Cover; made using a painting done by Bhanuka when she was 2 years old

Assessment of Operational Factors, Structural Properties and Disease Associations Influencing Bone Mineral Density Variation

Sarath Lekamwasam

ERASMUS UNIVERSITEIT ROTTERDAM

Assessment of Operational Factors, Structural Properties and Disease Associations Influencing Bone Mineral Density Variation

Beoordeling van operationele factoren, structurele eigenschappen en geassocieerde ziekten die variatie in bot mineraal dichtheid beïnvloeden

Proefschrift

ter verkrijging van de graad van doctor aan de

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Assessment of Operational Factors, Structural Properties and Disease Associations Influencing Bone Mineral Density Variation

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By

Sarath Lekamwasam Kathaluwa Liyanage born in Baddegama Sri Lanka

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Dedicated to my wife, Vajira and two children, Bhanuka and Raveen

Contents

Abbreviations

ANOVA: analysis of variance

BMD: bone mineral density

BMC: bone mineral content

BMI: body mass index

CSA: cross-sectional area

CSMI: cross-sectional moment of inertia

CV: coefficient of variation

DXA: dual-energy X-ray absorptiometry

FN: femoral neck

HSA: hip structure analysis

LS: lumbar spine

LSC: least significant change

NHANES: National Health And Nutrition Examination Survey

ROI: region of interest

SD: standard deviation

SEM: standard error of mean

WHO: World Health Organization

Chapter 1

General Introduction

Introduction

Osteoporosis is the major metabolic bone disease seen worldwide and resulting fragility fractures are recognized as a major public health issue (1). According to the WHO working group estimations in 1994, nearly 30% of European women over 50 years have osteoporosis (2). In general, osteoporosis is commoner among Caucasians and Asians while women of Afro-Caribbean descent have a less likelihood to develop the disease (2).

It is estimated that, 30 to 50% of women and 15 to 30% of men experience an osteoporosis-related fracture during their lifetime (3). Osteoporosis-related fractures are associated with increased mortality, morbidity and reduced quality of life (4). A study in Switzerland showed that the annual costs of hospitalization for osteoporosis-related fractures were greater than those of other non-communicable diseases including stroke, myocardial infarction and breast cancer (5) .

Osteoporosis-related fractures

Osteoporosis-related fractures create a huge economic burden on current health care systems. In 2000, 3.79 million osteoporosis-related fractures occurred in Europe, of which 0.89 million were hip fractures (6). The total direct costs involved with osteoporosis-related fractures were estimated to be 21 billion US dollars and, based on the projected demographic changes in Europe, this is expected to reach 51 billion US dollars in 2050 (6).

Although fracture at any site could be attributed to osteoporosis, fractures of the spine, proximal femur and distal forearm are the most frequent osteoporosis-related fractures. Osteoporotic fractures are commonly seen in postmenopausal women with each fracture type showing specific epidemiological and etiological properties.

Of all fractures, hip fracture is the most sinister complication of osteoporosis as it is associated with increased morbidity and mortality. In women, the age-standardized mortality ratios (ratios of observed deaths to expected deaths in the age-matched population) for hip, vertebral and other major osteoporotic fractures are 2.32, 1.66 and

1.92, respectively, while the corresponding figures in men are 3.17, 2.38 and 2.22 (7). The survivors of hip fracture experience chronic pain, reduced mobility and increasing degree of dependence (4). The direct and indirect costs involved with hip fractures alone are substantial. It is estimated that, in Europe, 179,000 men and 611,000 women sustain hip fractures each year and the estimated cost is Euro 25 billion (8)**.**

Osteoporosis-related vertebral fractures commonly occur in the lower thoracic or upper lumbar vertebrae. The incidence of vertebral fracture increases with age. In one analysis, the age-standardized incidence of vertebral fracture among women and men were 10.7 and 5.7 per 1000 person-years, respectively (9). The true prevalence of vertebral fracture is not known as only one third of vertebral fractures come to clinical attention (10).

Fractures of the distal radius and ulnar are commonly seen in middle aged and elderly women and falling on the outstretched hand is the commonest cause (2). Frozen shoulder and algodystrophy are known complications of forearm fractures (11).

Osteoporosis; definition and diagnosis

Osteoporosis is defined as *"a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk"* (2).

Although the diagnosis of osteoporosis can be made in a patient presenting with a fragility fracture, bone mineral density (BMD) measured by Dual Energy X-ray Absorptiometry (DXA) is used to diagnose osteoporosis, particularly in patients who have not yet suffered a fracture. Furthermore, BMD has other clinical applications. It determines fracture risk in a given patient and also helps in assessing the effectiveness of therapy (2).

