiffness decreased by 1.85%, approximating 2.5 times the precision, giving intermediate sensitivity to change. A larger cross-sectional study of 270 female nursing home residents (mean age 85 years) incorporated longitudinal data for 60 women after 1 year (101). This shorter study failed to show a significant decrease in BUA, whereas VOS reached statistical significance decreasing by 0.3% ($p=0.001$). The coefficient of variation for this study was 1.8% for BUA and 0.3% for

VOS. Other groups have shown QUS to be sensitive to change in high risk populations, including otherwise healthy patients with acute spinal injury (303), prolonged bed rest (304), and in children with rheumatic diseases (305). Daly et al (306) used QUS to look at bone changes with exercise, measuring calcaneal BUA and VOS over an 18-month period in elite male gymnasts and matched normoactive controls. Over 18 months, BUA increased significantly in the gymnasts from baseline whereas VOS did not increase in either group.

In an interventional clinical trial (108) BMD in postmenopausal osteoporotic women treated with alendronate increased by 5.0%, compared with a rather modest increase in VOS (0.7%) and BUA (1.4%) after two years. Change in BMD was poorly correlated with change in QUS. The minimum significant difference between two measurements was 0.8% for VOS and 5.6% for BUA, consistent with our findings. Among the QUS parameters, the authors concluded the calculated value of 'stiffness' showed the greatest longitudinal sensitivity, which was only slightly lower than BMD. Another study of the effect of anti-resorptive therapy on QUS parameters over 2 years in osteoporotic women (107) concluded that the minimum significant difference in BUA was 3 times greater than that for BMD. Sahota et al (106) showed a similar relationship between QUS and BMD over 4 years therapy with hormone replacement therapy in 60 early post-menopausal women. Therapy with calcitonin (109) gave a significant improvement in VOS over 2 years but no improvement in BUA. Conversely, BUA was sensitive to increases with vitamin D and calcium supplementation (110) over a similar time period in elderly institutionalized women who were vitamin D deficient, whereas VOS was seen to decrease. Studies of osteoporosis therapies must be interpreted with caution, as the effect of the

intervention may differ between therapies and therefore cannot be attributed to the method of measurement alone.

In conclusion, QUS measurements were highly reliable and sensitive to longitudinal change. However, the accuracy of BUA measurement could be problematic, and as a result, its use in the diagnosis of osteoporosis remains contentious.

# CHAPTER 4

# PREVALENCE OF OSTEOPOROSIS

# IN THE FRAIL ELDERLY

# PREVALENCE OF OSTEOPOROSIS IN THE FRAIL ELDERLY

## 4.1 Introduction

Osteoporosis, a disease characterised by skeletal fragility, is a major public health problem. Hip fractures are the most costly osteoporotic fracture to treat and are due to a fall or injury in over 90% of cases (307). Nursing home and hostel residents account for approximately 40% of total hip fractures (308) and as populations age, health care costs in this frail elderly group will increase substantially.

Skeletal bone quantity can be assessed by measurement of bone mineral density (BMD), usually by dual energy x-ray absorptiometry. BMD is considered the best predictor for risk of fracture, however its routine use in the frail and institutionalised older person is often impractical. Recently quantitative ultrasound (QUS), a less expensive and more portable technology, has been shown to predict risk of osteoporotic fracture in older women, independently of BMD (55;56) and may have particular use in a high risk elderly population. However there have been few studies of gender differences in QUS.

The aims of this study are as follows:

(1) To describe bone density as measured by QUS of the calcaneus in a large population of frail elderly residents of hostels and nursing homes
(2) To identify differences in QUS between men and women
(3) To show whether QUS changes with age similarly in men and women
(4) To show whether QUS changes with age similarly in this frail elderly population as in previously studied groups

(5) To describe the relationship of QUS to risk factors for falling in this population.

## 4.2 Methods

All subjects enrolled in the FREE study (described in detail in Chapter 2) up until the end of June 2001 were included in this analysis. Broadband ultrasound attenuation (BUA) and velocity of sound (VOS) were measured at the left calcaneus in all participants using the same McCue CUBA Mark II ultrasound machine, and BUA measured in a smaller number using the Metra QUS-2 ultrasound machine. Each QUS measurement was repeated twice in the study population and the average of the two values used in the analysis.

The following clinical risk factors were assessed in all subjects at interview: age, gender, weight, height, activities of daily living status (Barthel Index) (261), cognitive function (Standardised Mini Mental Status Examination or SMMSE) (265), co-morbidities (by Resident Classification Scale graded 1 (lowest care) to 8 (highest level of care required)) (262), medications, falls risk and history of previous low trauma fracture (after age $\geq$ 50). Falls risk was tested by assessments of quadriceps strength and static balance, according to published methods proven to predict falls and fractures in the elderly (169;245), explained in detail in Chapter 2.

QUS measurements in the elderly population were expressed as T-scores using the BUA and VOS means and standard deviations from a healthy control population. Controls comprised healthy twin pairs (a total of 264 males and 936 females) aged 18-85 years as previously reported (37). Only one twin from each identical pair, randomly selected, was included. Individuals with a history of underlying bone disease, past or present corticosteroid use, serious concomitant disease and weight over 100kg were excluded. T-scores were calculated using the mean and standard

deviation compared to the control subjects aged 20-30 years, defined as representing 'young normals'.

Statistical analyses were carried out using the SPSS 11.0 statistical software package. Independent sample student's t-test was use to compare means between continuous variables, and Pearson's chi-squared statistic calculated to test differences between proportions. One-way analysis of variance (ANOVA) was used to evaluate univariate associations for continuous variables. Multiple linear regression was performed using a stepwise backward method. Comparison of regression lines was carried out using the method described by Armitage (309).

## 4.3 Results

By June 2001, 1193 residents from 52 randomly selected aged care institutions had been enrolled representing a 50% participation rate for eligible residents. This participation rate is only moderate, but expected and reflects the difficulty in obtaining informed consent from proxy informants in this population. Residents who required proxy consent were less likely to participate in the study than those able to give independent consent (27% vs 68%, $p<0.0001$). Responders and non-responders were identical with respect to mean age, sex distribution and time of residence in institutionalized care (mean differences not statistically significant, $p>0.09$).

The study sample comprised 294 men and 899 women. The men were on average 5 years younger than the women (mean $\pm$ SE age 81.2 $\pm$ 7 and 86.7 $\pm$ 6 vs years respectively, $p < 0.001$). Summary findings according to sex and residential status (nursing home or hostel) are shown in Table 4.1.

**Table 4.1**. Characteristics of hostel and nursing home populations, divided by gender

| Mean (SD) | Men | | Women | |
|---|---|---|---|---|
| Institution Type | Nursing Home | Hostel | Nursing Home | Hostel |
| Number of residents | **124** | **170** | **460** | **439** |
| Age (years) | 82.5 (8.8) | 81.5 (7.5) | 86.2 (7.1) | 81.5 (6.4) |
| Weight (kg) | 67.3 (12.1) | 73.9 (14.2) | 55.7 (12.4) | 58.8 (12.8) |
| SMMSE (score, 0-30) | 15.9 (9.7) | 24.4 (5.7) | 15.3 (10) | 24.1 (6.3) |
| EQ-5D (score, 7-18) | 11.9 (2.9) | 9.4 (2.1) | 12.1 (2.8) | 9.8 (2.3) |
| Quads Strength (kg) | 21.7 (9.4) | 27.3 (8.5) | 15.9 (5.5) | 15.9 (6.2) |
| Static Balance (score, 1-5)* | 2.1 (1.2) | 4.1 (1.1) | 1.9 (1.1) | 3.9 (1.2) |
| BUA CUBA (dB/MHz) | 65.6 (24.1) | 73.6 (20.0) | 41.2 (18.8) | 49.2 (16.9) |
| BUA QUS-2 (dB/MHz) | 70.6 (22.8) | 74.6 (20.1) | 51.6 (15.6) | 53.3 (14.8) |
| Prevalence of prior fracture | 19.0% | 15.7% | 36.9% | 35.7% |
| Length of stay (years) | 2.41 (2.17) | 3.9 (3.9) | 2.42 (2.63) | 4.44 (5.39) |
| 25-OH-vitamin D (nmol/L) | 21.4 (1.9) | 26.2 (2.2) | 16.9 (1.3) | 17.3 (0.9) |

*Static balance was measured on a scale of 1 to 5, where 1 represents 'not able to stand unsupported' and 5 represents 'good balance (able to stand for 30 seconds on an uneven surface unsupported)'.

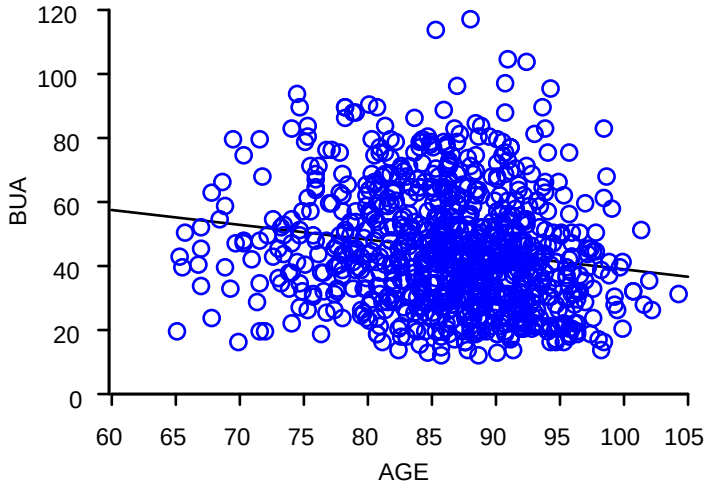
In nursing home residents, men were younger ($p < 0.002$), heavier ($p < 0.001$), and had higher BUA and VOS ($p<0.0001$) than women (Table 4.1). There were no significant differences in length of stay or cognitive status. Similarly in hostel residents, men were younger ($p < 0.001$), heavier ($p < 0.001$), had better static balance ($p=0.013$) and higher BUA and VOS ($P<0.0001$) than women. There were no significant differences in SMMSE, but length of stay was longer in women than men

in hostels ($p < 0.051$). Residents of nursing homes had not been institutionalized for as long as those in hostel accommodation ($p<0.001$), but no gender difference was seen. Gender remained significantly associated with BUA ($p<0.0001$), VOS ($p<0.0001$) and 25(OH)D levels ($p=0.005$) after adjusting for age and institution type. A history of previous low trauma fracture after age 50 was more common in women than men ($p < 0.001$) but did not differ by institution. Overall fracture prevalence was 32%; sites of fracture, some of which were multiple in certain subjects, were hip (11.7%), wrist (2.9%), humerus (2.7%), and other (16.0%). Mean BUA was 44 ($\pm$ 18) dB/MHz and mean VOS 1553 ($\pm$39) m/s in subjects with a history of previous fracture compared to BUA 56 ($\pm$ 22) dB/MHz and VOS 1578 ($\pm$52) m/s in those without ($p < 0.001$ for both comparisons). Those individuals reporting previous hip fracture had significantly lower BUA measures than individuals reporting other fractures (mean difference 8.3 dB/MHz, $p < 0.001$) but VOS did not reach a statistically significant difference. Use of medications for osteoporosis was infrequent (bisphosphonates 2.3%, raloxifene 0.7%, hormone replacement therapy 2.8%, vitamin D 4% and calcium supplements 13.7%). The above results were unaffected if these subjects were excluded.

BUA measured by the CUBA was highly correlated with BUA measured by the QUS-2 ($R^2 = 0.74$, $p<0.001$), the latter reading on average 10% higher. There was no significant decline in BUA or VOS measured by either machine with age in men however in women BUA declined by 2-8-4.7% per decade ($p<0.0001$) and VOS by 1% per decade ($p< 0.001$) (Figure 4.1).

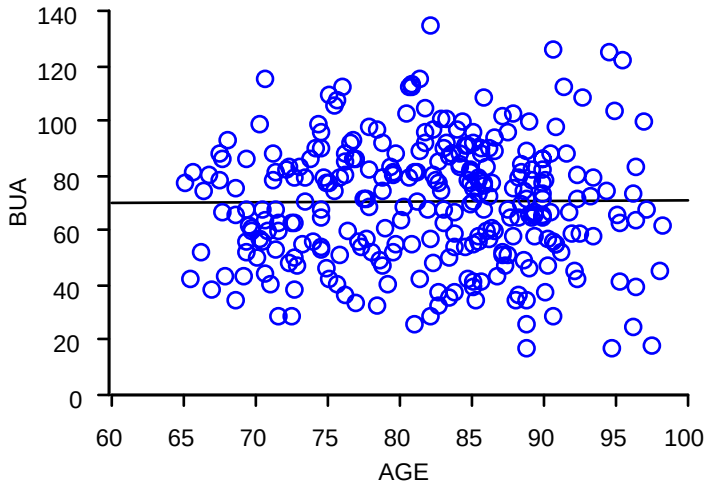
**Figure 4.1:** BUA (dB/MHz) measured by CUBA versus age (years) in (a) women and (b) men

(a)




BUA = 85-0.46*Age; $R^2$ = 0.029

(b)




When compared to a healthy population of volunteers in Sydney aged 18-80 years (Figure 4.2), the data suggest that although the sex difference in QUS measures is

maintained into very old age, only minor loss occurs at the calcaneal site in BUA and VOS with very old age in both men and women. These results were obtained from a cohort measured over 10 years before, using a different software version for the ultrasound machine so it was decided not do a formal statistical comparison.

**Figure 4.2**: BUA changes with age, in a 'normal' healthy population of men and women and the institutionalized elderly.

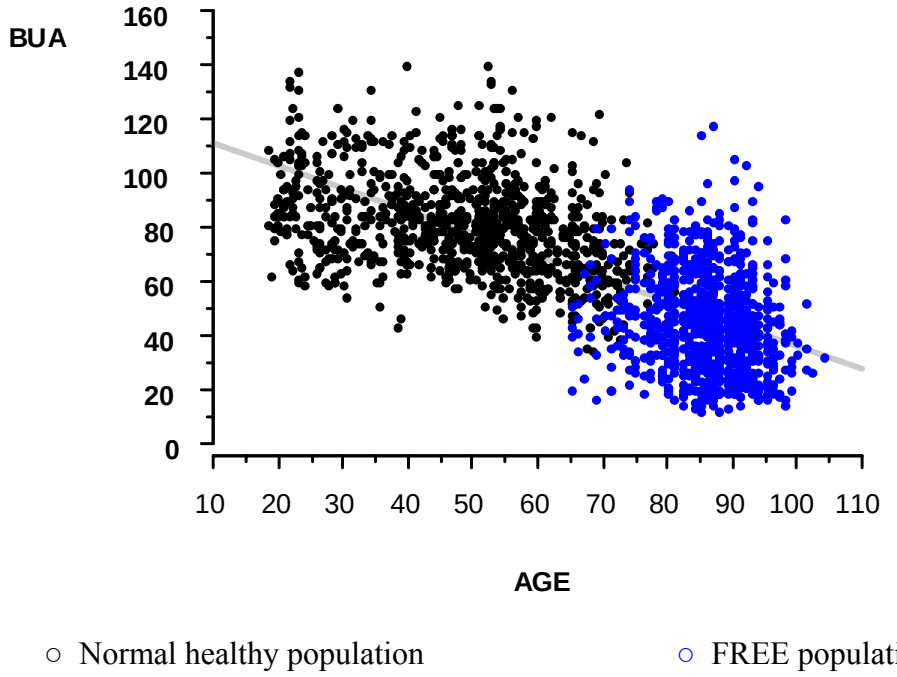
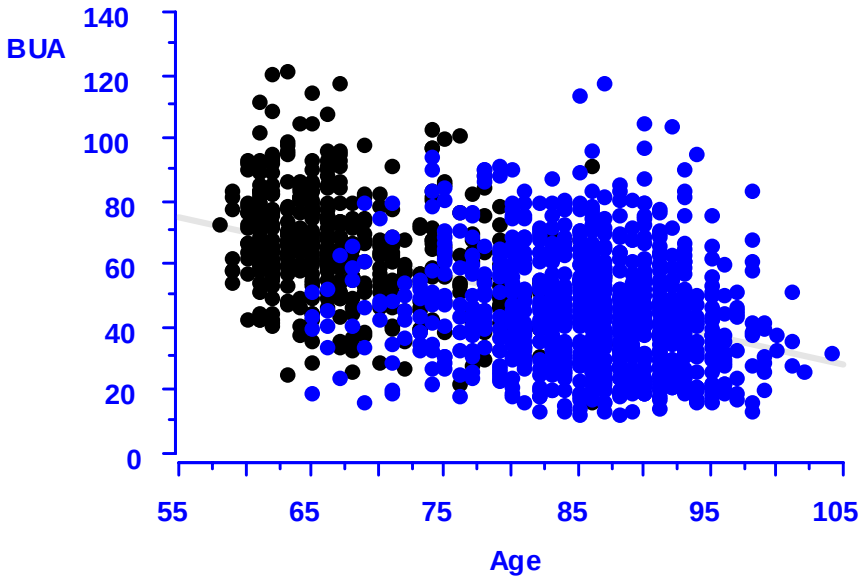


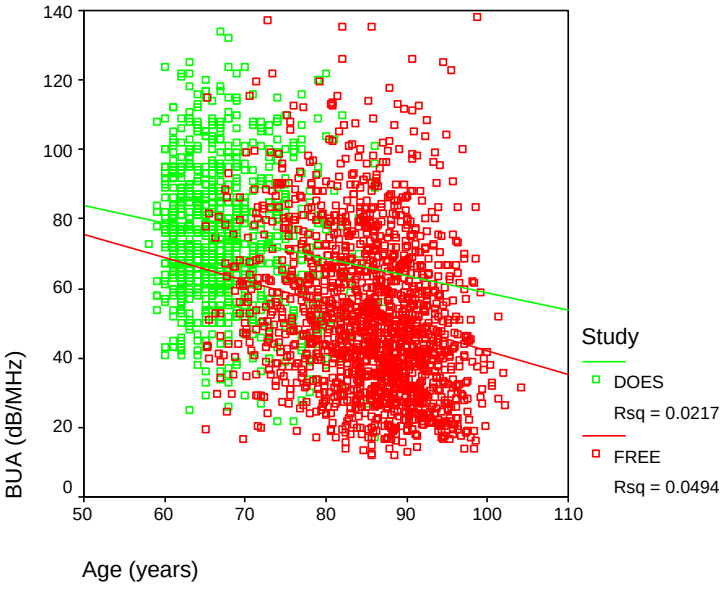

Figure 4.3 shows the data from this elderly population in comparison to an aged cohort of female subjects measured as part of the Dubbo Osteoporosis Epidemiology Study (310) with the same CUBA machine. The DOES population comprises 452 subjects (age range 58-92 years). Similarly to the young normal population, comparison of the linear regression of age vs BUA for each group (DOES n = 452, FREE n = 1197) suggests a significant difference in intercept (mean $\pm$ SE 126.4 $\pm$ 8.9

**Figure 4.3 (a):** BUA in institutionalized elderly women, compared with a cohort of independent older women taken from the DOES study (310), related to age.




○ Dubbo Osteoporosis Epidemiology Study ○ FREE population

**Figure 4.3 (b):** BUA in institutionalized elderly women, compared with a cohort of independent older women taken from the DOES study (310), related to age, shown with separate regression lines.



vs 91.4 $\pm$ 6.7, $p<0.05$) but not for the slope of the regression lines (mean slope $\pm$ SE – 0.90 $\pm$ 0.13 vs -0.531 $\pm$ 0.078, $p=0.1$) suggesting a similar pattern of bone loss with age and considerable generalizability of the BUA data across different populations.

Compared to a young normal population sample measured in Sydney using a McCue CUBA II (37), the mean BUA T score at age 85 was –1.35 in men compared to –2.33 in women and at age 95 –1.72 versus –2.55 for men and women respectively. For VOS the mean T score at age 85 in men was –1.67 compared to –3.32 in women and at age 95 it was –1.95 versus –3.54 for men and women respectively. Compared to 186 healthy women aged 65-85 years living in the community, mean BUA was 1.2 standard deviations lower in the institutionalized females. Similarly compared to 37 healthy men aged 65-85 years, mean BUA was 0.8 standard deviations lower in the institutionalized males. BUA and VOS were significantly inversely related to Resident Classification Scale, a measure of comorbidities ($p < 0.0001$ respectively).

Univariate analyses showed there were significant correlations between BUA and VOS and body weight ($p<0.0001$) in both sexes. There were significant correlations in women but not men between BUA, VOS and quadriceps muscle strength ($p < 0.0009$ and 0.02 respectively). In multiple regression analysis, weight was the only significant predictor of BUA in men (Table 4.2). However in women, significant predictors of BUA included weight and history of previous fracture, age and type of institution (Table 4.2). When both men and women were included in the multivariate model, significant predictors of BUA values included gender, institution type, weight

and history of fracture, which together account for 38% of the variability of BUA. Age did not contribute significantly to the model.

**Table 4.2.** Independent predictors of BUA in men and women.

Males

| Model variables | β estimate | Standard error | t value | p value |
|---|---|---|---|---|
| Intercept | 38.32 | 6.81 | | |
| Weight | 0.46 | 0.09 | 4.90 | <0.0001 |

Females

| Model variables | β estimate | Standard error | t value | p value |
|---|---|---|---|---|
| Intercept | 40.99 | 9.68 | | |
| Age | -0.22 | 0.09 | -2.47 | 0.014 |
| History of fracture | -5.52 | 1.12 | -4.94 | <0.0001 |
| Weight | 0.45 | 0.049 | 9.19 | <0.0001 |
| Institution type | -6.89 | 1.19 | -5.77 | <0.0001 |

Pooled population

| Model variables | β estimate | Standard error | t value | p value |
|---|---|---|---|---|
| Intercept | 53.02 | 5.22 | | |
| Gender | -17.11 | 1.44 | 11.90 | <0.0001 |
| Institution type | -5.57 | 1.13 | -4.94 | <0.0001 |
| History of fracture | -5.34 | 1.07 | -4.98 | <0.0001 |
| Weight | 0.47 | 0.043 | 10.86 | <0.0001 |

## 4.4 Discussion

This study measured sex differences in QUS parameters in a frail elderly institutionalized population of men and women. It was carried out on the first 1000 residents enrolled in the FREE study, in late 2000 and 2001. Past history of minimal trauma fracture in this group was low compared to the total population at the end of the study (Chapter 2), but otherwise the subgroup is representative of the whole study. There are no clear reasons for this phenomenon; there were no notable changes in interviewers who might have elicited a more definitive response from residents. Standards of care in nursing homes and hostels are constantly under scrutiny with quality assurance programs. It is possible that the quality of medical record reporting had improved over the period of the study, resulting in a larger proportion of previous fractures being reported. Personal recall of previous fracture is thought to be reliable in the elderly (286;288), but it may be that the discrepancies seen are a reflection of inherent measurement error due to recall bias. The lower prevalence of reported previous low trauma fracture in this subgroup does not impact on the results of the ensuing study of QUS and gender differences in the frail elderly.

As expected, the prevalence of low bone density as measured by quantitative ultrasound was high in the elderly FREE cohort. Women had significantly lower bone density than men of a similar age, an expected finding as the female population is by definition post-menopausal and has therefore undergone a period of accelerated bone loss as a response to withdrawal of physiologic oestrogen. At advanced age, the rates of bone loss were seen to be similar between men and women suggesting hormonal changes have a less important role in this population.

Although rates of BMD loss measured at the femoral neck have been reported to increase significantly in both sexes with advancing age (310), there have been few studies of other skeletal sites and most studies include only small numbers of very elderly men. This study suggests only minor loss occurs at the calcaneal site in BUA and VOS with advanced age in either sex. However one limitation of this study is its cross-sectional nature which allows only inferences about rates of loss. Another explanation would be that increased mortality associated with low bone mass has lead to a survivor bias for 'healthier' elderly subjects who are losing at a slower rate. This seems unlikely given the subjects were all 'institutionalized' and so were frail elderly. Of interest, the sex difference in QUS parameters is maintained into very old age.

A number of studies have examined QUS in older women, mainly in relation to its value as a predictor of osteoporotic fracture risk (55;56). Studies in elderly women have identified age, body composition and physical activity as determinants of QUS parameters (40;45), but there have been few studies of QUS in men, or indeed elderly men. One study compared QUS in 169 normal men and 210 normal women aged 20-80 years (41). BUA was higher in men than women at all ages but showed little decline in either sex after age 60. Another study of 224 men attending an osteoporosis clinic identified significant correlations between weight (and body mass index) and BUA, but no age related decline in QUS measures was observed, except in VOS in 76 fracture cases (27). In both these studies only a small number of subjects were aged greater than 70 years. Pluijm et al (58) measured BUA in 132 men and 578 women aged $\geq$ 70 but did not report determinants of QUS or sex differences. Truscott (40) examined age-related trends in QUS in 2087 women aged from 16 to 93. No

decline in QUS measures was observed between the age bands 75-79 and 80-84, however there were a total of only 20 subjects in these groups.

When compared to an independently living population aged over 65 years (taken from the Dubbo study (310)), the frail elderly group were seen to lose bone at a similar rate. However, the baseline bone density was lower in the FREE study as seen by the different intercepts of regression lines for the two groups. This is logical, as the Dubbo group are by definition healthier and more mobile than those of the FREE study who require supportive care with activities of daily living, and it could be assumed that independently living individuals spend more time actively weight bearing (recognized as important to maintain bone density). Interestingly this has an effect on baseline but not rate of bone loss. It might be concluded that other factors, such as age and hormonal changes, are more important than exercise and weight bearing for maintaining bone density from any baseline.

There are currently few published studies of the prevalence of osteoporosis in the frail institutionalized elderly. Intuitively it would be expected that BMD and QUS should be low in this aged, frail population, but the practicalities of measuring BMD in this relatively frail group have precluded large studies. A recent North American study (18) of 1427 elderly female nursing home residents using distal radius BMD measured by single energy x-ray absorptiometry reported that 82% were osteoporotic (T-score < -2.5) and 54% fell under a T-score of -3.5.

It is also important to consider the meaning of a T-score derived from calcaneal ultrasound in terms of fracture risk. Faulkner et al (11) illustrated the differential

classification of an individual as osteoporotic or not using T-scores derived from different techniques of bone mass estimation, including DXA, QCT and QUS at different skeletal sites. It is likely that a QUS-derived T-score of -2.5 is in fact related to a much higher fracture rate than a hip DXA-derived T-score of -2.5; one cannot use the two derivations interchangeably in the estimation of the prevalence of osteoporosis.

Prospective information on fracture incidence will be important to define appropriate cut-offs for QUS measures as they pertain to fracture risk in the frail institutionalized elderly population. This information will then allow more definitive recommendations about the usefulness of BUA and/or QUS in assessing osteoporosis in the frail elderly.

# CHAPTER 5

# DISTRIBUTION, DETERMINANTS AND ASSOCIATIONS OF 25-OH-VITAMIN D LEVELS IN AGED CARE FACILITIES

# DISTRIBUTION, DETERMINANTS AND ASSOCIATIONS OF 25-OH-VITAMIN D LEVELS IN AGED CARE FACILITIES

## 5.1 Introduction

Vitamin D deficiency is a silent epidemic, affecting men and women both in Australia (311-313) and around the globe (311;314-317). Its prevalence increases in older populations as mobility and general health decline (318-320), related to inadequate sunlight exposure, poor diet and increasing renal insufficiency (321;322). Institutionalized elderly persons are at particular risk for low 25-OH-vitamin D levels (323-327), but there is less known about the relationships between vitamin D, gender, season and biochemical measures of calcium homeostasis in this frail elderly population.

The aims of this study are as follows:

1: To describe the distribution of serum 25-OH-vitamin D levels in elderly men and women living in residential aged care facilities (hostels and nursing homes) in northern Sydney.

2: To determine if serum 25-OH-vitamin D levels differ with age, gender, residential status or season.

3: To describe the association between 25-OH-vitamin D levels and other bone-related biochemical parameters, including serum creatinine (as a surrogate for renal function), serum parathyroid hormone (PTH), corrected serum calcium and

serum albumin levels. What is the independent influence of age, gender and institution on these associations?

4: To define hypovitaminosis D by relating 25-OH-vitamin D levels to subclinical secondary hyperparathyroidism.

5: To identify the key independent predictors of serum 25-OH-vitamin D level (continuous) and hypovitaminosis D (categorical) in the frail elderly.

6: To estimate the prevalence of vitamin D supplementation in this population, including the use of vitamin D supplements, analogues, combinations of these or other bone active medications.

7: To identify the determinants of the use of vitamin D supplementation. Is the use of vitamin D supplements associated with age, gender or residential status? Does this supplementation impart a benefit on circulating 25-OH-vitamin D levels?

This chapter will describe the distribution and determinants of serum 25-OH-vitamin D levels in an elderly population living in aged care facilities, and identify the significant biochemical interrelationships with serum 25-OH-vitamin D in this population.

## 5.2 Methods

### 5.2.1 Subjects

Each resident enrolled in the FREE study (a full description of the FREE study population methods is given in Chapter 2) was asked to give a blood sample for 25-OH-vitamin D and other biochemical analyses. Sixty-three percent of the cohort (268 men and 1000 women) agreed. Remaining study participants or their carers declined venesection and a small percentage of venesections were technically overly difficult and abandoned after one failed attempt. Carer consent was obtained where appropriate. Current medications were recorded from interview and verified by medical records and medication charts, including prescription drugs and over-the-counter vitamin preparations. Individuals with biochemical primary hyperparathyroidism (15 residents with an elevated parathyroid hormone and associated hypercalcaemia) or major renal insufficiency alone (6 individuals with a serum creatinine >300 μmol/L) were excluded from the analyses, resulting in a final study population of 979 women and 264 men.

### 5.2.2 Biochemical measurements

Serum 25-hydroxyvitamin D (25OHD), intact parathyroid hormone (PTH), calcium (adjusted for circulating albumin levels), creatinine and inorganic phosphorus levels were measured in 1268 residents using methods described in Chapter 2. Creatinine clearance was calculated using the Cockcroft-Gault formula. For males:

$$\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{age}) * \text{weight}}{72 * \text{serum creatinine (mg/100ml)}}.$$

The same calculation is used in women, adjusted by x 0.85.

### 5.2.3 Statistical analysis

Analyses were carried out using the SPSS 11.0 statistical software package. Independent sample student's t-test was use to compare means between continuous variables (log transformed if required to confer normality), and Pearson's chi-squared statistic calculated to test differences between proportions. Vitamin D levels were treated both as a continuous variable, and divided into categories to define 'hypovitaminosis D'. One-way analysis of variance (ANOVA) was used to evaluate univariate associations for continuous variables. Logistic and multiple linear regressions were performed using a stepwise backward method.

## 5.3 Results

### 5.3.1 Baseline demographics

Nine hundred and seventy-nine women and 264 men were included in the analysis. The women were on average 3.7 years older than the men ($p<0.0001$) and were less mobile, being more likely to require a walking aid (usually a frame). Demographics of the group are shown in Table 5. 1.

**Table 5.1:** Demographics of institutionalized elderly cohort with biochemical measures.

| | | Gender | | Test statistic | Significance |
|---|---|---|---|---|---|
| | | Male | Female | | |
| Age (mean) | | 83.10 | 86.76 | t=7.2097 | p<0.0001 |
| Institution | Hostel | 136 (48.5%) | 560 (57.2%) | $\chi^2$=2.73 | p=0.11 |
| | Nursing Home | 128 (51.5%) | 419 (42.8%) | | |
| Mobility | Walks unaided | 94 (35.9%) | 287 (29.6%) | $\chi^2$=11.65 | p=0.009 |
| | Uses a stick | 65 (25.0%) | 213 (22.0%) | | |
| | Uses a frame | 59 (22.5%) | 324 (33.4%) | | |
| | Wheelchair | 44 (16.4%) | 146 (15.0%) | | |
| On Vitamin D supplements | | 16 (6.1%) | 115 (11.7%) | $\chi^2$=7.13 | p=0.007 |

Descriptive statistics for biochemical variables are shown in Table 5.2. Fourteen individuals exhibiting biochemical primary hyperparathyroidism were excluded from analysis. This group had serum PTH levels ranging from 72.3 pg/mL to 602 pg/mL (median 108 pg/mL) and corrected calcium levels between 2.57 mmol/L and 3.08

mmol/L (median 2.66 mmol/L). Five individual with PTH levels above 400 pg/mL but no available calcium measures were also excluded – this did not significantly change any of the calculations. Finally, six individuals with renal insufficiency (creatinine values greater than 300 μmol/L) associated with elevated PTH but normal corrected calcium levels were also excluded.

**Table 5.2:** Biochemical measures grouped by gender and institution, given as mean +/- standard error of the mean (range), median.

| | Hostel | | Nursing Home | |
|---|---|---|---|---|
| | Male | Female | Male | Female |
| 25-OH-vitamin D (nmol/L) | 35.8 +/- 1.48 (5 - 92), 34 | 29.8 +/- 0.64 (2 – 104), 27 | 29.5 +/- 1.59 (5 – 103), 26 | 25.7 +/- 0.80 (2 – 101), 21 |
| PTH (pg/mL) | 57.5 +/- 3.58 (12.6 – 238.0), 45.5 | 72.8 +/- 2.04 (4.6 – 337.0), 61.2 | 65.2 +/- 3.39 (12.2 – 209.0), 57.3 | 71.2 +/- 2.44 (5.6 – 309.0), 55.8 |
| Corr. Calcium (mmol/L) | 2.34 +/- 0.017 (1.96 - 2.91), 2.33 | 2.36 +/- 0.009 (1.87 – 2.73), 2.35 | 2.34 +/- 0.018 (2.01 – 2.60), 2.36 | 2.36 +/- 0.010 (1.86 – 2.68), 2.37 |
| Inorg. phosphorus (mmol/L) | 1.15 +/- 0.021 (0.75 - 1.66), 1.14 | 1.25 +/- 0.012 (0.77 – 2.11), 1.25 | 1.13 +/- 0.020 (0.76 – 1.67), 1.11 | 1.20 +/- 0.012 (0.59 – 1.77), 1.21 |
| Albumin (g/L) | 42.0 +/- 0.38 (32 – 49), 42.0 | 41.7 +/- 0.23 (30 – 58), 42.0 | 40.1 +/- 0.44 (32 – 50), 40 | 39.3 +/- 0.22 (26 – 47), 39 |
| Creatinine clearance (μmol/L) | 70.0 +/- 21.4 (33.2 – 131.1), 58.0 | 44.7 +/- 18.6 (16.1 – 140.8), 54.0 | 57.4 +/- 21.3 (22.9 – 124.4), 41.4 | 44.0 +/- 18.4 (11.8 – 147.3), 40.6 |

Nine hundred and sixty-two residents (77.4%) had low 25-OH-vitamin D levels when compared to the laboratory normal range (39 – 140 nmol/L). Serum parathyroid hormone was low in 103 residents (8.3%) and high in 508 individuals (40.9%)

(normal range 23.7 – 66.2 pg/mL). Hypocalcaemia was seen in 38 residents (7.2%) and hypercalcaemia in 22 (4.2%), (normal range 2.15 – 2.55 mmol/L). Inorganic phosphorus was elevated in 136 (25.7%) individuals (normal range 0.6 – 1.3 mmol/L). Albumin was low in 181 (34.2%) and elevated in two individuals (normal range 40 – 50 g/L). One hundred and twenty men (94.5%) had a reduced creatinine clearance (normal range in males 97 – 137 ml/min), and 399 women (97.6%) had a creatinine clearance which fell below the normal range for females (88 – 128 ml/min).

### 5.3.2 Distribution of 25-OH-vitamin D levels

Table 5.3 shows the prevalence of 'hypovitaminosis D' in men and women, using different cut-off values previously described in the literature concerning 25-OH-vitamin D in elderly populations (322;328;329). The majority of both men and women had low 25-OH-vitamin D levels independent of which cut-off value is used to define 'hypovitaminosis D'.