Prevalence of postmenopausal osteoporosis

In 1994, the WHO made guidelines to diagnose osteoporosis (table). These guidelines, based on T score, provide different cut-off values for osteopenia and osteoporosis (2). T score indicates the number of standard deviations the patient's BMD deviates from the reference mean value of the sex-matched young adult population. It is calculated using the mean BMD and standard deviation of the young reference population using the following formula.

$$\text{T score} = \frac{\text{Patient's BMD} - \text{Mean BMD of the Young Normal population}}{\text{SD of the Young Normal population}}$$

Table: The WHO diagnostic categories based on T Scores

WHO category	T Score
Greater than -1.00	Normal
Between -1.00 and -2.50	Osteopenia
Less than -2.50	Osteoporosis
Less than -2.50 and history of a fragility fracture	Severe (or established) osteoporosis

The WHO working group in 1994 decided to take T score of -2.5 to define osteoporosis since it identified nearly 30% of women over 50 years as having the disease and this approximated to the proportion of population having lifetime fracture risk (2). Subsequent studies, however, showed a wide variation in the prevalence of postmenopausal osteoporosis (12-18). Holt *et al* demonstrated a substantial difference in the prevalence of osteoporosis between USA and UK women older than 50 years (18). Among Thai postmenopausal women, osteoporosis prevalence varies between women of more than five years since menopause and women of less than five years since menopause (10% vs 5.7% in the spine) (19). It also varies according to the site selected to define the disease. Among Chinese women between 20-89 years, the prevalence of osteoporosis varies from 15% to 28% between hip and lumbar spine (15).

Prevalence of postmenopausal osteoporosis among Sri Lankans is not known. Apart from the limited availability of central-type DXA and financial constrains, the low priority given for the disease may have contributed to the lack of studies. Lack of prevalence data hinders the disease being recognized a health priority. Furthermore, preventive measures of osteoporosis could be implemented better if they are backed by country-specific epidemiological data.

We, therefore, designed a study to estimate the prevalence of osteoporosis among postmenopausal women in Sri Lanka. While the entire study sample underwent phalangeal BMD estimation, a randomly selected subgroup had BMDs in spine and hip estimated using a central-type DXA machine. The approximate estimate of the disease prevalence was estimated by extrapolating the results of the subgroup analysis to the entire study sample and was the subject of the study in Chapter 2.1.

Age-related trends in BMD

Bone is a living tissue and undergoes modeling and remodeling during different phases of skeletal growth. Accordingly, BMD which partly incorporates bone mass also shows age-related changes. During childhood BMD rapidly increases to reach a peak value (peak bone mass; PBM) around 20-30 years. BMD shows a rapid decline in old age, especially in women during the postmenopausal period(2).

The age at which individuals reach their peak BMD is not uniform and varies according to ethnicity. Looker *et al*, found that individuals reach the peak BMD in the proximal femur between 20-30 years of age in all three major ethnic groups in the USA; non-hispanic whites, non-hispanic black and Mexican-Americans (12). However, studies in other populations have shown a delay in reaching the PBM. According to Ghannam *et al*, Saudi women reached peak spine BMD around 35 years but earlier at proximal femur (13). In Greek women, peak spinal BMD was observed between 30-35 years while maximum femoral neck BMD was seen between 25-30 years (14). Similar to the USA findings, Chinese women reached the maximum BMD in the proximal femur between 20-24 years, but peak BMD in the forearm bones was delayed until 40-44 years (15). Although the exact reasons for delay in reaching the

PBM in certain populations and in certain skeletal sites are not known, variations in genetic, social, and nutritional factors in different populations may play a role. Nearly 70% of BMD variation is genetically determined and non-genetic factors such as smoking, alcohol consumption and health-related factors contribute to the remaining variation (16). As these factors; genetic and non-genetic, differ in diverse ethnic groups, the behavior of BMD can be expected to vary in different populations.

Age-related trends in BMD among Asians, especially those in South Asia, are not well known. It is important to know the age in which PBM is achieved in a particular population, so that measures that promote bone health can be maximized during this period to help gaining a higher PBM. Lack of data in these countries may partly be due to the limited availability of central-type DXA and financial constrains. Central-type DXA, due to its dimensions and weight, has practical limitations when applying to community-based studies. Peripheral-type DXA which are portable and more user-friendly can be an option for community-based studies in these countries. Although these devices limit BMD assessment to peripheral skeletal sites, their ability to predict fractures has been documented in community-based studies (17). Using a peripheral-type DXA, we studied the age-related changes in phalangeal BMD in a group of men and women selected from seven provinces in Sri Lanka and this was the subject area of the study described in Chapter 2.2.

Dual Energy X-ray Absorptiometry

DXA is the current gold standard for measuring BMD. Owing to the easy operability and low radiation risk, DXA is the technology recommended for routine patient evaluation (20). Basically, DXA machines are of two types; central and peripheral. Both types use two photoelectric beams; low and high energy, which get preferentially attenuated by different body tissues. The low energy beam is attenuated by both soft and bone tissues while the high energy beam is attenuated only by the bone tissue. The degree of attenuation of the two beams is used to calculate the energy absorbed by the hydroxyapatite crystals in bone tissue and this enables the system to calculate the BMD in the pathway of the x-ray beam. While peripheral devices are designed to measure BMD in a solitary site in the appendicular skeleton, central-type

DXA are capable of measuring multiple sites in the axial and appendicular skeleton (21).

DXA scanners use either a narrow cylindrical x-ray beam, known as pencil-beam, which moves in a rectilinear fashion to acquire bone image or a fan-beam, a slit-like opening in collimator to generate a fan shaped x-ray beam which sweeps over the region of interest. In comparison to pencil-beam, fan-beam technology is faster, hence has a shorter scanning time (21).

Accuracy and Precision of DXA

In measuring BMD, DXA maintains a high degree of precision and accuracy(20). Measurement precision and accuracy are two critical issues in any technology used in the biomedical field and DXA manufacturers have taken all steps to achieve a high degree of accuracy. Precision becomes a key issue when replicate BMD measurements are taken to study BMD trends over a period of time. Precision error determines the degree of BMD change that is required to define a "real change" when replicate BMD measurements of the same patient in the same site are obtained. At 95% confidence level, BMD difference in excess of 2.77 times the precision error (2.77 x precision error) is considered to be a real and statistically significant BMD change and it is referred to as the Least Significant Change (22). As 2.77 remains constant for this confidence level, the Least Significant Change is proportionate to the precision error of the machine.

Precision of DXA varies across operators and machine types. Hence, precision error should be estimated for a DXA scanner when it is operated by a particular operator (23). Precision error can be of short-term which is applicable to repeated scans performed within days or weeks or long-term which applies when repeated measurements are taken with a longer time gap, measured in years.

Many factors related to machine, operator or patient determine DXA precision (24). Age (25) and amount of ascites (26) have been shown to influence short-term BMD reproducibility. Maggio *et al* found BMD precision error to be greater in elderly,

regardless of sex, as compared to young individuals (25). Operator-related factors are known to contribute to both long and short-term precision errors. Differences in patient positioning and defining the regions of interest (ROI), both of which are heavily operator dependent, could contribute to these variations (21).

Patient positioning and precision of DXA

Correct patient positioning is vital when performing DXA. Although DXA manufacturers follow similar principles, there are disparities in their recommendations regarding patient positioning. Technicians should be aware of the importence of patient positioning during DXA and particular attention should be paid especially when replicate BMD measurements are taken (27). Although errors in positioning are known to affect precision, the degree of BMD variation or the degree of misclassification attributable to a particular incorrect positioning is not well known.

We, therefore, decided to examine the effect of variations in leg positioning on the measurement of BMD in different sites. First, the impact of hip flexion on the measurement of spine BMD was tested in two studies and is described in Chapters 3.1 and 3.2. While the first study (3.1) addressed the effect of a lesser degree of hip flexion on the precision, the second study (3.2) questioned whether same measurement accuracy can be maintained if legs were kept flat while estimating the spine BMD. Furthermore, we quantified the effect of minor variations in leg rotation on the precision of hip BMD measurements and is described in the Chapter 3.3.

All Norland DXA machines use a pencil-type x-ray beam to acquire DXA images and approximately 3-4 min is taken to complete a scan. As patients are required to keep their legs-up during spine BMD estimation in Norland machines, patients with degenerative diseases affecting lower limbs would find it difficult to stay positioned during the procedure. Although these patients are able to maintain a lesser degree of hip flexion without compromising their comfort, the acceptability of such a change is not certain. If a lesser degree of hip flexion does not alter BMD values substantially, patients who are uncomfortable with conventional 90 degree hip flexion can be allowed to have their spine scanned with a lesser degree of hip flexion, the idea motivated us for the study described in Chapter 3.1.

Norland and Hologic manufacturers use a leg block to flex hip and knee joints by 90 degrees when measuring spine BMD. It is expected that this procedure would reduce the lumbar lordosis allowing separation of intervertebral spaces for clear demarcation of individual vertebrae(21). However, there is no uniform agreement to date between DXA manufacturers. The real effect of using a leg block to position legs is not certain and this made the basis for our study described in Chapter 3.2. In contrast to the study included in Chapter 3.1 which assessed the effect of the lesser degree of hip flexion on the precision of spine BMD estimations, the analysis included in Chapter 3.2 examines whether the same accuracy can be achieved with legs flexed or legs completely flat on the bed. A previous study using a Hologic scanner showed that there is no real difference in spine BMD when measured with legs-up or legs-flat (28). Yet, more data are required to examine the difference in spine BMD measured in these two positions. It will be easier for operators if all DXA manufacturers are uniform in their recommendations regarding leg positioning. Furthermore, it will be advantageous for patients to keep their legs-flat during the lumbar spine scan if positioning does not make a difference in BMD values.