**Table 5.3:** Classification of residents with low 25-OH-vitamin D levels

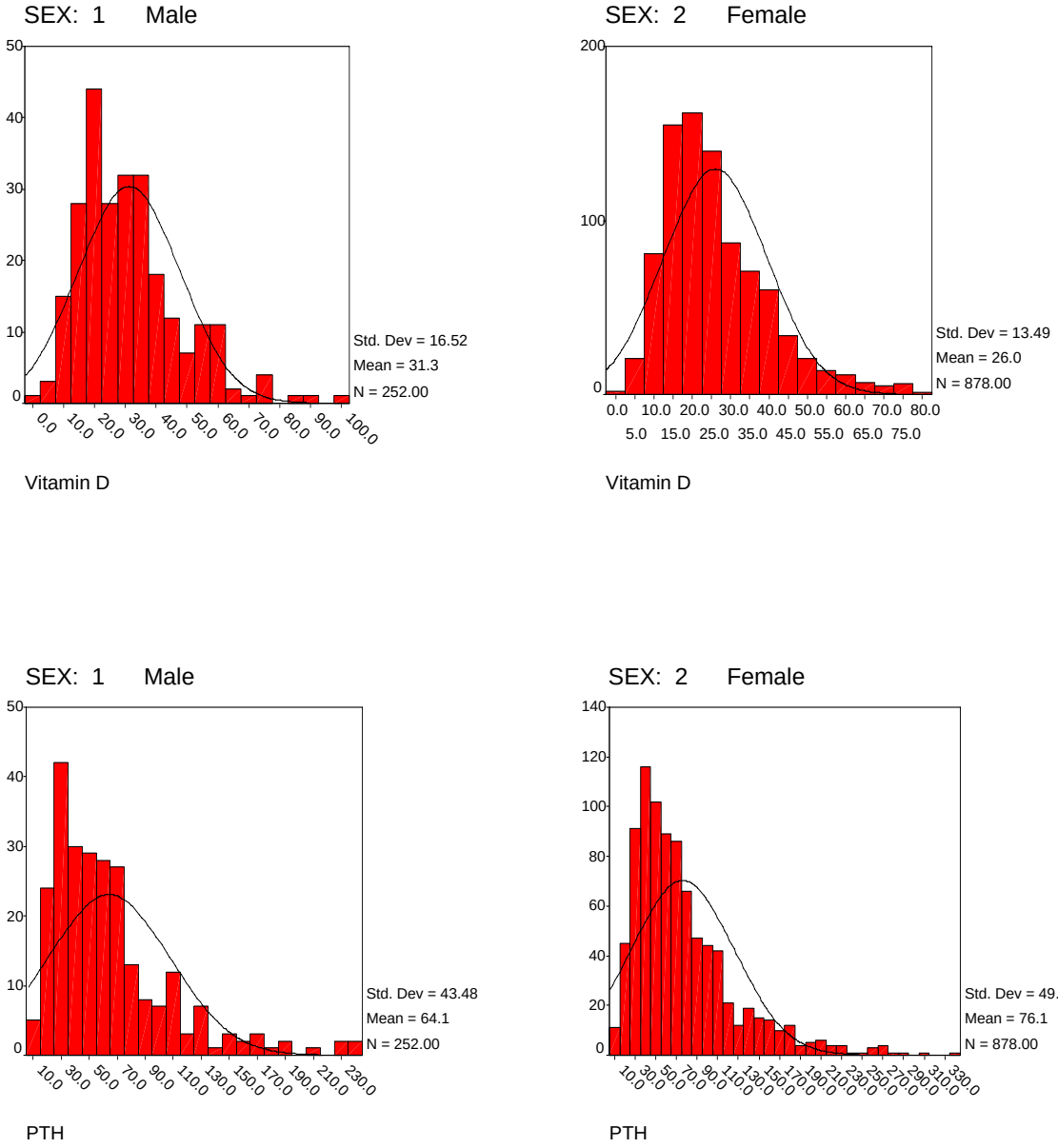
| Gender | 25-OH-vitamin D cut-off | Hypovitaminosis D (number, %) | Mean age (years) | Mean vit D (nmol/L) | Mean PTH (pg/mL) |
|---|---|---|---|---|---|
| Male | Vit D < 25 | 109 (42.9%) | 83.31 | 17.7 | 72.9 |
| | Vit D < 30 | 139 (54.4%) | 83.12 | 19.9 | 68.5 |
| | Vit D < 39 | 187 (75.4%) | 83.71 | 23.7 | 65.9 |
| | Vit D < 50 | 217 (85.3%) | 83.34 | 26.0 | 63.1 |
| | Vit D 25-50 | 108 (42.4%) | 83.38 | 34.5 | 53.3 |
| | Low quartile < 18 | 46 (15.5%) | 83.87 | 12.9 | 70.9 |
| | Low tertile < 20 | 62 (24.6%) | 83.67 | 14.4 | 71.4 |
| | Low quintile < 17 | 38 (13.9%) | 82.29 | 12.0 | 68.3 |
| | | | | | |
| Female | Vit D < 25 | 525 (57.2%) | 87.00 | 17.0 | 78.2 |
| | Vit D < 30 | 643 (70.2%) | 86.86 | 19.0 | 76.7 |
| | Vit D < 39 | 732 (84.7%) | 86.92 | 21.6 | 76.8 |
| | Vit D < 50 | 884 (94.2%) | 86.81 | 24.3 | 73.5 |
| | Vit D 25-50 | 359 (37.0%) | 86.60 | 35.0 | 66.6 |
| | Low quartile < 18 | 267 (25.6%) | 86.65 | 12.8 | 83.6 |
| | Low tertile < 20 | 336 (36.9%) | 86.63 | 14.0 | 80.5 |
| | Low quintile < 17 | 232 (21.2%) | 86.72 | 12.2 | 80.7 |

### 5.3.3 Determinants of serum 25-OH-vitamin D levels

Serum 25-OH-vitamin D and PTH were not normally distributed (Figure 5.1), and so have been log transformed to allow comparisons as continuous variables. Serum 25-OH-vitamin D decreased with increasing age in the total cohort ($t = -2.71$, $p = 0.007$),

but did not reach statistical significance in either males or females alone. Serum 25-OH-vitamin D levels were higher in hostel accommodation than in nursing home residents in both males (mean difference 6.24 nmol/L, 95% confidence interval 1.94 - 10.94, $p = 0.005$) and females (mean difference 4.10 nmol/L, 95% confidence interval 2.13 - 6.08, $p<0.0001$). Males had significantly higher 25-OH-vitamin D levels than women, independent of institution. Serum 25-OH-vitamin D levels were significantly associated with the use of a walking aid ($F=10.73$, $df=3$, $p<0.0001$), being highest in those residents able to walk independently or with a stick, and lowest in those who use a wheelchair. There was no association between current smoking and 25-OH-vitamin D (mean 25-OH-vitamin D levels in smokers 27.4 nmol/L compared to 27.2 nmol/L in non-smokers, $t=0.214$, $p=0.9$).

**Figure 5.1:** Distribution of serum 25-OH-vitamin D and PTH for males and females.



There were a similar proportion of men and women venesected each season, shown in Table 5.4 ($\chi^2$=4.73, df=3, p=0.19).

**Table 5.4**: Number of residents recruited each season for men and women.

| Season | Gender | | |
|---|---|---|---|
| | Male | Female | Total |
| Spring | 71 (26.9%) | 264 (27.0%) | 335 |
| Summer | 73 (27.7%) | 231 (23.5%) | 304 |
| Autumn | 42 (15.9%) | 210 (21.5%) | 252 |
| Winter | 78 (29.5%) | 274 (28.0%) | 352 |
| Total | 264 | 979 | 1243 |

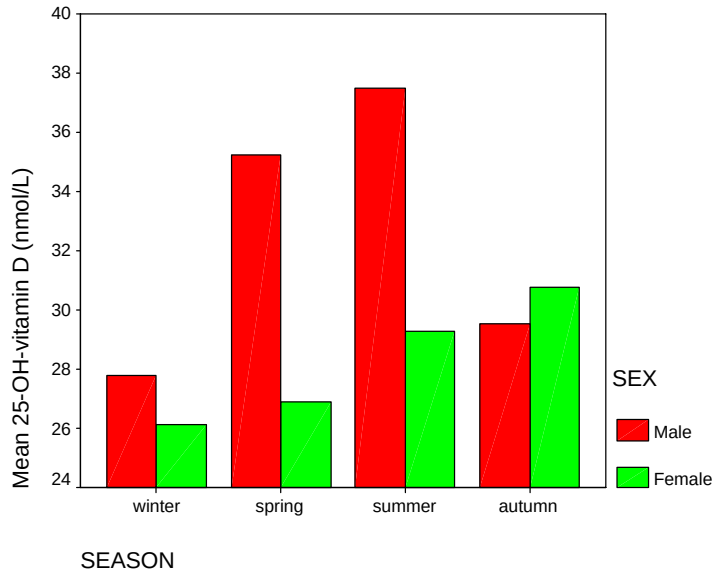
When those individuals taking vitamin D supplements are excluded from the analysis (n=131), 25-OH-vitamin D levels were significantly associated with season in both males (F=4.76, df=3, p=0.003) and females (F=6.46, df=3, p<0.0001). Levels were lowest in winter in both sexes (Table 5.5), but males had an earlier peak in spring/summer compared to an autumn peak in women (Figure 5.2).

**Table 5.5:** Mean 25-OH-vitamin D level (standard error of the mean) for each season

| Season | Gender | | Mean Difference | 95% Confidence Interval | Significance |
|---|---|---|---|---|---|
| | Male | Female | | | |
| Spring | 34.91 (2.017) | 24.84 (0.848) | 10.07 | 5.72 - 14.42 | p<0.0001* |
| Summer | 34.77 (2.259) | 26.80 (0.932) | 7.97 | 3.11 - 12.82 | p=0.002* |
| Autumn | 28.33 (1.879) | 29.21 (1.071) | -0.89 | -5.21 – 3.43 | p=0.7 |
| Winter | 26.55 (1.815) | 23.93 (0.799) | 2.61 | -1.37 - 6.55 | p=0.2 |

*statistically significant difference between males and females, p<0.05.

**Figure 5.2:** Changes in 25-OH-vitamin D levels with season in males and females.



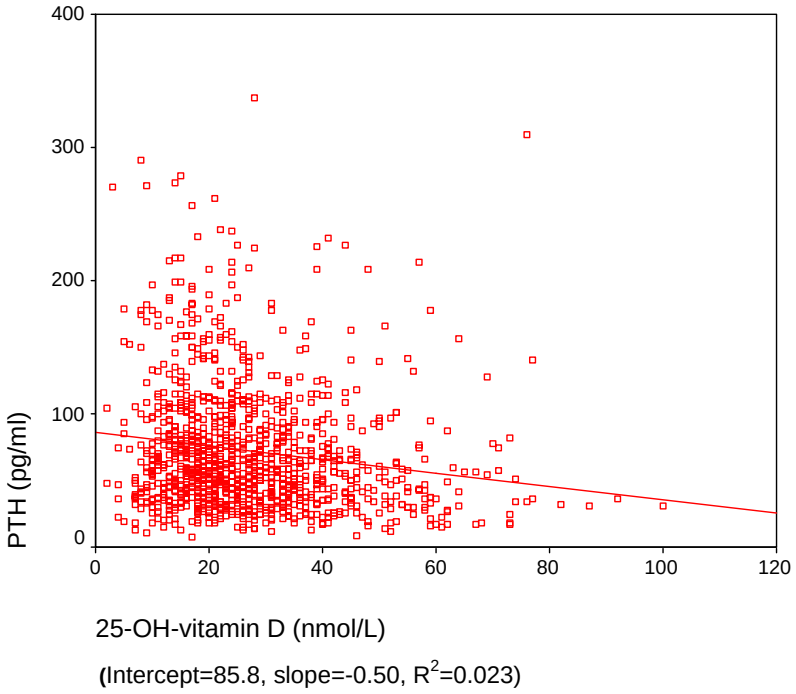

### 5.3.4 Serum 25-OH-vitamin D and associated biochemical parameters

Males had significantly higher creatinine levels and lower PTH and phosphate levels than women, independent of institution ($p<0.05$). Using the laboratory-derived upper limit of normal for creatinine clearance, 120 men (94.5%, normal range in males 97 – 137 ml/min), and 399 women (97.6%, normal range 88 – 128 ml/min) had a degree of renal insufficiency. There was no statistically significant difference in PTH levels between institution type in either gender ($p>0.1$). Serum albumin was lower in nursing homes than in hostels in both males and females ($p<0.001$), and phosphate levels were higher in hostels than nursing homes in females ($p=0.02$) but not significantly different between institutions in males ($p>0.5$). Creatinine clearance was not significantly different between institutions in either males ($p=0.4$) or females ($p=0.7$).

Albumin decreased with increasing age in both males and females ($p<0.05$), and PTH increased with age ($p<0.005$). Creatinine clearance decreased with age in both males and females ($p<0.0001$), and calcium and phosphate were not related to age in either gender ($p>0.2$).

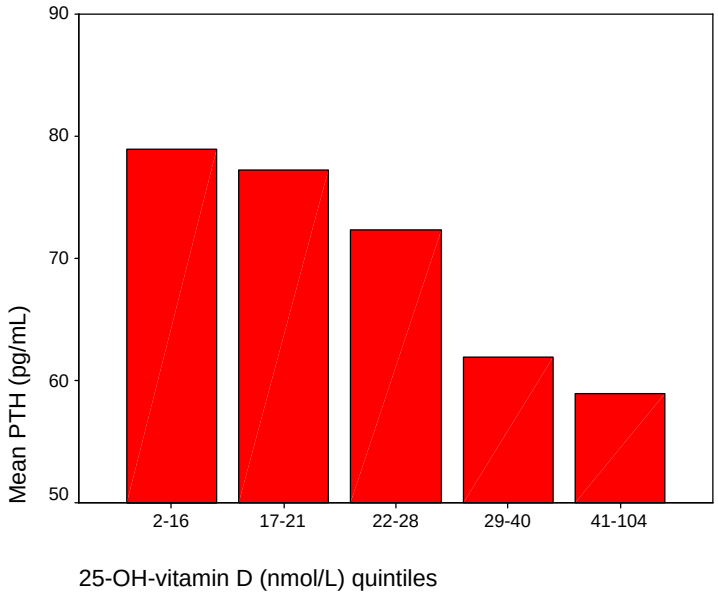
Parathyroid hormone levels increased as 25-OH-vitamin D decreased in both men and women (Figure 5.3) as would be expected biologically. There was not a clear level of serum 25-OH-vitamin D below which a rise of PTH is seen (secondary hyperparathyroidism) which might support a definition of hypovitaminosis D. Log transformation of 25-OH-vitamin D, iPTH or both does not reveal any point of inflection or level of 25-OH-vitamin D above which iPTH levels might increase exponentially.

**Figure 5.3:** Parathyroid hormone levels related to 25-OH-vitamin D.



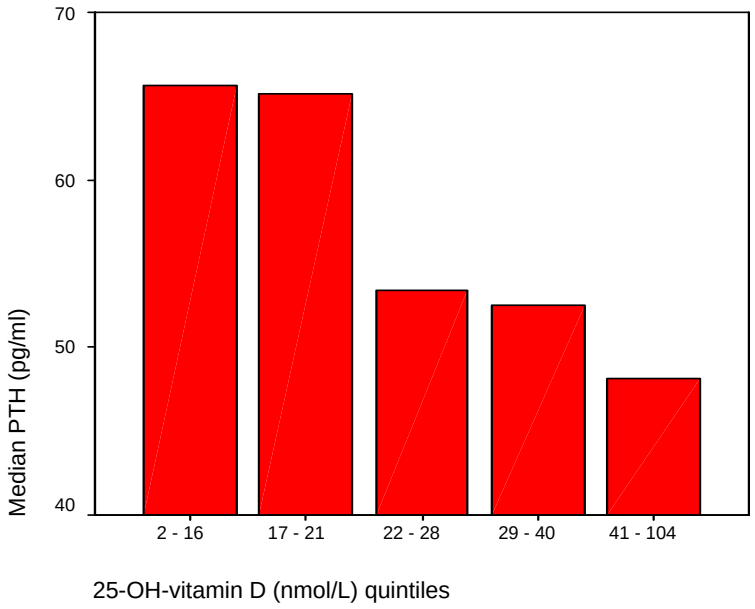
However when 25-OH-vitamin D was split into quintiles, mean PTH levels were seen to rise between the third and fourth quintiles (Figure 5.4), representing a mean 25-OH-vitamin D level of 29 nmol/L, supporting the use of either 25 or 30 nmol/L as an appropriate cut-off for defining hypovitaminosis D in this frail elderly population.

**Figure 5.4:** Mean PTH values relating to 25-OH-vitamin D quintiles.




Examination of each of the quintiles for 25-OH-vitamin D does not reveal the serum levels to be normally distributed within each quintile. When the median iPTH values are plotted against 25-OH-vitamin D quintiles, a lower cut-off level of 22 nmol/L is seen (Figure 5.5).

**Figure 5.5:** Median PTH values relating to 25-OH-vitamin D quintiles




Univariate analysis corrected for age showed 25-OH-vitamin D levels to be significantly and inversely associated with PTH in men ($t= -3.630$, $p<0.0001$) and in women ($t= -3.718$, $p<0.0001$). In females, 25-OH-vitamin D was associated with creatinine clearance ($t= -2.901$, $p=0.004$) and with albumin ($t=2.429$, $p=0.016$) but there was no association observed in the smaller sample of males ($p>0.2$). Serum 25-OH-vitamin D was not associated with calcium or phosphate in either gender ($p>0.15$).

### 5.3.5 Independent predictors of 25-OH-vitamin D levels

All significant univariate parameters were entered into a multiple regression model for men and women separately (Table 5.6). With multiple regression modeling, lower vitamin D levels in men were associated only with higher PTH and the use of a walking aid. Lower creatinine clearance, higher PTH, more advanced age and the use

of a walking aid were significant independent predictors of low vitamin D levels in females. When the total cohort is examined, female gender, reduced mobility, higher PTH, increasing age, cooler season and lower creatinine clearance were independently related to lower 25-OH-D levels.