When BMDs of the proximal femur are measured, the legs need to be rotated internally to counteract the spontaneous ante-version of the femoral neck. Rotation brings the femoral neck perpendicular to the x-ray beam, thus, preventing overlapping of the bone image(21) . However, the same degree of rotation should be achieved in subsequent scans for accurate interpretation of BMD trends. The effect of malrotation of femoral neck on BMD estimations has not been well studied. Previous studies on hip rotation have either used cadaveric specimens (29) or are few in numbers (30, 31). Very little is known about the effect of leg rotation on BMD interpretation in a clinical setting. As BMDs of the proximal femur are used to diagnose osteoporosis, estimate fracture probability and monitor treatment-related changes (23), more studies are needed to clarify the effect of leg rotation on BMD interpretation. We describe, in Chapter 3.3, the effect of leg rotation on BMD precision using a group of patients referred for clinical evaluation.

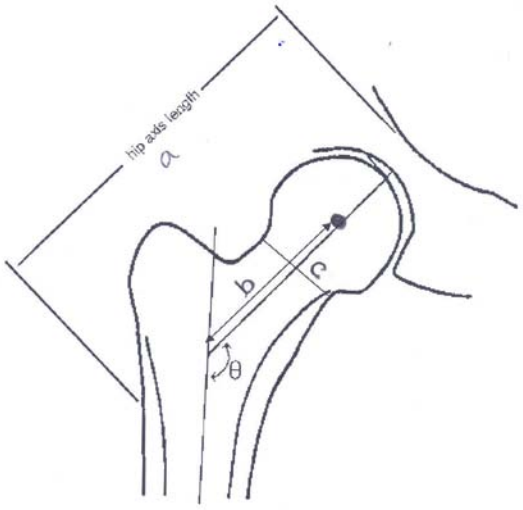
Hip geometry

Independent of BMD, indices of hip geometry determine fracture risk (32). Hip geometry, estimated using BMD images, incorporates material properties (BMD) and measurements in the cross-section of the bone to illustrate structural properties of bone.

Indices of hip geometry

Although there are many indices of bone structure, commonly used indices and their descriptions are given below (33).

1) Hip axis length: the linear measurement from the middle of the inner surface of the acetabulum to the lateral border of the shaft of the femur drawn through a mid point in the femoral neck ***(line "a" in the picture)***.
2) Neck-shaft angle: the angle between the neck axis and the axis of the femoral shaft ***(angle " " in the picture)***.
3) Femoral neck length: the length of the femoral neck from the midpoint of the femoral head to the axis of the femoral shaft ***(line "b" in the picture)***.
4) Femoral neck width: the subperiosteoal diameter of the femoral neck at its narrowest diameter. ***(line "c" in the picture).***
5) Dmax: the distance between bone edge and the centroid mass.
6) Cross-sectional area(CSA): the cortical bone equivalent area of the cross-section of the region of interest with all soft tissue voids eliminated.
7) Cross-sectional moment of inertia (CSMI): a property of the cross-sectional area that represents the magnitude of the greatest bending rigidity.
8) Section modulus(SM): an index of bending rigidity calculated by adjusting the CSMI for the distance between bone edge to the centroid (Dmax).
9) Buckling ratio: an index of bone instability (estimated as Dmax/cortical thickness)



Picture; Some indices of hip geometry

Indices of hip geometry

Indices of hip geometry are estimated from BMD images using the analytical programs developed by Beck *et al* in 1990 (34) or Turner and Markwardt in 1994 (35). The original program by Beck *et al* was based on Hologic BMD images while Turner and Markwardt used Lunar BMD images. These programs have followed the principles described by Martin and Burr (36) and assume the proximal femur as a one continuous cylindrical beam from the upper shaft to femoral neck. Furthermore, they assume that cortical envelop in a given area is circular and has equal thickness right round (34,35).

Similar to BMD, the indices of hip geometry show age-related trends. Beck *et al* examining age trends in hip geometry in NHANES cohort, found a gradual decline in the cortical thickness, CSMI, SM and CSA of the femoral neck among postmenopausal women (34). Simultaneously, there was an expansion of the narrow neck diameter, attributed to the apposition of bone material under the periosteal surface (34). Hip geometry measures have shown a regional variation, especially among Europeans (37).

Most of the hip geometry studies available have used white populations of Northern European origin and do not allow one to make conclusions on behavior of hip geometry in other ethnic groups. In the study described in Chapter 4.2, we studied for

the first time the behavior of hip geometry indices in a group of women selected, randomly, from our university study area in Galle, Sri Lanka.

Unlike BMD, the determinants of hip geometry remain largely unknown. Gender and racial differences of hip geometry have been observed (38) and they are believed, at least partly, to explain the geographical variation of hip fracture incidence reported earlier. Yan *et al* (2004), comparing a group of native Chinese with a comparable group of Europeans, found significantly lower BMD, BMC and bone area of the femoral neck ($P<0.01$) among Chinese men and women (39). After adjusting for bone area, weight and height, there was no significant ethnic difference in BMC in either gender. CSMI and SM, however, were significantly lower, while HAL, femoral neck length and femoral neck diameter were significantly lesser in Chinese men and women compared to European counterparts (39).

Similar to BMD, indices of hip geometry are genetically determined (40). Cooper *et al*, demonstrated that weight at 1 year is significantly associated with BMC of lumbar spine ($r=0.32$) and femoral neck ($r=0.26$), raising the possibility that adult BMC is programmed during early period of life. Apart from BMD and BMC, bone size of 10-year old children is related to their weight and height at 1 year (41). Currently, it is not well known whether indices of hip geometry are also programmed during early life. If this is true it will help the understanding of the mechanisms of hip fracture. In Chapter 4.3, we describe the associations between the indices of hip geometry in old age and anthropometric measurements at the age of 1 year.

Body composition

Associations between BMD, lean mass and fat mass have been demonstrated, previously (42-45). In these studies, lean mass is more strongly associated with BMD in pre-menopausal women than fat mass (42,43), while the latter is the major determinant of BMD in postmenopausal women (44,45). Such associations between BMD and other body compartments have potential clinical implications. Positive association between lean mass and BMD could reflect the coexistence of both low BMD and low lean mass in a given patient. Such a patient will have an increased risk

of fracture due to the combination of low BMD and low BMI, as both are recognized independent risk factors of fractures (2). If fat mass and BMD have inverse associations, patients with osteoporosis are likely to have a higher fat mass which increases their cardiovascular risk (46) but at the same time provides some degree of protection against hip fractures, through an effect independent of BMD.

Furthermore, previous studies have shown an association between BMD and serum lipid levels (47,48-50). Yet, results of these studies are conflicting since BMD showed both positive (49, 50) and inverse correlations (47, 48) with serum lipid levels. If an inverse correlation between BMD and atherogenic lipids are established, clinicians would be required to assess the cardiovascular risk of patients with low BMD and make a holistic approach in treating them to reduce the overall mortality risk. Some drugs are known to have effects on both bone and lipid metabolic pathways. SERMs such as raloxifene while improving BMD reduced serum lipid levels (51). Similarly, statins while lowering serum lipids, improved BMD(52). These studies suggest the possibility of a common metabolic pathway or interconnections between the lipid and bone metabolism.

Most of the studies examining body composition and lipids abnormalities have been done in Caucasian populations and studies from Asia are limited. Non-communicable disease prevalence among Asians is a major concern today. Prevalence estimates of osteoporosis, cardiovascular diseases, hypertension and diabetes show a wide geographical variation (53, 54). Compared to other regions, Asians have a higher prevalence of osteoporosis (2) and non-communicable diseases including diabetes and dyslipidemia (55). According to future predictions, the incidence of osteoporosis-related fractures and cardiovascular diseases would increase, exponentially, in Asian countries (1). Despite these predictions, the understanding of the underlying mechanism of the high occurrence of non-communicable diseases in the Asian region is incomplete and lack of data largely contributes to this. Therefore, we decided to explore the association between osteoporosis and cardiovascular diseases among Sri Lankan women. In Chapters 5.1 and 5.2, we describe the association of BMD with other body compartments and serum lipid, respectively. In general, there is a paucity of information regarding body composition and lipid abnormalities in South Asian populations.

Determinants of BMD

There are many determinants of BMD. Nearly 70% BMD variation is explained by genetic factors (16). Further, body mass index in adult life (56) and weight in infancy (57) are determinant of bone mass in adulthood. Environmental factors such as calcium intake (58), physical activity (58), parity (59) and social habits such as smoking (60) and alcohol consumption (61) are associated with BMD. New associations of BMD are being recognized and they are being used in clinical settings to screen people for low BMD and also to determine their fracture risk (62, 63).

Patients with chronic respiratory diseases tend to have low BMD and higher fracture risk with some studies showing an association between BMD and measures of respiratory function(64, 65). This association, however, could be explained by many confounders including smoking, corticosteroid use and poor physical growth. This could be clarified by demonstrating an association, independent of confounders, especially among healthy subjects. In the studies described in Chapters 5.3 and 5.4, we analyzed a group of community-dwelling men and women. In addition to their BMD and FEV1 measurements, confounders such as BMI, smoking habits and corticosteroid use were estimated. This allowed us to study the direct and independent relationship between BMD and respiratory function FEV1 and its gender difference.