**Table 5.6:** Independent determinants of serum 25-OH-vitamin D

| | Variable | B | Std. Error | t | Significance |
|---|---|---|---|---|---|
| Males ($R^2$=0.14) | (Constant) | 4.264 | 0.217 | 19.653 | <0.0001 |
| | Ln PTH | -0.178 | 0.053 | -3.331 | 0.001 |
| | Walking aid | -0.116 | 0.029 | -3.951 | <0.0001 |
| Females ($R^2$=0.06) | (Constant) | 5.112 | 0.545 | 9.381 | <0.0001 |
| | Age | -0.011 | 0.005 | -2.056 | 0.04 |
| | Ln PTH | -0.149 | 0.053 | -2.812 | 0.005 |
| | Cr. clearance | 0.007 | 0.002 | -3.261 | <0.0001 |
| | Walking aid | -0.086 | 0.028 | -3.045 | 0.003 |
| Entire cohort ($R^2$=0.10) | (Constant) | 5.090 | 0.479 | 10.625 | <0.0001 |
| | Age | -0.009 | 0.005 | -2.000 | 0.046 |
| | Gender | -0.151 | 0.064 | -2.367 | 0.018 |
| | Ln PTH | -0.141 | 0.046 | -3.064 | 0.002 |
| | Cr clearance | -0.006 | 0.002 | -3.386 | 0.001 |
| | Walking aid | -0.100 | 0.024 | -4.158 | <0.0001 |
| | Season | 0.052 | 0.024 | 2.205 | 0.028 |

Excluded variables: In males, season, age; in females, season, institution, albumin; in total cohort, institution, albumin.

Independent predictors of hypovitaminosis D, defined as a serum 25-OH-vitamin D level less than or equal to 30 nmol/L in this population, are shown in Table 5.7. As for the continuous variable 25-OH-vitamin D, hypovitaminosis D is predicted by higher serum PTH values, use of a walking aid and lower creatinine clearance. In men, use of a walking aid, PTH and creatinine clearance remain independently associated with vitamin D deficiency. Season is an important predictor of hypovitaminosis D in women, along with use of a walking aid and PTH levels.

**Table 5.7:** Independent determinants of hypovitaminosis D (25-OH-vitamin D <= 30 nmol/L)

| | Variable | Wald statistic | df | Signif. (p) | Likelihood ratio (LR) | 95% confidence interval for the LR |
|---|---|---|---|---|---|---|
| Males ($R^2$=0.18) | Walking aid | 3.35 | 1 | 0.07 | 1.02 | N/A |
| | ln(PTH) | 5.30 | 1 | 0.002 | 2.32 | 1.13 – 4.74 |
| | Cr clearance | 3.35 | 1 | 0.07 | 1.02 | 1.00 – 1.05 |
| Females ($R^2$=0.10) | Walking aid | 19.48 | 3 | 0.0001 | N/A | N/A |
| | Season | 12.47 | 3 | 0.006 | N/A | N/A |
| | ln(PTH) | 5.37 | 1 | 0.02 | 1.67 | 1.08 – 2.57 |
| Whole cohort ($R^2$=0.11) | Gender | 9.25 | 1 | 0.002 | 0.47 | 0.28 – 0.76 |
| | Walking aid | 28.39 | 3 | 0.0001 | N/A | N/A |
| | ln(PTH) | 11.39 | 1 | 0.001 | 1.87 | 1.30 – 2.68 |
| | Cr clearance | 5.77 | 1 | 0.02 | 1.02 | 1.00 – 1.03 |

Excluded variables: In males, season, age, institution; in females, age, institution, creatinine clearance, albumin.

### 5.3.6 Vitamin D Supplementation

The use of vitamin D supplementation and other bone-active medications was low overall in this population (Table 5.8). There was not a statistically significant difference between men and women in the use of mixed vitamin supplements containing either vitamin D or calcium; however the use of specific bone-targeted compounds including calcium alone, vitamin D analogues (calcitriol) and bisphosphonates was more frequently seen in females than males. A small number of individuals were taking both vitamin D supplements and analogues.

**Table 5.8:** Frequency of bone-active medication use among men and women living in aged care facilities.

| Medication | Male | Female | Test statistic | Significance |
|---|---|---|---|---|
| Vitamin D analogue | 8 (3.0%) | 91 (9.3%) | $\chi^2$=11.113 | p<0.0001* |
| Vitamin supplements containing D | 12 (4.5%) | 76 (9.6%) | $\chi^2$=3.272 | p=0.079 |
| Any vitamin D preparation | 16 (6.1%) | 115 (11.7%) | $\chi^2$=7.13 | p=0.007* |
| Calcium | 13 (4.9%) | 94 (9.6%) | $\chi^2$=5.782 | p=0.018* |
| Vitamin supplements with calcium | 21 (8.0%) | 117 (12.0%) | $\chi^2$=3.365 | p=0.077 |
| Hormone therapy | 1 (0.4%) | 33 (3.4%) | $\chi^2$=6.696 | p=0.005* |
| Bisphosphonates | 3 (1.1%) | 57 (5.8%) | $\chi^2$=9.938 | p=0.001* |

*statistically significant difference, p<0.05

Supplementation was equally distributed between hostel and nursing home accommodation ($\chi^2$=3.85, p=0.05). Residents taking vitamin D preparations were much more likely to be taking concomitant calcium supplements ($\chi^2$=235.0, p<0.0001). Age did not appear to influence the use of vitamin D compounds (Table

5.9). Mean 25-OH-vitamin D levels were 45.2 nmol/L in the supplementation group, which was significantly higher than 27.2 nmol/L for the group without supplementation (mean difference 18.0 nmol/L, 95% CI for the difference 14.0-22.0, p<0.0001), although still below the 50 nmol/L cut-off recommended for vitamin D sufficiency by many authors. This significant difference is maintained in men and women (Table 5.9).

**Table 5.9:** Comparison of residents on vitamin D supplementation at baseline with those not receiving supplements (mean (sd)).

| | Male | | Female | |
|---|---|---|---|---|
| | Vit D Suppl | No Suppl | Vit D Suppl | No Suppl |
| N | 16 (6.1%) | 248 (93.9%) | 115 (11.7%) | 864 (88.3%) |
| Age (years) | 81.16 (7.246) | 83.23 (7.727) | 86.85 (5.174) | 86.75 (6.518) |
| 25-OH-vitamin D (ng/mL) | 55.56 (24.147) | 31.28 (16.505)* | 43.71 (21.944) | 25.99 (13.388)* |
| PTH (pg/mL) | 46.24 (32.771) | 62.23 (43.574) | 50.36 (45.016) | 74.98 (48.686)* |
| Corrected calcium (mmol/L) | 2.379 (0.0946) | 2.335 (0.1407) | 2.440 (0.1267) | 2.349 (0.1330)* |
| Creatinine (μmol/L) | 119.30 (39.721) | 100.81 (26.539) | 90.05 (28.984) | 89.34 (28.040) |
| Albumin (g/L) | 40.6 (3.44) | 40.3 (1.32) | 41.1 (3.45) | 40.8 (2.96) |

*significantly different to supplemented group, p<0.001

Corrected calcium levels were significantly higher in those individuals receiving vitamin D supplements (mean difference 0.082, 95% CI 0.045-0.119). Mean PTH levels were significantly lower in the supplementation group, 49.9 pg/mL compared to 72.1 pg/mL in those not receiving supplements, mean difference 22.3 pg/mL (95% CI 14.3-30.3, p<0.0001). When men and women are considered separately, corrected calcium remains higher and PTH lower in the supplementation group although this

does not reach statistical significance in males (p=0.33 and p=0.12 respectively), likely due to smaller numbers of male participants in the study. Albumin levels were similar between supplemented an d non-supplemented residents (males, t=0.29, p=0.77; females, t=0.55, p=0.58).

## 5.4 Discussion

Sydney is situated at 33 degrees 55' south of the Equator, with average temperatures in summer of 23 degrees Celsius and 17 degrees Celsius in winter. At this latitude, similar to Buenos Aires, there is sufficient sunlight to provide adequate UV exposure for vitamin D synthesis in the skin of healthy individuals all year round (330), with an average of 340 sunny days each year. Despite this, serum 25-OH-vitamin D levels were almost universally low in this cohort of frail elderly people living in residential aged care facilities in northern Sydney. Similarly, a cross-sectional study of 99 elderly men and women conducted in Melbourne, Australia (324) showed that 52% of residents of the aged care facilities studied had 25-OH-vitamin D levels below the normal range, compared to 77% in this more northerly group. Equally low levels of vitamin D in aged care facilities have been described elsewhere (323;326;327), which would suggest that elderly persons living in such facilities are not benefiting from sunlight-derived vitamin D.

Males had higher 25-OH-vitamin D levels than women independent of season or institution, as has been shown previously (331). Residents in hostel accommodation had higher 25-OH-vitamin D and higher albumin levels than their counterparts in nursing homes. If one considers that serum albumin is a reasonable measure of general nutrition and morbidity (332-334), it is logical to infer that differences in vitamin D status between institutions are likely to reflect the poorer mobility and general health of nursing home residents rather than inadequate nutrition. Nevertheless, nutritional intake may confound the relationship between 25-OH-vitamin D and residential status, when you consider that poor nutritional intake impacts on general health and mobility. It might also be that poor general health was

the primary event, and subsequent reduction in dietary intake is seen. It would be interesting to examine the relationship of 25-OH-vitamin D and residential status when variables such as dietary intake are also considered.

Sunlight exposure is important for maintaining adequate 25-OH-vitamin D levels. Melin et al showed prospectively that seasonal variation of 25-OH-vitamin D levels requires three or more hours per week of sunlight exposure during summer months in Scandinavia (335), and that 25-OH-vitamin D levels measured in autumn reflect this exposure during summer. Individuals living in aged care facilities are less mobile than those living independently, and therefore less likely to get outdoors, contributing to an increased prevalence in hypovitaminosis D (323;326) which is not compensated by dietary intake (327). It has previously been shown that seasonal variation of 25-OH-vitamin D levels is less marked in residents of aged care facilities than in independently-living elderly people (325;336). Nevertheless, we have seen a distinct seasonal variation of 25-OH-vitamin D levels in this institutionalized group, with lowest levels occurring in winter as has been shown in previous cross-sectional (337-340) and longitudinal studies (341) in independently-living elderly populations. Serum 25-OH-vitamin D peaks during the spring/summer in men and in autumn in women; this difference might be explained by the poorer mobility of the female group, resulting in fewer trips outside and hence a slower accumulation of sunlight exposure over the warmer months.

Age-related changes in biochemistry were seen as expected, with increasing age conferring lower albumin and 25-OH-vitamin D and higher PTH levels in both genders. Creatinine clearance was seen to decrease with age in both males and

females as expected. Overall, biochemical changes in this frail elderly group did not behave differently to expected changes in any older population. It was of concern to note that although general nutrition was good in two thirds of the group, reflected by normal albumin values, 35% of residents of hostels and nursing homes have sub-optimal albumin levels. This proportion of nutritional deficiency warrants further investigation and appropriate intervetional program to improve general nutrition.

Serum 25-OH-vitamin D levels were inversely associated with PTH levels as expected, reflecting secondary hyperparathyroidism occurring in response to low vitamin D stores. Creatinine clearance (as a surrogate for renal function) was an important determinant of 25-OH-vitamin D in women but not in men; it is possible that this was due to insufficient numbers of male participants to confer statistical significance. It is also possible that creatinine clearance is in part measuring general debility, which then confers poorer mobility, reduced sunlight exposure and subsequently lower vitamin D acquisition in women than in men.

There has been much debate about the most appropriate definition of hypovitaminosis D, with cut-off values previously quoted from as low as 8-10 nmol/L (342) up to 50-80 nmol/L (314;322;343;344). Differences in 25-OH-vitamin D assays might account for some of this variability (345;346), and so associating low 25-OH-vitamin D levels with other parameters such as PTH is important to assess clinical significance. The most commonly used cut-off is below 30 nmol/L (315;318;329;339;347;348), on the basis that at this level of 25-OH-vitamin D a mild increase in serum parathyroid hormone is seen in response to subclinical hypovitaminosis D (329) and so has clinical significance. Our laboratory uses a standard cut-off of 39 nmol/L, being the

lower end of the 'normal' range in healthy adults. This study however supports the use of 22-30 nmol/L as a cut-off for defining hypovitaminosis D in the frail elderly living in aged care facilities. Nevertheless, thinking of 25-OH-vitamin D on a continuum instead of in discrete terms may be more appropriate when assessing a patient's risk for comorbidities such as osteoporosis, fracture and general health.

This study showed creatinine clearance and PTH are both independent predictors of 25-OH-vitamin D levels in females, those individuals with lower creatinine clearance and higher PTH values having significantly lower 25-OH-vitamin D levels. Creatinine clearance was not an independent predictor of vitamin D in males, again most likely due to insufficient numbers of males in this study. This relationship may well be confounded by muscle bulk in men, with higher baseline creatinine levels in men obscuring any effect of renal insufficiency on 25-OH-vitamin D levels. Mobility, as measured by the use of a walking aid, was also an independent predictor of 25-OH-vitamin D; both men and women who were independently mobile or used a stick had higher 25-OH-vitamin D levels than those using a frame or wheelchair. If this is interpreted as a surrogate for sunlight exposure, then those individuals who are healthier (higher creatinine clearance and higher albumin in women, hostel accommodation in men) and more mobile are more likely to obtain vitamin D from direct sunlight, and less likely to develop secondary hyperparathyroidism.

Vitamin D supplementation was infrequent in the FREE study, introducing a potential for selection bias. Nevertheless, vitamin D supplementation was seen to appropriately increase serum 25-OH-vitamin D levels in this elderly group, with a mean difference in levels between residents on supplements and those not taking vitamin D of

18mnol/L, bringing those individuals on treatment just above most cut-offs for hypovitaminosis D. It has been suggested that the elderly require higher doses of vitamin D to overcome hyperparathyroidism related to increasing creatinine levels (349). With a well recognized relationship between low 25-OH-vitamin D levels and a higher risk of osteoporosis and ensuing fracture, the low rate of vitamin D supplementation seen in this frail elderly population was disappointing. Only 10.5% of residents (n=131) were receiving vitamin D supplementation or vitamin D analogues, leaving 60% (n=741) of the total cohort with untreated low 25-OH-vitamin D levels (<30 nmol/L). Despite taking a wide variety of preparations and doses for unspecified indications, those on supplements had higher 25-OH-vitamin D levels and lower PTH levels suggesting appropriate biochemical responses to such therapy. Vitamin D supplementation has been shown to improve bone mineral density (350-352), muscle strength (227;230) and falling rates (230), and is a simple and economical intervention which might improve quality of life in this frail population. Its underutilization in frail elderly persons suggests an important lack of awareness and education which needs to be addressed.

Elderly institutionalized men and women have a high prevalence of hypovitaminosis D which is not adequately addressed by appropriate replacement therapy, and may have important implications for bone and muscle health. The relationship between low 25-OH-vitamin D, falls and fractures is an important area for future study in this high-risk elderly population.

# CHAPTER 6

# VITAMIN D AND OSTEOPOROSIS

## 6.1 Introduction

Vitamin D is important for maintaining calcium homeostasis and in the mineralization of healthy bone. Ageing results in impairment of vitamin D metabolism, with reduced capacity to generate pre-vitamin D in the skin in response to ultraviolet light exposure (353) combining with poor oral intake resulting in low circulating 25-OH-vitamin D levels. The ability to convert 25-OH-vitamin D to its active form, 1,25-OH-vitamin D, in the kidney (regulated by PTH) is also reduced (354;355). Calcium absorption from the intestine is modulated by circulating vitamin D metabolites (356), and with ageing the normal absorption of approximately 30% of dietary calcium is reduced, initiating the ionized calcium-driven feedback loop which results in normalization of serum calcium by way of compensatory secondary hyperparathyroidism, increased renal tubular reabsorption of calcium and increased bone resorption. A low calcium/phosphorus product is also seen, which causes an increase in the deposition of unmineralized osteoid.

It has been shown in Chapter 5 that there is widespread vitamin D insufficiency and secondary hyperparathyroidism in the frail elderly living in aged care facilities. But does this abnormal calcium homeostasis translate into lower bone mass and an increased risk of fracture? Cross-sectional studies have shown BMD is lower at the hip and lumbar spine in younger vitamin D deficient populations (347;357;358), and interventional studies of calcium and vitamin D supplementation have shown reduced bone loss (229) or significant BMD increases at both sites (351;352;359-361). Fracture incidence has also been shown to be significantly reduced by vitamin D supplementation (260;350;362;363).

There is less known about the relationship between 25-OH-vitamin D levels and QUS measures, which may be of more relevance to frail populations.

The aims of this study are as follows:

1: To confirm the distribution of BUA and VOS as measured by quantitative ultrasound of the calcaneus in a subpopulation of elderly men and women living in residential aged care facilities (hostels and nursing homes) in northern Sydney.

2: To establish the effect of vitamin D supplementation on BUA and VOS.

3: To describe the association between QUS measures and bone-related biochemical parameters, including serum 25-OH-vitamin D levels and serum parathyroid hormone (PTH).

4: To define hypovitaminosis D by relating 25-OH-vitamin D levels to BUA and VOS measures.

5: To identify the key independent predictors of BUA and VOS in the frail elderly.

This large cross-sectional study aims to show the relationship between serum 25-OH-vitamin D levels and bone mass as measured by QUS in frail elderly men and women, and to describe the independent predictors of low BUA and VOS.

## 6.2 Methods

### 6.2.1 Subjects

The population described in Chapter 5 has been used for this analysis, comprising 979 women and 264 men enrolled in the FREE study between 1999 and 2002. Individuals with biochemical primary hyperparathyroidism or significant renal failure were excluded (Chapter 5.2).

### 6.2.2 Measurements

Serum 25-OH-vitamin D analysis and quantitative ultrasound of the left calcaneus were performed as described in Chapter 2.

### 6.2.3 Statistical analysis

For describing the basic population demographics and the effect of vitamin D supplementation on QUS measures, Pearson's chi-squared statistic was used for comparing frequencies between categorical variables, and student's independent t-test for comparing the means of continuous variables. Univariate analysis for BUA and VOS was performed using one-way ANOVA for continuous variables, log transforming 25-OH-vitamin D to fulfill assumptions of normality. Associations with categorical variables were carried out using independent sample t-tests for binomial variables and one-way ANOVA for multinomial variables. Multivariate analysis was carried out including all significant univariate variables, using multiple linear regression.