In summary, many areas in relation to BMD assessment and DXA technology which need further clarifications are addressed in this thesis. These include the effect of patient positioning on the estimation of both spine and hip BMDs which would be a great interest to technicians and clinicians interpreting DXA scans. In addition to estimating the prevalence of osteoporosis among postmenopausal women in Sri Lanka, this thesis assesses the factors that are associated with BMD of subjects in an Asian population. These include effect of age, interaction with other body compartments and serum lipids. The association between spine BMD and respiratory function FEV1 is also addressed using a UK study sample. Furthermore, the association between body measurements in postnatal period and hip geometry indices are explored to test the hypothesis that hip structure indices have undergone programming in early life.

Outcome of these analyses would help to clarify many issues. In general, it would estimate the error attributable to flaws in patient positioning, answer questions whether hip geometry is programmed in early life and whether BMD has an independent association with cardiovascular and respiratory function. Specific to Sri Lanka, it would show the age in which peak bone mass is achieved and the prevalence of postmenopausal osteoporosis, information needed to plan health promotional activities in the country and to convince authorities about the gravity of the problem.

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Chapter 2

Bone mineral density for the diagnosis of osteoporosis

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ORIGINAL ARTICLE

Prevalence of osteoporosis among postmenopausal women in Sri Lanka: a cross-sectional community study

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Abstract

Objective: This study was designed to estimate the prevalence of osteoporosis among postmenopausal women selected from seven provinces in Sri Lanka.

Method: The study was a community-based cross-sectional survey of a group of 1642 community-dwelling postmenopausal women in seven provinces, except the North and East, in Sri Lanka. Phalangeal bone mineral density (BMD) was measured in all subjects using an AccuDEXA. In a subgroup of 150 women BMDs in the spine from L2–L4 and proximal femur were measured using a Norland Eclipse central DXA machine. In this subgroup, the diagnosis of osteoporosis was made according to the WHO criteria based on T-scores of the spine or femoral neck. The sensitivity, specificity, positive predictive value and negative predictive value of different phalangeal BMD levels were examined and the prevalence of osteoporosis was calculated using the most acceptable cut-off value.

Results: A sharp decline in phalangeal BMD (0.006 g/cm^2/year) was seen during the postmenopausal period. Phalangeal T-score of −2.00, which had sensitivity, specificity, positive predictive value and negative predictive value of 78%, 85%, 91% and 68% respectively, was selected as the most suitable value to predict osteoporosis: 357 women had phalangeal T-scores either equal to or lower than −2.00. When the positive predictive value and negative predictive value of this cut-off value were applied, 736 women (44.9%) in our sample were likely to have osteoporosis.

Conclusions: Osteoporosis is a prevalent disease among postmenopausal women in Sri Lanka. Similar prevalence figures have been reported from other Asian countries.

Key words: epidemiology, osteoporosis.

INTRODUCTION

Osteoporosis is the major metabolic bone disease seen in the world and it has affected 75 million people in Europe, USA and Japan.[1] Previous studies have indicated that one-third of women and one-fifth of men over the age of 50 years will experience an osteoporosis-related fracture during their lifetime.[2,3] The incidence of hip fracture is predicted to increase by 310% in men and 240% in women during the next 25 years and nearly half of these fractures will occur in Asian countries.[4] In Asia, the incidence of hip fracture has already shown an upward trend. In China, between 1988 and 1992, the incidence of hip fracture increased by 34% in women and 33% in men.[5] Similar trends have been observed in Singapore and Hong Kong.[6,7]

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Despite the upward trend seen in osteoporosis-related fractures, the awareness of the disease remains low, especially among Asians. The prevalence of osteoporosis among Asians, particularly those who are in South Asian countries, is not well known. The prevalence of osteoporosis in Sri Lanka remains unknown as there are no large community-based studies. The current study was carried out to estimate the prevalence of osteoporosis in a sample of women recruited from seven provinces in the country.

MATERIALS AND METHODS

The Community Osteoporosis Survey in Sri Lanka was initiated in October 2004 and 9719 subjects, over the age of 20 years, were recruited from all provinces except the north and east which were not included due to security reasons. From each province, a minimum of two separate areas, one rural and one urban, were selected. These areas were identified based on the type of local administration, adhering to the method used by the Department of Census and Statistics during the 2001 population census.[8] In each scanning centre, posters were displayed and public announcement systems were used 2–3 days ahead, to inform the public about the nature and the purpose of the study. On the day of scanning, volunteers were recruited after an initial interview. They all filled a brief health-related questionnaire and signed a consent form. Weight was measured while wearing light clothes and without footware. We intended to include 500 women (including 200 postmenopausal women) and 250 men from each province, to a total of 5250 subjects. Women were not randomized at the time of recruitment and scanning was continued until this number was met. In many provinces the number was exceeded as we had to include all subjects gathered on that particular day.