## 6.3 Results

### 6.3.1 Baseline demographics

Demographics for the group, including age, QUS values and mean serum 25-OH-vitamin D levels are shown in Table 6.1.

**Table 6.1:** Mean Vitamin D levels and QUS values for men and women in hostels and nursing homes

| | Male | | Female | |
|---|---|---|---|---|
| | Hostel (N=136) | Nursing home (N=128) | Hostel (N=560) | Nursing home (N=419) |
| Age (years), mean (sd), range | 82.5 (7.5), 65.2 – 100.7 | 83.7 (7.9), 65.6 – 101.7 | 86.8 (6.1), 65.6 - 100.7 | 86.8 (6.8), 65.1 – 101.3 |
| BUA (dB/MHz), mean (sd), range | 77.4 (22.0), 16.5 – 135.3 | 69.5 (24.8), 18.8 – 138.2 | 50.5 (17.1 13.9 – 119.8 | 41.8 (17.9), 12.2 – 117.9 |
| VOS (m/s), mean (sd), range | 1608.8 (45.6), 1473.5 – 1738.5 | 1590.8 (51.6), 1472.5 – 1748.5 | 1567.7 (42.5), 1484.0 – 1733.5 | 1551.4 (42.1), 1459.5 – 1721.0 |
| 25-OH-vitamin D (nmol/L), mean (sd), range | 36 (17), 5 - 92 | 30 (18), 5 - 103 | 30 (15), 2 - 104 | 26 (16), 2 - 101 |
| 25-OH-vitamin D < 30 nmol/L (number, %) | 57 (41.9%) | 82 (64.1%) | 329 (58.8%) | 314 (74.9%) |

### 6.3.2 Demographic determinants of BUA and VOS

Females were older than males (mean difference 3.7 years, 95% confidence interval (CI) for the difference 2.7 – 4.7 years, t-7.10, $p<0.0001$). Serum 25-OH-vitamin D was an average of 4.7 nmol/L (95% CI for the mean difference 2.3 – 7.1 nmol/L)

higher in men than women (t=3.86, p<0.0001). BUA was significantly higher in men (mean difference 27.1 dB/MHz, 95% CI 23.5 – 30.8, t=14.79, p<0.0001) than women, as was VOS (males an average of 39.8 m/s higher than women, 95% CI for the difference 32.8 – 46.9 m/s, t=11.06, p<0.0001). Quantitative ultrasound measures were significantly lower in individuals with primary hyperparathyroidism (mean BUA 39.1 dB/MHz, p=0.02 and mean VOS 1544.6 m/s, p<0.05). There were significantly more women with hypovitaminosis D (25-OH-vitamin D <30 nmol/L) than men, $\chi^2$=15.13, p<0.0001).

Resident mobility was assessed by their use of a walking aid (Table 6.2). Individuals were ranked on their minimum requirements; a resident classified as using a walking frame was unable to walk only using a stick. Those individuals classified as 'unable to walk unassisted' could mobilize with the assistance of nursing staff, but were unable to walk independently using a walking frame.

**Table 6.2:** Number (%) of men and women classified by mobility.

| Mobility | Men (n=262) | Women (n=970) | Total group (n=1232) |
|---|---|---|---|
| No walking aid | 94 (35.9%) | 287 (29.6%) | 381 (30.9%) |
| Walking stick | 65 (24.8%) | 213 (22.0%) | 278 (22.6%) |
| Walking frame | 59 (22.5%) | 324 (33.4%) | 383 (31.1%) |
| Unable to walk | 44 (16.8%) | 146 (15.1%) | 190 (15.4%) |

### 6.3.3 Vitamin D supplementation

Those individuals receiving vitamin D supplementation at the time of enrolment into the study have been retained in the analysis. There is no statistically significant difference in BUA between these people and those not receiving supplements (supplemented group BUA=48.3 dB/MHz compared to 52.4 dB/MHz in the non-supplemented group, mean difference 4.1 dB/MHz, 95% confidence interval for the difference -0.7 to 8.9 dB/MHz, p=0.1). For the whole group, VOS is significantly lower in the supplemented group (1558.9 m/s compared to 1569.2 m/s in the non-supplemented, mean difference 10.3 m/s, 95% CI 0.1 to 20.6, p=0.047). When the cohort is split by gender (Table 6.3), vitamin D supplementation has no effect on either BUA or VOS measures in men or women.

**Table 6.3:** Comparison of residents on vitamin D supplementation at baseline with those not receiving supplements.

| | Male | | Female | |
|---|---|---|---|---|
| | Vit D Suppl | No Suppl | Vit D Suppl | No Suppl |
| N | 16 (6%) | 248 (94%) | 115 (11.5%) | 864 (88.5%) |
| Age (mean (sd)) | 81.2 (7.3) | 83.2 (7.7) | 86.9 (5.2) | 86.8 (6.5) |
| BUA (dB/MHz) | 85.6 (26.1) | 72.4 (23.4) | 42.6 (15.6) | 46.5 (18.3) |
| VOS (m/s) | 1598.3 (39.3) | 1599.2 (50.1) | 1552.9 (39.1) | 1560.2 (43.2) |
| 25-OH-vitamin D | 55.6 (24.2) | 31.3 (16.5)* | 43.7 (21.9) | 26.0 (13.5)* |

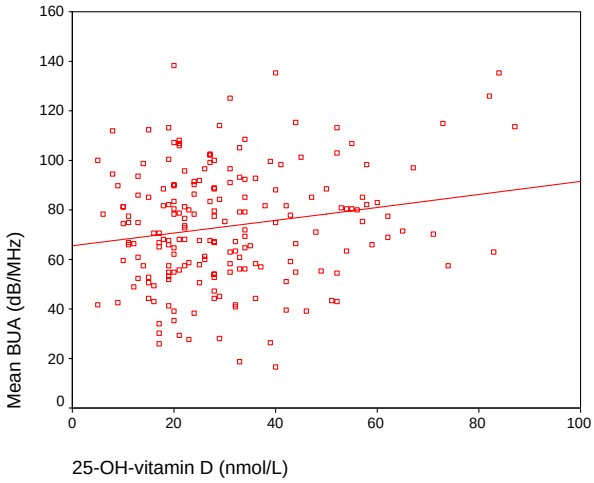
*significantly different to supplemented group, $p<0.05$

### 6.3.4 Quantitative ultrasound and 25-OH-vitamin D

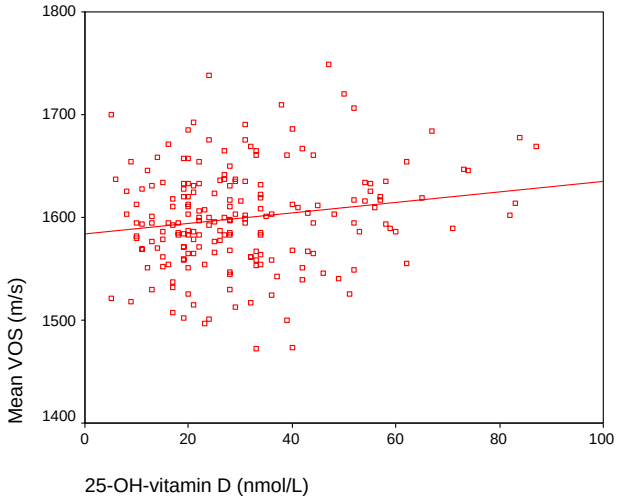
Figures 6.1 to 6.3 show the linear relationship between 25-OH-vitamin D and QUS parameters. In order to examine these relationships more closely, it was necessary to

log-transform 25-OH-vitamin D to fulfil assumptions of normality (as shown in Chapter 5) for univariate analysis. In men, BUA was not significantly related to log transformed 25-OH-vitamin D (F=3.13, p=0.08) or lnPTH (F=1.88, p=0.2). In women, mean BUA was significantly associated with lnPTH (F=4.30, p=0.04) but not with log transformed 25-OH-vitamin D (F=1.51, p=0.2). Mean VOS was not associated with 25-OH-vitamin D or PTH in men (25-OH-vitamin D, F=3.09, p=0.08; PTH F=1.49, p=0.2) or in women (25-OH-vitamin D, F=1.69, p=0.2; PTH F=2.69, p=0.2).

**Figure 6.1:** Mean BUA and VOS vs 25-OH-vitamin D in men

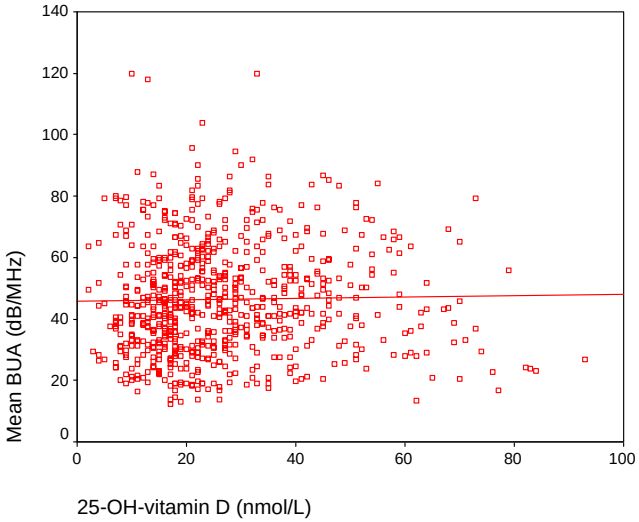



**(**Intercept=65.5, slope=0.26, $R^2$=0.03)

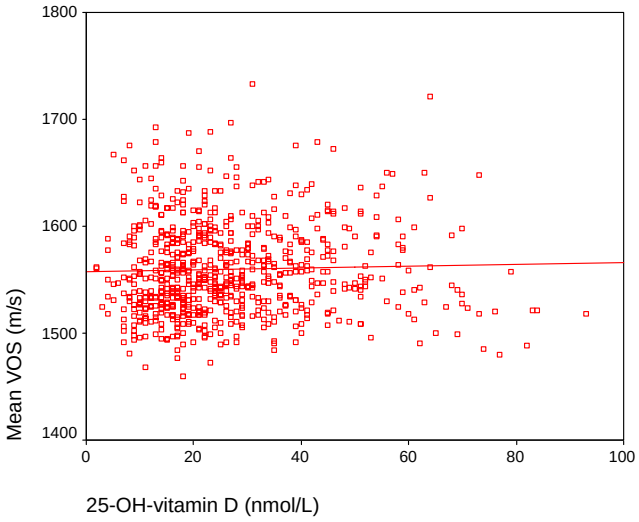



**(**Intercept=1584.1, slope=0.51, $R^2$=0.029))

**Figure 6.2:** Mean BUA and VOS vs 25-OH-vitamin D in women

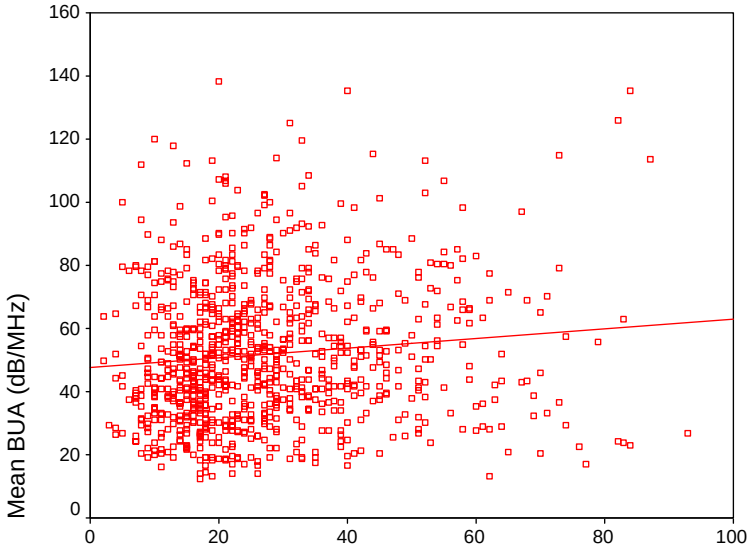



(Intercept=45.6, slope=0.02, $R^2$=0.0004)

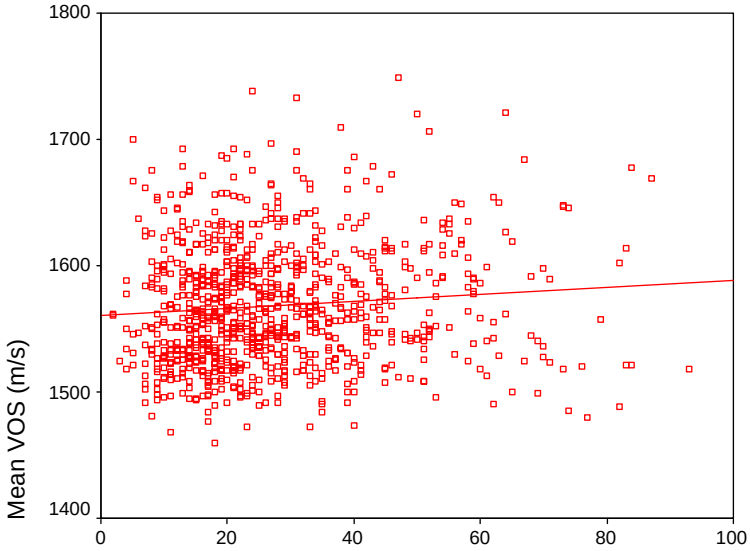



(Intercept=1557.7, slope=0.08, $R^2$=0.0008)

**Figure 6.3:** Mean BUA and VOS vs 25-OH-vitamin D in the whole cohort




(Intercept=47.8, slope=0.15, $R^2$=0.011)




(Intercept=1560.4, slope=0.2, $R^2$=0.009)

### 6.3.5 Univariate associations with BUA and VOS

Those variables shown to be related to BUA and VOS in Chapter 4 were also included for analysis. Univariate analysis of mean BUA in men showed a significant

relationship between BUA and weight (F=23.23, p<0.0001), but BUA was not related to age (F=0.25, p=0.6). In women, mean BUA was significantly associated with age (F=21.45, p<0.0001) and weight (F=102.47, p<0.0001). Mean VOS in men did not reveal statistically significant associations with either age (F=0.009, p=0.9) or weight (F=1.32, p=0.3). In women, mean VOS was significantly associated with both age (F=11.87, p=0.001) and weight (F=8.53, p=0.004). Serum albumin was not associated with BUA in men (F=-0.093, p=0.93) or with VOS in men (F=-0.516, p=0.61). Similarly in women, there was no association between albumin and BUA (F=ß0.572, p=0.57) or between albumin and VOS (F=-0.202, p=0.84)

Interestingly, when men and women are considered together, univariate analysis reveals that mean BUA is significantly associated with age (F=39.95, p<0.0001), weight (F=266.74, p<0.0001), lnPTH (F=14.21, p<0.0001) and 25-OH-vitamin D (F=10.95, p=0.001), and mean VOS also shows statistically significant univariate associations with age (F=24.43, p<0.0001), weight (F=51.77, p<0.0001), lnPTH (F=9.10, p=0.003) and vitamin D (8.77, p=0.003). Serum albumin was not associated with BUA (F=0.393, p=0.70) or with VOS (F=0.053, p=0.96) in the whole group.

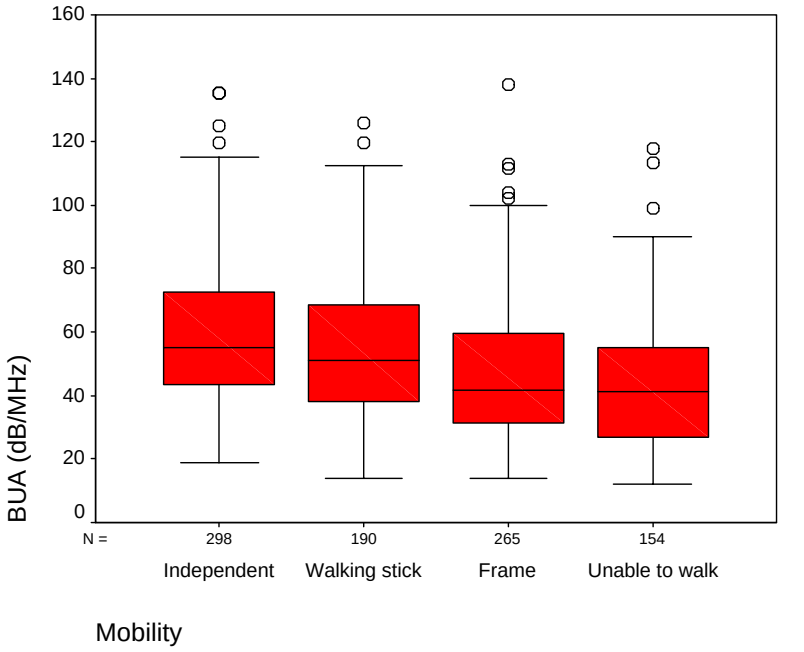
Both QUS measures and 25-OH-vitamin D levels decrease with decreasing mobility as measured by the use of walking aids in men and women (table 6.4). In men, QUS variables are significantly higher in more mobile individuals (for BUA, F=4.64, p=0.004, and for VOS F= 4.51, p<0.0001), and serum 25-OH-vitamin D levels are higher (F=3.51, p=0.02). Similarly significant relationships are seen in women, with higher mobility inferring higher BUA (F=22.6, p<0.0001), VOS (F=21.7, p<0.0001)

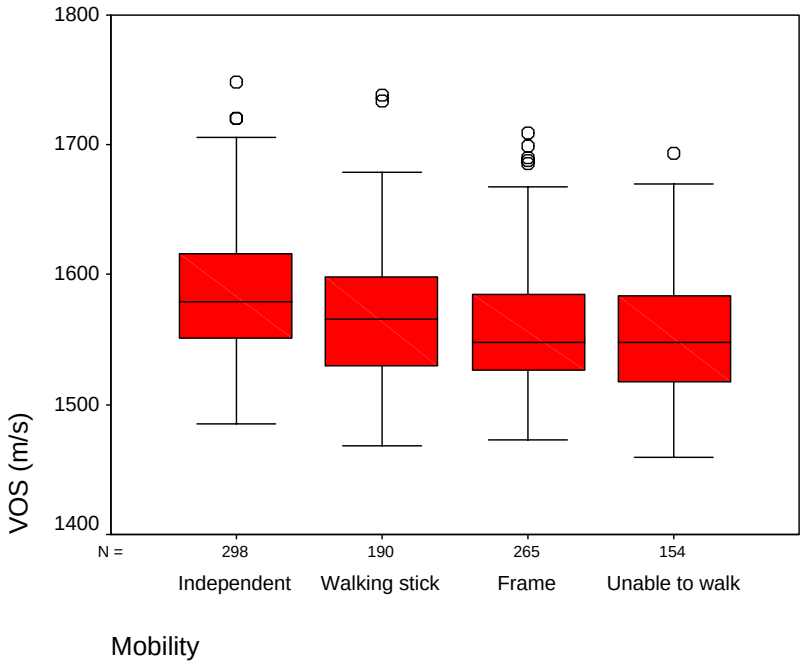
and serum 25-OH-vitamin D ($F=7.7$, $p<0.0001$). These relationships are shown pictorially in Figures 6.4 and 6.5.

**Table 6.4:** Mean QUS and 25-OH-vitamin D levels for each category of mobility in men and women.

| | Mobility | Men (mean (sd)) | Women (mean (sd)) |
|---|---|---|---|
| BUA (dB/MHz) | Independent | 79.8 (23.3) | 52.5 (16.2) |
| | Stick | 74.9 (23.1) | 48.6 (18.3) |
| | Frame | 69.6 (25.6) | 42.9 (17.6) |
| | Unable to walk | 62.8 (19.4) | 38.0 (17.5) |
| VOS (m/s) | Independent | 1615.1 (48.1) | 1576.1 (41.2) |
| | Stick | 1597.3 (48.8) | 1561.2 (45.4) |
| | Frame | 1591.2 (53.2) | 1550.4 (38.9) |
| | Unable to walk | 1581.2 (41.9) | 1544.1 (42.9) |
| 25-OH-vitamin D (nmol/L) | Independent | 36.0 (18.2) | 29.2 (15.3) |
| | Stick | 35.0 (16.2) | 30.4 (16.0) |
| | Frame | 29.9 (19.6) | 28.3 (16.3) |
| | Unable to walk | 26.8 (16.5) | 22.7 (13.9) |

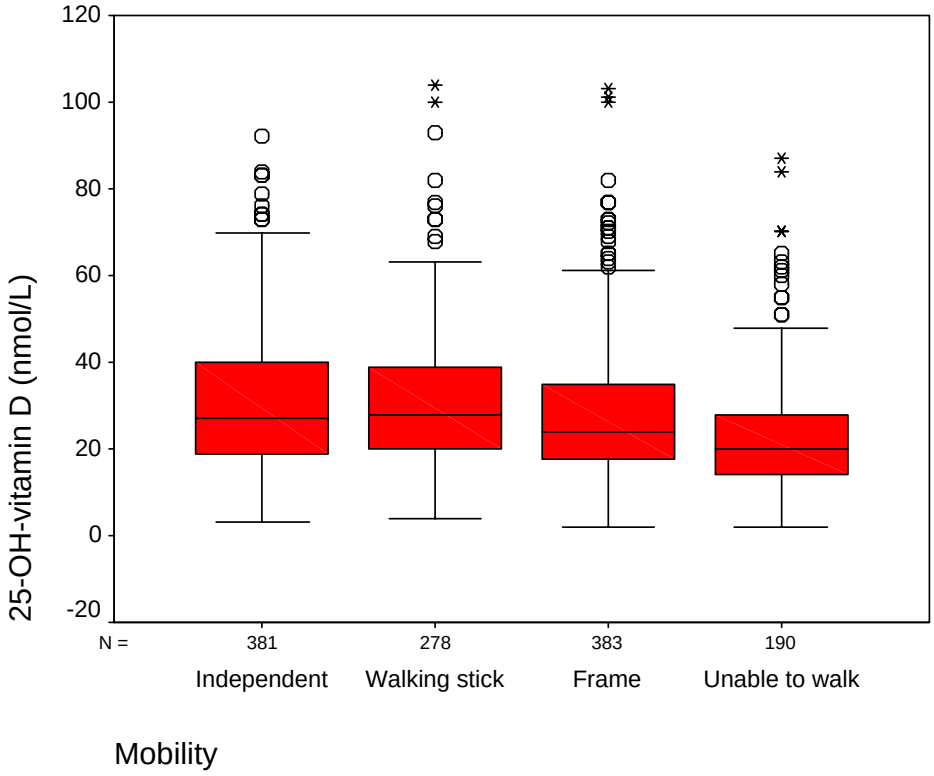
**Figure 6.4:** Box and whisker plots* of BUA and VOS related to level of mobility in the whole cohort.




*Boxes represent the interquartile range around the median

**Figure 6.5:** Box and whisker plots* of 25-OH-vitamin D levels related to level of mobility in the whole cohort.



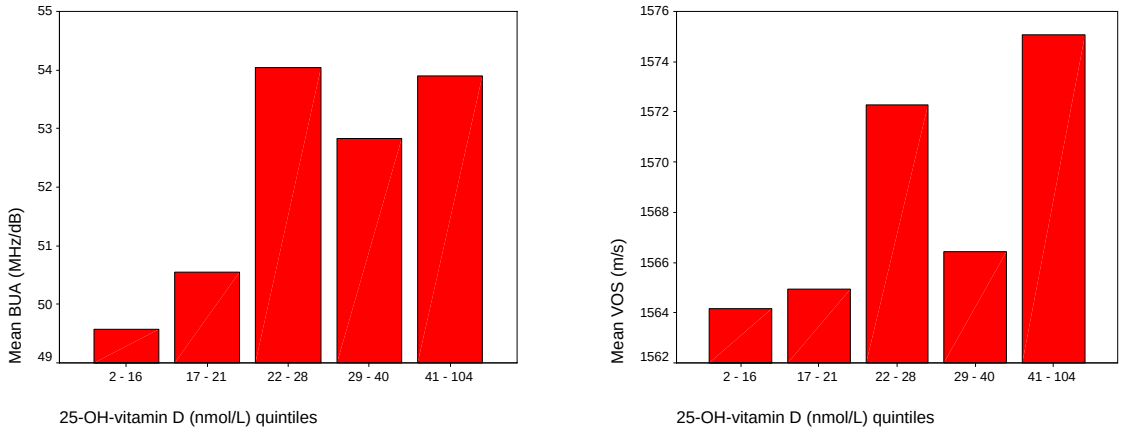

*Boxes represent the interquartile range around the median

Both BUA and VOS were significantly lower in nursing home residents than in hostel dwellers. In men, mean BUA in nursing homes was 69.53 dB/MHz, compared to 77.40 dB/MHz in hostels (mean difference 7.87 dB/MHz, 95% CI 1.20 – 14.53, p=0.02), and mean VOS in nursing homes was 1590.79 m/s compared to 1608.77 m/s in hostels (mean difference 18.00 m/s, 95% CI 4.14 – 31.83 m/s, p=0.01). In women, mean BUA in nursing homes was 41.77 dB/MHz, compared to 50.50 dB/MHz in hostels (mean difference 8.74 dB/MHz, 95% CI 6.18 – 11.29, p<0.0001), and mean VOS in nursing homes was 1551.39 m/s compared to 1537.74 m/s in hostels (mean difference 16.35 m/s, 95% CI 10.17 – 22.53 m/s, p<0.0001).

### 6.3.6 Hypovitaminosis D and QUS measures

In order to establish the existence of a distinct 25-OH-vitamin D level below which BUA and VOS are significantly low, QUS parameters were plotted against quintiles of vitamin D (Figure 6.6). Low levels of vitamin D are seen to correspond to low levels of both BUA and VOS, but the cut-off value is approximately 22 nmol/L, lower than that identified by secondary hyperparathyroidism (Chapter 5).

**Figure 6.6:** Mean BUA and VOS values relating to 25-OH-vitamin D quintiles




When men and women are considered separately, hypovitaminosis D (defined at two different cut-off levels, 25-OH-vitamin D <30 nmol/L as was related to secondary hyperparathyroidism in Chapter 5, and 25-OH-vitamin D <22 nmol/L, as is suggested by Figure 6) was not related to either BUA or VOS (tables 6.5, 6.6) in men. A cut-off of 30 nmol/L was also too high to show a significant relationship between 25-OH-vitamin D and QUS in women; using the lower cut-off of 22 nmol/L revealed significantly lower BUA in these vitamin D-deficient women, but no significant differences in VOS. When the group was combined, both QUS variables are significantly lower in individuals with either definition of hypovitaminosis D.

**Table 6.5:** Unadjusted relationship between hypovitaminosis D and QUS variables (where the mean difference is the magnitude of QUS in 25-OH-vitamin D replete residents less QUS in residents with 25-OH-vitamin D < 30 nmol/L)

| | | Mean difference | 95% CI | t | p |
|---|---|---|---|---|---|
| BUA (dB/MHz) | Men | 4.32 | -2.52 – 11.16 | 1.25 | 0.2 |
| | Women | 1.94 | -0.89 – 4.78 | 1.35 | 0.2 |
| | Total cohort | 4.43 | 1.38 – 7.49 | 2.85 | 0.005* |
| VOS (m/s) | Men | 9.47 | -4.78 – 23.72 | 1.31 | 0.2 |
| | Women | 5.46 | -1.31 – 12.23 | 1.58 | 0.1 |
| | Total cohort | 9.22 | 2.47 – 15.96 | 2.79 | 0.005* |

*statistically significant at $p<0.05$

**Table 6.6:** Unadjusted relationship between hypovitaminosis D and QUS variables (where the mean difference is the magnitude of QUS in 25-OH-vitamin D replete residents less QUS in residents with 25-OH-vitamin D < 22 nmol/L)

| | | Mean difference | 95% CI | t | p |
|---|---|---|---|---|---|
| BUA (dB/MHz) | Men | 3.49 | -3.52 – 10.50 | 0.98 | 0.3 |
| | Women | 3.08 | 0.45 – 5.71 | 2.30 | 0.02* |
| | Total cohort | 4.87 | 1.98 – 7.77 | 3.30 | 0.001* |
| VOS (m/s) | Men | 9.44 | -5.13 – 24.00 | 1.28 | 0.2 |
| | Women | 5.65 | -0.65 – 11.95 | 1.77 | 0.08 |
| | Total cohort | 8.91 | 2.75 – 15.07 | 2.84 | 0.005* |

*statistically significant at $p<0.05$

### 6.3.7 Independent predictors of BUA and VOS

Results for multivariate analysis for BUA and VOS are shown in Table 6.7. All variables which were significantly associated with the QUS parameters (age, gender, institution type, mobility, lnPTH, ln25-OH-vitamin D, weight) were included in the analysis. Only mobility, lnPTH, weight and gender remain independently related to BUA in this elderly population, accounting for 41% of the variability of BUA. VOS is predicted by mobility, weight and gender alone, comprising 21% of the variability of VOS. 25-OH-vitamin D becomes nonsignificant in both models. When a binomial variable of 'hypovitaminosis D' is substituted for the continuous log transformed 25-OH-vitamin D variable, hypovitaminosis D is not an independent predictor of either BUA or QUS for either a 22 or 30nmol/L cut-off ($p>0.8$), data not shown.

**Table 6.7:** Multivariate analysis of BUA and VOS

| | Variable | β | t | p |
|---|---|---|---|---|
| BUA<br>$R^2 = 0.41$ | Mobility | -0.239 | -9.032 | 0.0001 |
| | lnPTH | -0.058 | -2.177 | 0.03 |
| | Weight | 0.315 | 10.904 | 0.0001 |
| | Gender (female) | -0.366 | -12.613 | 0.0001 |
| VOS<br>$R^2 = 0.21$ | Mobility | -0.259 | -8.461 | 0.0001 |
| | Weight | 0.093 | 2.775 | 0.006 |
| | Gender (female) | -0.318 | -9.500 | 0.0001 |

Excluded from model: For BUA: Age, Institution, lnvitD. For VOS: Age, Institution, lnvitD, lnPTH.

When men and women are considered separately, slightly different parameters are independent predictors for QUS (Tables 6.8, 6.9), but 25-OH-vitamin D levels remain unrelated to BUA and VOS.

**Table 6.8:** Multivariate analysis of BUA (dB/MHz) in men and women

| | Variable | β | t | p |
|---|---|---|---|---|
| Men<br>$R^2 = 0.19$ | Mobility | -0.265 | -3.819 | 0.0001 |
| | Age | 0.215 | 3.061 | 0.003 |
| | Weight | 0.345 | 4.980 | 0.0001 |
| Women<br>$R^2 = 0.23$ | Mobility | -0.261 | -6.792 | 0.0001 |
| | Weight | 0.336 | 9.714 | 0.0001 |
| | Institution | -0.083 | -2.138 | 0.03 |
| | lnPTH | -0.069 | -2.030 | 0.04 |

Excluded from model: For men: Institution, lnvitD, lnPTH. For women: Age, lnvitD.

**Table 6.9:** Multivariate analysis of VOS (m/s) in men and women

| | Variable | β | t | p |
|---|---|---|---|---|
| Men<br>$R^2 = 0.06$ | Mobility | -0.245 | -3.358 | 0.001 |
| Women<br>$R^2 = 0.10$ | Mobility | -0.284 | -7.682 | 0.0001 |
| | Weight | 0.086 | 2.293 | 0.02 |
| | Age | -0.075 | -1.985 | 0.05 |

Excluded from model: For men: Age, Institution, lnvitD, lnPTH, weight. For women: Institution, lnvitD, lnPTH.

## 6.4 Discussion

Vitamin D deficiency was extremely common in both elderly men and women living in institutions in Sydney, but serum 25-OH-vitamin D was not independently associated with BUA or VOS in this study. Elderly populations have previously been reported as having low 25-OH-vitamin D levels (327;339) at similar latitudes in Europe and the US, and a case-control study of elderly men in Virginia showed 25-OH-vitamin D levels to be significantly lower in men residing in nursing homes than living independently (326). There is some observational evidence suggesting that 25-OH-vitamin D levels relate to bone mass. In a group of postmenopausal women undergoing screening for osteoporosis, those with subclinical vitamin D deficiency were found to have lower vertebral bone mass as measured by quantitative computed tomography than those with normal 25-OH-vitamin D levels (364). A Spanish group has also recently shown a correlation between 25-OH-vitamin D levels and BMD at the lumbar spine and femoral neck in otherwise healthy postmenopausal women (358).

However the relationship between QUS measures and 25-OH-vitamin D is not as clear. A cross-sectional study of elderly institutionalized men and women showed 25-OH-vitamin D levels to be associated with both BUA and VOS, largely through the effect of secondary hyperparathyroidism (365). Calcium and vitamin D supplementation in this group was shown to have a significant beneficial effect on BUA over 2 years compared to placebo, but no effect on VOS (110). An observational study of perimenopausal women did not reveal a similar association between vitamin D supplementation and QUS measures in this younger cohort (366). In the FREE study, cross-sectional analysis did not reveal a relationship between vitamin D supplementation and BUA or VOS, despite significantly higher 25-OH-

vitamin D levels in the supplemented group. This may be related to the small numbers of patients receiving vitamin D supplements, since the trend in women was for those on supplements to have lower BUA and VOS measures (despite not reaching statistical significance). It may be that these individuals were preferentially identified as having a high risk of osteoporosis and thus self-selected to have lower QUS readings.

Serum 25-OH-vitamin D was univariately related to BUA in this group of frail elderly men and women. When vitamin D status was considered as 'hypovitaminosis D' at a cut-off of <30nmol/L or <22nmol/L, those individuals classified as being vitamin D deficient had significantly lower BUA and VOS measures. This suggests that a 25-OH-vitamin D level less than 30nmol/L may have an important effect on bone health (as there is on the development of secondary hyperparathyroidism, seen in Chapter 5). Prospective studies of QUS as a predictor of fracture have shown that a decrease of 1 standard deviation in BUA is associated with an approximate doubling of hip fracture risk (54;56;58); the clinical significance of the smaller differences in BUA shown in this study is not clear but prospective fracture analysis will address this issue. When VOS is considered, a distinct cut-off to define 'hypovitaminosis D' is not so clear, and seems to be higher as seen in Figure 6.6. However, the previous studies of prospective fracture support the lower cut-off seen with BUA (22-30nmol/L). Prospective fracture data from the FREE study will help to more clearly elucidate whether BUA or VOS is more important for fracture risk in this frail elderly cohort.

It makes sense to assess 25-OH-vitamin D levels in relation to serum PTH levels, as this will reflect changes over a shorter time frame. Quantitative ultrasound is measuring the outcome of longer periods of vitamin D deficiency. Nevertheless, this

has important clinical implications, with univariate analysis suggesting that vitamin D supplementation in the elderly should be considered even in mild cases of suboptimal serum 25-OH-vitamin D, and widens the population at risk of impaired bone metabolism. If those patients with low 25-OH-vitamin D levels can be identified before longstanding bone changes have occurred, then any intervention is likely to be more successful in ultimate fracture prevention.

Independent predictors of BUA include mobility, weight, gender and PTH but not 25-OH-vitamin D. However, when mobility is not included in the analysis, 25-OH-vitamin D remains in the model as a significant independent predictor. It has been shown that 25-OH-vitamin D levels are strongly linked to mobility, which suggests that 25-OH-vitamin D is either an intervening variable that plays a role in determining mobility perhaps by improving muscle strength (and hence is lost in a multivariate analysis), or that mobility is a strong determinant of vitamin D status independent of bone health. Weight bearing is important in maintaining BMD, and hence it is logical to assume that the relationship between mobility and QUS measures might be solely due to the amount of time a resident spends standing or walking. The picture is complicated by vitamin D, as an individual who is more mobile is more likely to get outside into the sunlight and have adequate UV light exposure to synthesize vitamin D. Conversely, if it is assumed that vitamin D plays a role in maintaining muscle strength (200;202), it may be that those individuals with higher 25-OH-vitamin D levels are going to be more mobile independent of sunlight exposure. It is likely that 25-OH-vitamin D, mobility and QUS are closely entwined in elderly persons; the relationship between 25-OH-vitamin D and muscle strength relating to falls will be addressed in Chapter 7.