Bone mineral density (BMD) of the middle phalanx of the middle finger in the non-dominant hand (PBMD) was measured by dual energy X-ray absorptiometry (DXA) using an AccuDEXA scanner (Schick Technologists Inc., New York, USA). All scans were done by two trained technicians and the calibration of the machine was performed on each scanning day to ensure the accuracy of readings. Automatically saved data were transferred to the Center for Metabolic Bone Diseases in Galle at the end of each month to be included in a central database.

A subgroup of 150 women was selected randomly from 380 postmenopausal women who were recruited from the southern province. These women underwent a second DXA scan using Norland Eclipse XR (Norland Corp., Fort Atkinson, WI, USA) scanner. BMDs of the lumbar spine from L2 to L4 in the anteroposterior projection (SBMD), femoral neck (FNBMD) and trochanteric region (TRBMD) were measured. *In vitro* calibration of the Norland machine was done on each scanning day using the calibration phantoms provided by the manufacturer.

Statistics

Of 9719 subjects in the main study sample, data of all healthy postmenopausal women ($n = 1642$) were included in this analysis. Data of women with history of epilepsy, inflammatory arthritis, endocrine diseases, chronic bronchial asthma, malabsorption, chronic renal or liver diseases, vasculitis and other chronic inflammatory diseases were excluded from the analysis. Similarly data of women who had taken medications such as corticosteroids, anticonvulsants, heparin, vitamin D, hormone replacement therapy, antiresorptive drugs and pharmacological doses of calcium were excluded (total number of exclusions = 186) Descriptive data of the study sample are given either as mean (SD) or numbers (%) unless stated otherwise. Subjects were categorized to 5-year age groups according to the time since menopause (Group $1 < 5$, Group 2 = 5–9, Group 3 = 10–14, Group 4 = 15–19, Group 5 = 20–24, and Group $6 \geq 25$ years). Mean PBMD values of each group were estimated and compared using ANOVA. Percentage PBMD loss was calculated taking the mean PBMD of Group 1 (within 5 years of menopause) as the reference value:

$$\text{Percentage PBMD loss} = (\text{PBMD of the subject} - 0.485)/0.485 \times 100 \quad (1)$$

Percentage PBMD loss appeared to have a skewed distribution, hence, median (IQR) values were estimated and compared using Kruskal–Wallis test. Linear regression model was fitted with PBMD as the dependent variable and age as the independent variable to determine the annual BMD loss. *t*-scores of PBMD, SBMD and FNBMD were calculated using the Asian reference data provided by the manufacturers of the two machines. Women were diagnosed as having osteoporosis if they had *t*-scores less than –2.5 in the spine, femoral neck or both sites.[9] The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of different *t*-scores of PBMD were calculated. Receiver operating characteristic (ROC) curves were constructed for different *t*-scores of PBMD to select a suitable cut-off value. Two-tailed $P = 0.05$ was taken as the level of

statistical significance. SPSS for Windows (version 10) was used for all calculations. Ethical approval for the study was obtained from the Ethical Review Committee of the Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka.

RESULTS

Mean age of 1642 postmenopausal women in the sample was 56.5 years (SD 6.8) while mean weight and age at menopause were 55.8 kg (SD 9.97) and 47.2 years (SD 3.13), respectively. Median (IQR) number of children was 3 (2–4). Seventeen (1%) women had smoked previously and 23 women (1.4%) had consumed alcohol occasionally. Twenty-two (1.4%) women had taken hormone replacement therapy for a period more than 6 months. At the time of recruitment to the study, 1150 (70%) women were living for more than 5 years in urban administrative areas while the rest were living in rural administrative areas.

BMD results

A sharp decline in PBMD was seen in the postmenopausal period. When compared with the second group, the percentage BMD loss doubled in the third group indicating a rapid initial loss (Table 1). The percentage BMD loss in different age groups was highly significant ($P < 0.001$), when assessed by Kruskal–Wallis test. Although BMD declined progressively, the rate of bone loss was less rapid in old age. According to the linear regression model, the annual BMD loss was 0.006 g/cm^2 (standard error [SE] 0.0003, $P < 0.001$).

Specificity and sensitivity of PBMD in detecting osteoporosis

Sixty-three women in the subgroup of 150 postmenopausal women had *t*-scores less than –2.50 in the spine and a further two women in the femoral neck; hence, 65 women qualified for the diagnosis of osteoporosis. When different *t*-score thresholds of PBMD were tested for their ability to predict osteoporosis, *t*-score of –1.00 showed the highest sensitivity (89%) but lower specificity (45%). When *t*-score –2.5 was considered, the specificity improved to 90%, while sensitivity dropped to 62%. Trade-off between the sensitivity and specificity was evident when we used different *t*-score thresholds (Table 2).