Parathyroid hormone levels remain an independent predictor of BUA but not VOS in multivariate analysis. It has been shown previously in case control studies that primary hyperparathyroidism is associated with low BUA measures (367-369), and that surgical correction results in significant improvement of BUA but not VOS (367). This is supported by the lower BUA seen in individuals with biochemical primary hyperparathyroidism in this elderly cohort. When secondary hyperparathyroidism is considered, Krieg et al (365) in a smaller study of 264 women and 103 men living in aged care facilities found that VOS was also related to PTH levels, but did not correct for mobility. It was suggested that the relationship between secondary hyperparathyroidism and QUS is likely to be mediated by low 25-OH-vitamin D levels, but the bone changes reflect the effect of the PTH levels directly rather than vitamin D deficiency. Continuous exposure to PTH at a bone level results in mobilization of calcium from the bone surface (370) and to an increase in the number and activity of osteoclasts (371), and secondary hyperparathyroidism might therefore predispose to changes which might be detectable by QUS.

Vitamin D and PTH play a role in determining BUA and VOS at the calcaneus in the frail elderly, however how much is a direct action on bone and how much is via improved general health and mobility is not clear. Nevertheless, this study gives further evidence to support vitamin D supplementation in D-deficient elderly persons.

# CHAPTER 7

# VITAMIN D AND PTH AND THEIR RELATIONSHIP TO FALLING IN THE ELDERLY

## 7.1 Introduction

Falling is a serious health problem in the elderly, bring with it significant morbidity and mortality. There are a myriad of factors associated with an increased risk of falling in this group, including increasing age, balance, muscle strength and cognitive function (Chapter 1.4). The elderly are at particularly high risk, with 33% of community dwellers over the age of 65 having at least one fall each year (176;177;372). The risk is higher in the institutionalized elderly (293;294;373), and it is estimated that 6-7% of fallers sustain a fracture as a direct result of falling (177;374).

Vitamin D levels are low in residents of aged care facilities (326;327) as seen in Chapter 5, due to inadequate sunlight exposure, impaired ability to convert vitamin D in the skin and poor diet. Vitamin D insufficiency has also been related to poorer muscle strength (200;375), which could logically increase the risk of falling in this group. Cross-sectional studies have not consistently shown a higher incidence of falls in vitamin D deficiency (176;376-378). There is one large prospective study of time to first fall in women living in residential care (379) which shows that lower 25-OH-vitamin D levels are related to a shorter time to falling.

Parathyroid hormone has also been shown to be indirectly associated with muscle strength, with secondary hyperparathyroidism patients exhibiting muscle weakness (380). One study of falls in the elderly describes an independent association of higher PTH levels with an increased falls risk (OR 5.6 for each natural logarithmic unit of PTH) (208).

This study aims to:

(1) Prospectively measure the incidence of falls in a population of elderly residents of aged care facilities in Sydney, Australia

(2) Describe the demographic factors associated with falling in aged care facilities

(3) Describe the association between serum 25-OH-vitamin D levels and prospective falls in the elderly

(4) Describe the association between serum PTH levels and prospective falls in the elderly

(5) Establish the independent factors, both physical and biochemical, associated with prospective falls in the institutionalized elderly. Do 25-OH-vitamin D and PTH both contribute to falls risk in this population?

## 7.2 Methods

### 7.2.1 Subjects

The first 1010 women and 270 men enrolled in the FREE study to reach one year of prospective follow up have been included in this analysis. All falls and deaths were recorded over the follow up period, as described in Chapter 2.

### 7.2.2 Measurements

Measurements of physical function and biochemistry are described in full in Chapter 2. Potential risk factors for falling in an elderly population, including age, weight, type of accommodation, urinary incontinence, cognitive function and overall health as assessed by both RCS and implicit review were recorded. Two different methods of assessing balance were examined: the 30 second stand test on both firm and pliable surfaces, and the use of a walking aid in daily life as a surrogate for balance on mobilization.

### 7.2.3 Statistical analysis

Baseline characteristics were examined with relation to falls status using independent t-tests for continuous variables and chi-square tests for categorical variables. Risk to first fall was calculated using proportional cox regression.

## 7.3 Results

### 7.3.1 Distribution of falls

The number of falls occurring in the study population at 6 and 12 months is shown in Table 7.1. There was no significant difference in the incidence of falls at 6 months ($\chi^2$=16.78, df=15, p=0.3) or at 12 months ($\chi^2$=31.65, df=23, p=0.1) between men and women. In the first 6 months of follow-up, there were more falls in hostels than in nursing homes ($\chi^2$=26.96, p=0.03) but there was no significant difference between institution type after 12 months follow up ($\chi^2$=32.90, p=0.08).

**Table 7.1:** Incidence of falls at 6 and 12 months in men and women

| | At 6 months | | At 12 months | |
|---|---|---|---|---|
| | Men (N=270) | Women (N=1010) | Men (N=270) | Women (N=1000) |
| No falls | 172 (64%) | 628 (62%) | 142 (53%) | 492 (49%) |
| 1 fall | 48 (18%) | 203 (20%) | 51 (19%) | 224 (22%) |
| 2 falls | 14 (5%) | 73 (7%) | 21 (8%) | 98 (10%) |
| 3 falls | 16 (6%) | 39 (4%) | 11 (4%) | 64 (6%) |
| 4 falls | 4 (2%) | 20 (2%) | 6 (2%) | 34 (3%) |
| 5 falls | 6 (2%) | 20 (2%) | 9 (3%) | 17 (2%) |
| 6 falls | 2 (0.7%) | 7 (0.7%) | 7 (3%) | 24 (2%) |
| 7 falls | 1 (0.4%) | 9 (1%) | 3 (1%) | 11 (1%) |
| 8 falls | 1 (0.4%) | 2 (0.2%) | 2 (0.7%) | 13 (1%) |
| 9 falls | 3 (1%) | 3 (0.3%) | 2 (0.7%) | 6 (0.6%) |
| >=10 falls | 3 (1%) | 6 (0.6%) | 16 (6%) | 27 (3%) |

### 7.3.2 Serum 25-OH-vitamin D and balance

At baseline, univariate analysis showed serum 25-OH-vitamin D was significantly related to balance (F=14.09, df 4, p<0.0001) and to implicit review score (F=4.31, df 3, p=0.005). Those individuals who performed badly in either score were seen to have lower 25-OH-vitamin D levels than those with better balance performance (Figure 7.1) or higher implicit review scores (Figure 7.2). Balance was measured on both a firm and compliant surfaces, as described in Chapter 2.3, with 1 being an inability to stand for any length of time unaided on a firm surface and 5 being able to stand on a pliable surface for 30 seconds unsupported.

**Figure 7.1:** Relationship between mean 25-OH-vitamin D levels and balance

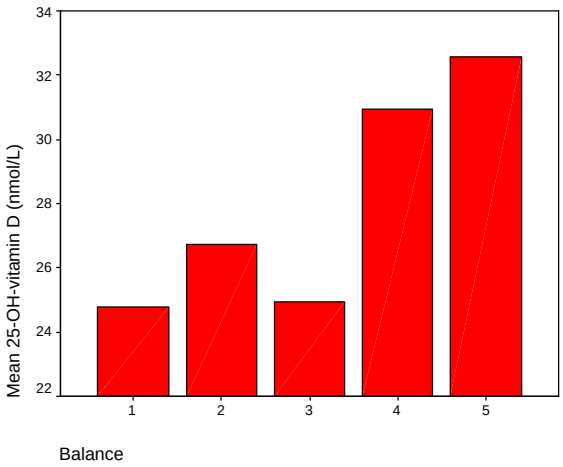



**Table 7.2:** Independent determinants of balance

| | $\chi^2$ statistic | P value |
|---|---|---|
| 25-OH-vitamin D < 30nmol/L | 67.12 | <0.0001 |
| Age | 32.65 | <0.0001 |
| Weight | 27.73 | <0.0001 |
| Gender | 11.86 | 0.02 |
| Incontinence | 91.00 | <0.0001 |

Logistic regression modeling showed that the relationships between hypovitaminosis D and balance (Table 7.2) and between low 25-OH-vitamin D and implicit review (Table 7.3) were independent of age, weight, gender or presence of urinary incontinence .

**Figure 7.2:** Relationship between mean 25-OH-vitamin D levels and function, as graded by the implicit review score.

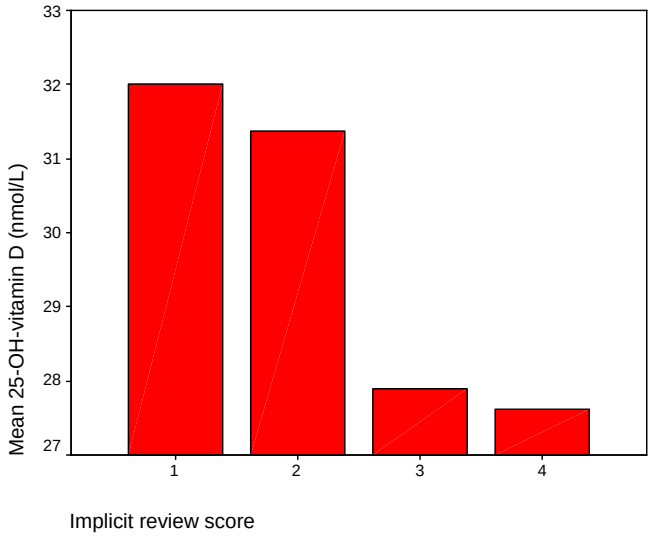



**Table 7.3:** Independent determinants of implicit review score

| | $\chi^2$ statistic | P value |
|---|---|---|
| 25-OH-vitamin D < 30nmol/L | 22.53 | <0.0001 |
| Age | 5.05 | 0.17 |
| Weight | 19.88 | <0.0001 |
| Gender | 4.59 | 0.21 |
| Incontinence | 51.90 | <0.0001 |

**Table 7.4:** Baseline characteristics and status with respect to falls at 6 months

| Characteristics | No falls in 6 months | One or more falls | P value |
|---|---|---|---|
| Age (years) | 85.5 +/- 6.9 | 86.7 +/- 6.7 | 0.004* |
| Female sex (%) | 628 (78.5%) | 382 (79.6%) | 0.67 |
| Hostel accommodation (%) | 483 (60.4%) | 235 (49.0%) | <0.0001* |
| Walking aid (%) | | | <0.0001* |
| No walking aid | 252 (31.5%) | 137 (28.5%) | |
| Walking stick | 194 (24.3%) | 92 (19.2%) | |
| Walking frame | 216 (27.0%) | 184 (38.3%) | |
| Unable to walk | 134 (16.8%) | 60 (12.5%) | |
| Balance | | | <0.0001* |
| Unable to stand unassisted | 154 (66.4%) | 78 (33.6%) | |
| Stands for <30 seconds | 61 (47.7%) | 67 (52.3%) | |
| Stands 30 seconds on firm surface | 99 (45.8%) | 117 (54.2%) | |
| Stands <30 seconds on soft surface | 186 (60.2%) | 123 (39.8%) | |
| Stands 30 seconds on soft surface | 297 (76.3%) | 92 (23.7%) | |
| Weight (kg) | 60.6 +/- 13.7 | 57.9 +/- 13.0 | 0.001* |
| BUA (dB/MHz) | 51.7 +/- 22.1 | 50.45 +/- 22.7 | 0.44 |
| VOS (m/s) | 1566.0 +/- 45.7 | 1567.3 +/- 47.6 | 0.62 |
| 25-OH-vitamin D (median) (nmol/L) | 29.6 +/- 17.0 (26) | 27.7 +/- 15.2 (24) | 0.04* |
| PTH (median) (pg/mL) | 75.1 +/- 71.9 (57.8) | 79.5 +/- 67.6 (59.5) | 0.28 |
| SMMSE | 21.6 +/- 8.1 | 19.2 +/- 8.7 | <0.0001* |
| Resident classification | | | <0.0001* |
| RCS 1 | 72 (9.0%) | 48 (10.0%) | |
| RCS 2 | 142 (17.8%) | 113 (23.5%) | |
| RCS 3 | 96 (12.0%) | 95 (19.8%) | |
| RCS 4 | 26 (3.3%) | 19 (4.0%) | |
| RCS 5 | 64 (8.0%) | 40 (8.3%) | |
| RCS 6 | 115 (14.4%) | 50 (10.4%) | |
| RCS 7 | 203 (25.4%) | 87 (18.1%) | |
| RCS 8 | 73 (9.1%) | 19 (4.0%) | |
| Implicit review | | | <0.0001* |
| No symptoms | 32 (80%) | 8 (20%) | |
| Mild symptoms | 255 (72.4%) | 97 (27.6%) | |
| Moderate and severe symptoms | 505 (57.7%) | 361 (42.3%) | |
| Incontinence | 352 (68.3%) | 163 (31.7%) | <0.0001* |

*statistically significant $p<0.05$.

**Table 7.5:** Baseline characteristics and status with respect to falls at 12 months

| Characteristics | No falls in 12 months | One or more falls | P value |
|---|---|---|---|
| Age (years) | 85.4 +/- 6.8 | 86.5 +/- 6.8 | 0.005* |
| Female sex (%) | 492 (77.6%) | 518 (80.2%) | 0.27 |
| Hostel accommodation (%) | 388 (61.2%) | 330 (51.1%) | <0.0001* |
| Walking aid (%) | | | <0.0001* |
| No walking aid | 203 (32.1%) | 184 (28.9%) | |
| Walking stick | 152 (24.1%) | 134 (21.0%) | |
| Walking frame | 162 (25.6%) | 238 (37.4%) | |
| Unable to walk | 113 (17.9%) | 81 (12.7%) | |
| Balance | | | <0.0001* |
| Unable to stand unassisted | 130 (56.0%) | 102 (44%) | |
| Stands for <30 seconds | 45 (35.2%) | 83 (64.8%) | |
| Stands 30 seconds on firm surface | 70 (32.4%) | 146 (67.6%) | |
| Stands <30 seconds on soft surface | 137 (44.3%) | 172 (55.7%) | |
| Stands 30 seconds on soft surface | 250 (64.3%) | 139 (35.7%) | |
| Weight (kg) | 60.3 +/- 13.8 | 59.0 +/- 13.2 | 0.10 |
| BUA (dB/MHz) | 51.4 +/- 22.2 | 52.0 +/- 23.4 | 0.71 |
| VOS (m/s) | 1565.0 +/- 45.1 | 1568.0 +/- 47.6 | 0.26 |
| 25-OH-vitamin D (median) (nmol/L) | 30.2 +/- 17.0 (26) | 28.0 +/- 15.6 (24) | 0.006* |
| PTH (median) (pg/mL) | 73.3 +/- 70.0 (56.9) | 80.1 +/- 70.6 (59.5) | 0.09 |
| SMMSE | 21.8 +/- 8.1 | 19.6 +/- 8.5 | <0.0001* |
| Resident classification | | | <0.0001* |
| RCS 1 | 55 (8.8%) | 65 (10.2%) | |
| RCS 2 | 112 (17.9%) | 143 (22.5%) | |
| RCS 3 | 74 (11.8%) | 117 (18.4%) | |
| RCS 4 | 21 (3.3%) | 24 (3.8%) | |
| RCS 5 | 46 (7.3%) | 58 (9.1%) | |
| RCS 6 | 91 (14.5%) | 74 (11.7%) | |
| RCS 7 | 172 (27.4%) | 118 (18.6%) | |
| RCS 8 | 56 (8.9%) | 36 (5.7%) | |
| Implicit review | | | <0.0001* |
| No symptoms | 32 (80.0%) | 8 (20.0%) | |
| Mild symptoms | 210 (59.7%) | 142 (40.3%) | |
| Moderate symptoms | 386 (44.1%) | 489 (55.9%) | |
| Incontinence | 294 (57.1%) | 221 (42.9%) | <0.0001* |

*statistically significant $p<0.05$

Tables 7.4 and 7.5 show the baseline characteristics of those residents who suffered one or more falls over 6 and 12 months respectively, compared to residents who did not fall over the same period. Fallers were seen to be older, more likely to use a walking aid, of lower weight and requiring more nursing care (as measured by resident classification score, RCS) than non-fallers. Fallers had lower serum 25-OH-vitamin D levels than non-fallers, but PTH levels were not significantly different between the groups although there was a trend at 12 months. Similar relationships were seen at both 6 and 12 months, and so further analyses have been limited to 12 month data. Time to first fall was calculated, as it gives more useful information than simple comparisons between fallers and non-fallers.

### 7.3.3 Survival analysis

The median time from baseline assessment to first fall was 274 days (range 244 to 304 days). One hundred and eighty-seven residents (14.6%) died over the first 12 months of follow-up. The incidence of a first fall decreased over time as shown in Figure 7.3, censoring residents at the time of their first fall, at death or at the end of follow-up. Serum 25(OH)D distribution was close to normal for this subgroup and hence not log transformed; PTH was log transformed to preserve analysis assumptions.

When time to first fall was considered (Table 7.6), similar relationships were seen with baseline demographic variables as were seen with fall status.

**Figure 7.3:** Survival curve for time to first fall.

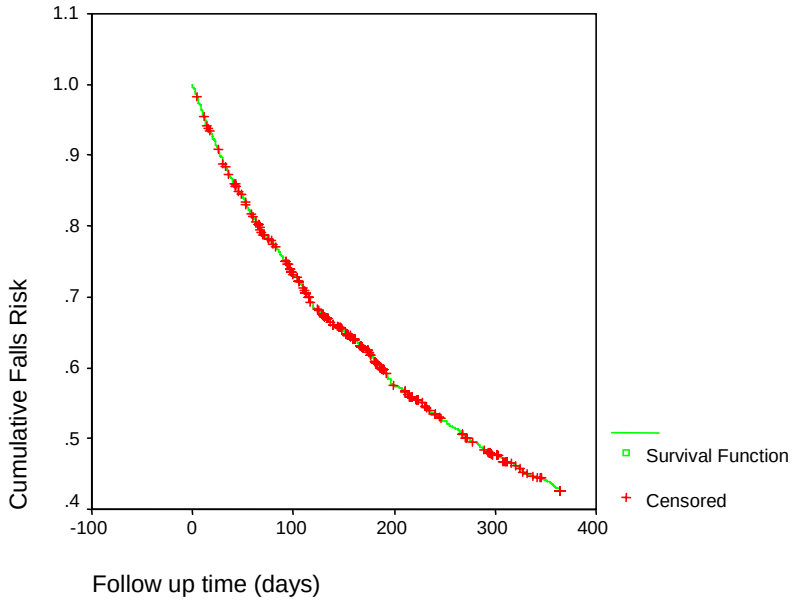



**Table 7.6:** Univariate associations with time to first fall

| | LR | Wald statistic | P value |
|---|---|---|---|
| Age | 1.02 | 15.28 | <0.0001* |
| Institution type | 0.71 | 19.20 | <0.0001* |
| Walking aid | N/A | 33.15 | <0.0001* |
| Balance | N/A | 27.77 | <0.0001* |
| SMMSE | 0.98 | 34.43 | <0.0001* |
| RCS | N/A | 43.38 | <0.0001* |
| Implicit review | N/A | 10.26 | 0.016* |
| Weight | 0.99 | 9.40 | 0.002* |
| Incontinence | 1.37 | 6.21 | 0.013* |
| 25-OH-vitamin D | 1.00 | 3.55 | 0.06 |
| PTH | 1.00 | 4.99 | 0.025* |

*statistically significant at p<0.05.

Cox regression analysis results for the entire cohort are shown in Table 7.7. Independent predictors for falling included increasing age (p =0.001), poor balance (p=0.001), incontinence (p=0.06) and implicit review (p=0.10). Whether treated as a continuous or a categorical variable (using cutoffs for hypovitaminosis D as described in Chapter 5), serum 25-OH-vitamin D was not significantly related to falling.

**Table 7.7:** Survival analysis for time to first fall

| | Hazards ratio (HR) | 95% Confidence Interval | | P value |
|---|---|---|---|---|
| | | Lower | Upper | |
| Age | 1.03 | 1.01 | 1.05 | 0.001 |
| Incontinence | 1.28 | 0.99 | 1.65 | 0.058 |
| Balance | N/A | N/A | N/A | 0.001 |
| Implicit review | N/A | N/A | N/A | 0.10 |

Excluded variables: 25-OH-vitamin D, lnPTH, SMMSE

Because it has previously been shown there may be different risk factors for falls in the population according to whether a subject can stand or not (381), a subgroup analysis was performed in more healthy individuals, ie. those aged < 90 years, relatively independent (RCS >=5) and able to walk. Univariate analysis in this subgroup of 455 residents showed 25-OH-vitamin D was related to time to first fall (HR 0.99, 95% CI 0.98-1.00, p=0.002). However in multivariate analysis that included age, balance, continence status and cognitive function, 25-OH-vitamin D was no longer significant (Table 7.8). In univariate analysis, serum PTH (log transformed) was also related to time to first fall (HR 1.43, 95% CI 1.20-1.70, p<0.0001). In multivariate analysis, PTH remained significant (HR 1.52, CI 1.21-

1.91, p<0.0001) as shown in Table 7.8. However PTH was not independently related to falls in elderly residents over the age of 90 years (p=0.9).

**Table 7.8:** Survival analysis for time to first fall in residents aged <90 years with RCS >=5 and able to walk.

| | Hazards ratio (HR) | 95% Confidence Interval | | P value |
|---|---|---|---|---|
| | | Lower | Upper | |
| lnPTH | 1.52 | 1.21 | 1.91 | <0.0001 |
| SMMSE | 0.97 | 0.94 | 1.00 | 0.047 |
| Incontinence | 1.51 | 1.11 | 2.05 | 0.009 |
| Balance | N/A | N/A | N/A | <0.0001 |
| Implicit review | N/A | N/A | N/A | 0.017 |

Excluded variables: 25-OH-vitamin D

## 7.4 Discussion

This study showed that 50% of residents in aged care facilities in Sydney will have one or more falls over a year, most of which occurred in the first 6 months. Fallers were more likely to live in hostels than nursing homes, were slightly older, lighter, more cognitively impaired, more likely to be incontinent and had poorer balance and general health scores than non-fallers, consistent with current falls literature (Chapter 1.4). Fallers had significantly lower 25-OH-vitamin D levels than non-fallers (median 25-OH-vitamin D level for fallers 24 nmol/L, compared to 26 nmol/L for residents who did not fall). Parathyroid hormone levels showed a trend towards being higher in fallers although this did not reach statistical significance.

It is considered that low 25-OH-vitamin D levels increase fracture risk (382) and that supplementation reduces the incidence of fractures in the elderly (383;384), but perhaps this effect may not be solely through changes in bone mass such as those seen in Chapter 6. Vitamin D deficiency may lead to reduced muscle strength through loss of type 2 muscle fibres (385), and hence an increased risk of falling. Cross-sectional studies relate lower 25-OH-vitamin D levels to reduced quadriceps and grip strength in elderly people (386;387). Bischoff et al (200) examined the relationship between muscle strength and vitamin D deficiency in ambulatory elderly subjects (103 women, 216 men, mean age for women 74, for men 77 years). Twelve percent of women and 18% of men had 25-OH-vitamin D values below the normal range (< 30 nmol/L). Strength of leg extension showed a modest, but significant, positive correlation with 25-OH-vitamin D in male but not female subjects. A study of both independent living and hospitalized people over 70 years of age (377) showed serum 25-OH-vitamin D

levels were significantly lower in those with poorer handgrip strength and stair-climbing ability.

Interventional studies have shown varied results. A small study in elderly women (378) showed that 6 months of vitamin D replacement improved extensor muscle strength and walking distance over 2 minutes in vitamin D-deficient (25-OH-vitamin D <20 nmol/L) older women. Measures of functional ability and activities of daily living in the frail elderly have been shown to improve in uncontrolled studies of vitamin D supplementation (388;389). Studies in healthier, non-vitamin D deficient populations have failed to show a significant improvement in quadriceps muscle function after vitamin D supplementation (390;391). A comprehensive review of the relationship between 25-OH-vitamin D and muscle function published in 2002 (375) concluded that there is a threshold effect, with vitamin D deficiency being associated with reduced muscle strength but the relationship not persisting in 25-OH-vitamin D replete individuals.

Few studies have prospectively looked at the effect of 25-OH-vitamin D levels on falling. Supplementation with oral calcium and vitamin D has been recently shown to reduce the incidence of fallers and falls by approximately 50% (230;392). Our study showed that balance was related to serum 25-OH-vitamin D, and that fallers had significantly lower 25-OH-vitamin D levels than non-fallers in residents of aged care facilities. This supports findings of a retrospective study by Stein et al (208) in a group of 83 ambulatory residents of hostels and nursing homes in Melbourne, Australia. The mean age was 84 years and the median 25-OH-vitamin D level was 27 (18-37) nmol/L, similar to the participants of the FREE study (393). Fallers had a median 25-OH-vitamin D level of 22 nmol/L, compared to 29 nmol/L for non-fallers

(p=0.019). Parathyroid hormone levels were also shown to be significantly associated with falling (OR=5.6, 95% CI 1.7-18.5 per logarithmic unit of PTH), independent of 25-OH-vitamin D levels.

The only large prospective study of vitamin D and falling in residential care facilities published to date has been an extension of this Melbourne cohort (379), measuring 25-OH-vitamin D and prospective falls in 1261 ambulatory women living in hostels and nursing homes. Higher serum 25-OH-vitamin D levels were independently associated with a lower risk for falling ($p<0.01$). Parathyroid hormone levels were not reported. When only residents of nursing homes were examined (who as a group had a higher incidence of falls than the hostel residents), the relationship was not seen. The authors postulate that the relationship might be obscured in this population by the substantially higher falls rate in this group. Our study did not show a relationship between vitamin D and falls risk by cox regression analysis, either in the population as a whole or in any subgroup analysis.

There are a number of explanations for the discrepancy seen between the two studies. Flicker et al found a relationship between 25-OH-vitamin D and time to first fall after correcting for psychotropic medication use, the presence of wandering behaviour and previous Colles fracture which were not examined in our group. Likewise, the Melbourne group did not report any association between vitamin D and mobility which was seen in the FREE study. It is likely that the use of different cofactors has impacted the different relationships seen in the two studies. If we accept earlier findings of differing risk factors for falling in the elderly dependent on frailty (381), our results are more in keeping with the Melbourne group. When the frailest elderly (aged >90 years or unable to stand unassisted) were excluded from the analysis, a

higher serum PTH was independently associated with increased falls risk in Sydney. It is plausible that the relationship between 25-OH-vitamin D and time to first fall in the more 'healthy' elderly population is mediated by PTH. It is possible that iPTH may be a more sensitive marker of vitamin D deficiency than serum 25-OH-vitamin D. Another explanation for the apparent discrepancy between the study of Flicker et al and the present study is that the assay used for PTH in the present study was in fact a more sensitive marker of vitamin D deficiency than the serum 25OH D assay employed. This merits further studies to tease out the proportional roles of 25-OH-vitamin D and PTH in falling in the elderly.

High levels of PTH have previously been linked to muscle weakness (380), which was reversible after treatment hyperparathyroidism and independent of vitamin D status. It may be that the effect we have seen on falling in this elderly population is reflecting a direct action of PTH on muscle, however serum 25-OH-vitamin D levels are known to be tightly linked to PTH and it might be that secondary hyperparathyroidism is in fact an intermediate variable in the relationship between hypovitaminosis D and falling. The absence of a relationship between 25-OH-vitamin D and falling in this subgroup analysis does not support the theory that both 25-OH-vitamin D and PTH act independently on muscle function and falling; more studies are required to further define the relationship.

A similar collinearity problem was encountered with balance, general health and 25-OH-vitamin D levels. Residents with lower 25-OH-vitamin D levels had significantly poorer balance and worse implicit review scores. It is likely that the relationship between balance and 25-OH-vitamin D is mediated in part by the action of 25-OH-vitamin D on muscle strength and function. Serum 25-OH-vitamin D levels may also

be an indirect measure of general health, reflecting mobility, nutrition and comorbidities which may all contribute to falls risk.

In conclusion, hypovitaminosis D was not shown to be independently predictive of falling in the frail institutionalized elderly, but may be indirectly related to falls risk through secondary hyperparathyroidism. Falling in this population is a common problem, with multiple interacting factors contributing to increase an elderly person's risk which still need to be adequately defined.

# CHAPTER 8

# SUMMARY AND FUTURE DIRECTIONS

# SUMMARY AND FUTURE DIRECTIONS

## 8.1 Introduction

In order to implement preventive health strategies, the first step is to fully understand the size of the problem. Osteoporotic fracture is an important issue both in terms of human morbidity and mortality, and with regard to the health care dollar. Costs associated with fracture increase substantially with age (394), just as the incidence of fracture also increases. Those elderly individuals who are too frail to live independently are at high risk of falling, of involutional osteoporosis and hence of osteoporotic fracture. This thesis aimed to describe the magnitude of the problem of osteoporotic fracture in the frail institutionalized elderly, by assessing risk factors for falls and fractures in a large population of elderly residents of hostels and nursing homes in Sydney, Australia. It is hoped that this will provide a valuable baseline from which interventional studies can be designed to identify the most appropriate, effective strategies for fracture prevention in the frail elderly.

## 8.2 Summary and implications of each study

This thesis described a range of features related to falls and fractures in the frail elderly. The study was unique in being a large, prospective study of risk factors in a group of frail elderly people in residential care facilities, a group who have not been previously extensively studied. The key findings of this thesis are summarized as follows:

(1) Quantitative ultrasound is a reliable tool for assessing bone density in the frail elderly, as both precision and sensitivity to longitudinal change were independent of age (Chapter 3).

Measurement of BUA and VOS was reliable, least significant change for BUA being 2.4% and for VOS 0.3% using the CUBA McCue instrument and 2.7% for BUA using the Metra QUS-2. Comparison of the instruments showed the QUS-2 measures BUA higher than the CUBA by 1.9 dB/MHz (+/- 9.55 dB/MHz). Moreover classification of individuals as osteoporotic by machine-derived T-score was different between instruments (k=0.44 in men and k=0.62 in women). In women, BUA was observed to decrease by 5.2% over 2 years without significant change in VOS, suggesting BUA is more useful in longitudinal studies.

Ultrasound measurements at the calcaneus are reliable and sensitive to longitudinal change even in the extreme elderly, which makes it a useful tool in frail, immobile populations. Measurements are however instrument-specific, and should be interpreted with caution in the assessment of fracture risk. It is now widely accepted that the same machine should be used for progress studies of DEXA measurements;

this study extends the recommendation to the use of QUS machines for measuring bone. The same QUS machine should be used for baseline and follow-up measurements in longitudinal studies to ensure meaningful conclusions.

(2) There is a high prevalence of low bone density as measured by QUS in the frail elderly (Chapter 4).

Broadband ultrasound attenuation and VOS were higher in men than women by approximately 30% and 2% respectively, and this difference was maintained at all ages. There was no significant decline in BUA or VOS with age in men; however, for women BUA declined by 2.8-4.7% per decade and VOS by 1% per decade. Mean BUA T-scores were -1.55 and -2.48 at age 90 years in men and women.

This study confirms that both men and women of advanced age are at significant risk of low bone density. In a group recognized to have a high incidence of falls, this is likely to be an important risk factor for future fracture. Although limited by its cross-sectional design, this study suggests only minor bone loss occurs at the calcaneal site with very old age in either sex. Treatment must be aimed not merely at preventing bone loss in this group, but at improving bone density in order to reduce potential fracture risk.

(3) The prevalence of low 25-OH-vitamin D is high in this population and under-treated (Chapter 5).

Over 77% of the population had low serum 25-OH-vitamin D levels compared to the laboratory reference range, and almost 41% had secondary hyperparathyroidism. A

25-OH-vitamin D cut-off of 30 nmol/L predicted secondary hyperparathyroidism. Independent predictors of lower serum 25-OH-vitamin D levels included female gender, increasing age, elevated PTH levels, cooler season, decreased mobility and lower creatinine clearance. Independent predictors of hypovitaminosis D (25-OH-vitamin D < 30 nmol/L) included female gender, reduced mobility higher PTH levels, and a lower creatinine clearance. Only 6% of men and 12% of women were on vitamin D supplementation. Vitamin D supplementation conferred significantly higher serum 25-OH-vitamin D and lower PTH levels, but this was not apparently related to nutritional status as albumin levels were not different between the groups.

Although Sydney has adequate sunlight hours all year long this population was not being exposed on a regular basis. Vitamin D supplementation is a simple and cheap intervention strategy that could be undertaken in a frail elderly population to improve calcium metabolism, particularly in less mobile individuals.

(4) The relationship between QUS and 25-OH-vitamin D levels was significant only in elderly people who were vitamin D deficient, and secondary hyperparathyroidism was an independent predictor of BUA (Chapter 6).

Mean 25-OH-vitamin D levels ranged from 26 nmol/L in female residents of nursing homes to 36 nmol/L in male residents of hostels. Women were more likely to be low in vitamin D than men. There was no difference in BUA between residents on vitamin D supplementation and those not receiving therapy. Univariate associations with BUA and VOS included age, weight, serum 25-OH-vitamin D and PTH levels. Quantitative ultrasound measures were seen to change significantly at a 25-OH-vitamin D cut-off of 22 nmol/L, lower than that seen to correspond to secondary

hyperparathyroidism in Chapter 5. Multivariate analysis showed BUA to be associated with mobility, gender, weight and PTH but not with serum 25-OH-vitamin D. Velocity of sound was not independently related to 25-OH-vitamin D or to PTH.

This study gives further evidence to support vitamin D supplementation in D-deficient elderly persons. Whether it is the improvement in 25-OH-vitamin D levels which is most important to maintain BUA or the suppression of secondary hyperparathyroidism is not clear. The relevance of PTH as an independent factor in bone density in the elderly requires further exploration.

(5) Falls are common in aged care facilities but not related to 25-OH-vitamin D (Chapter 7).

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The incidence of falls in aged care facilities was 50% over 12 months. Serum 25-OH-vitamin D levels were related to the incidence of falls in univariate analysis. Fallers were significantly older, lighter, required more walking aids, more nursing care and had lower serum 25-OH-vitamin D levels than non-fallers over 12 months. The median time to first fall was 274 days. Falling was independently associated with increasing age, poorer balance, incontinence and poorer implicit health grade but not 25-OH-vitamin D or PTH. When subgroup analyses were performed, falling was associated with higher PTH levels in residents under 90 years of age who could walk but not in older residents.

It may be that falling in the frail elderly is related to secondary hyperparathyroidism, which obscured a possible link with vitamin D deficiency. It is important that the mechanism of PTH action in muscle is more fully described in the setting of muscle

strength and balance in the elderly, in order to estimate the role of PTH in falling. The problem of falling in this group is however multifactorial, and vitamin D and/or PTH are possibly only a small part of the picture.

## 8.3 Future directions

This thesis has described the characteristics of elderly residents of aged care facilities in the northern Sydney area, with respect to risk factors for falls and fractures. We know that they are osteoporotic, which confers an increased risk of low-trauma fracture. We know they have a high incidence of falling, which also predisposes to fracture. The predictive role of serum 25-OH-vitamin D is less clear; this population is overwhelmingly deficient in 25-OH-vitamin D but this thesis does not show a straightforward relationship between vitamin D and either falling or QUS measures. The complex interplay between serum 25-OH-vitamin D and PTH and their relationship to objective measures of falls risks needs further investigation.

Analysis of muscle strength and quantitative balance will also be important to quantify the contribution of falls to the prospective incidence of fracture. Ultimately it is important that we are able to define discrete risk factors for osteoporotic fracture, which might be modified by targeted interventions to reduce the incidence of fracture in the frail institutionalized elderly and thereby improve not just morbidity and mortality, but quality of life. A trend is emerging that implicates vitamin D as important in both muscle and bone strength – prospective studies need to confirm this relationship to allow this relatively cheap and simple intervention to be introduced into everyday practice.

The most important issue to be addressed is which, if any, of the demographic and physiologic characteristics of this group predict fracture. The FREE study is measuring prospective fracture incidence at all sites, and so the baseline characteristics of the population described in this thesis will be examined for any

relationship to fracture. This will further define the role of both vitamin D and PTH in falls and fractures.

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# APPENDIX 1

## PATIENT INFORMATION SHEET

## PATIENT INFORMED CONSENT FORM

## PROXY INFORMATION AND CONSENT FORM

## DATA COLLECTION SHEET