Prevalence of low bone mass among women

A PBMD *t*-score of –2.00 was used to define 'low BMD' among postmenopausal women in the main study as we considered this to be the most appropriate cut-off point which detected osteoporosis with an acceptable level of sensitivity and specificity. ROC curves constructed for different *t*-scores justified the selection of –2.00 as the most appropriate cut-off value. Areas under the curve (SE and *P*-value) for *t*-scores of –1.00, –1.50, –2.00 and –2.50 were 0.67 (SE 0.08, $P = 0.034$),

Table 1 Absolute and percentage PBMD loss in 1642 postmenopausal women according to the time since menopause

	Group 1 (n = 472)	Group 2 (n = 525)	Group 3 (n = 314)	Group 4 (n = 155)	Group 5 (n = 99)	Group 6 (n = 75)
Time since MP†	Less than 5 years	5–9 years	10–14 years	15–19 years	20–24 years	25 or more years
Age (years)	50.8 (2.8)	54.0 (2.7)	58.3 (3.1)	63.4 (3.2)	67.6 (4.2)	72.9 (5.0)
BMD (g/cm^2)	0.485 (0.071)	0.457 (0.070)	0.428 (0.071)	0.408 (0.074)	0.385 (0.065)	0.342 (0.059)
% BMD loss‡	0	5.77 (–4.6–15.3)	11.3 (2.0–21.9)	16.7 (5.7–25.4)	21.8 (10.3–29.7)	31.5 (20.2–38.4)

†MP = menopause. PBMD = bone mineral density of the middle phalanx of the middle finger in the non-dominant hand.
‡Percentage bone loss given as median (IQR).

Table 2 Specificity and sensitivity of different PBMD *t*-scores in detecting osteoporosis in the subgroup of 150 postmenopausal women selected randomly from the southern province

Phalangeal *t*-score	Sensitivity	Specificity	Positive predictive value	Negative predictive value
–2.50	0.62	0.90	0.92	0.56
–2.00	0.78	0.85	0.91	0.68
–1.50	0.81	0.70	0.83	0.67
–1.00	0.89	0.45	0.75	0.69

PBMD = bone mineral density of the middle phalanx of the middle finger in the non-dominant hand.

0.75 (SE 0.07, $P = 0.002$) 0.81 (SE 0.06, $P < 0.001$) and 0.76 (SE 0.07, $P = 0.001$), respectively.

Among 1640 postmenopausal women, 357 were found to have PBMD *t*-scores either equal or less than –2.00. Since the PPV at this cut-off point was 0.91, 325 women out of the positive 357 were likely to have osteoporosis. With NPV of 0.68, a further 411 out of the remaining 1283 women who tested negative, were also likely to have osteoporosis. Hence, 736 women were likely to have osteoporosis and this estimated the prevalence of postmenopausal osteoporosis in our sample to be 44.9%.

DISCUSSION

Progressive reduction of BMD among postmenopausal women is a well-known phenomenon[10] and this was seen in this study population. The rate of loss was rapid soon after menopause but slowed down later as age progressed. Judging by the regression analysis, one would expect PBMD to decline by nearly 0.060 g/cm^2 after 10 years (12% reduction when compared with the mean BMD at menopause).

Rapid reduction of BMD in postmenopausal age is attributed to the reduced level of gonadal hormones. Since estrogen deficiency has its maximum effect on trabecular bone, the rapid initial reduction of BMD is believed to be related to the rapid resorption of trabecular bone mass. As trabecular bone mass gradually becomes smaller, the rate of bone loss becomes slower in old age.

Although PBMD can predict fractures,[11] it cannot be used to diagnose osteoporosis, as the WHO guidelines are based on BMD measured at spine, proximal femur or mid-radius sites.[9] In order to help clinicians, the sensitivity and specificity of different PBMD cut-off points in detecting osteoporosis has been defined. At a *t*-score of –2.50, sensitivity and specificity values in a previous study were 39% and 96%, respectively,[12] while the corresponding values in our study were 62% and 90%. This discrepancy could be due to many reasons such as differences in osteoporosis prevalence or the degree of physical activities, in different samples selected for calculations.

Limitations of AccuDEXA in screening for osteoporosis was evident as none of the PBMD *t*-scores examined, had acceptable sensitivity and specificity. PBMD *t*-score of –2.00 was considered to be the most useful cut-off point to diagnose osteoporosis as it had reasonable sensitivity and specificity. When using this cut-off value, clinicians need to know that only 91% of patients who have an abnormal report are likely to have osteoporosis and the balance is unlikely to have the disease. Further, 32% of patients who record a normal report are also likely to have osteoporosis.

We estimated that nearly 45% of postmenopausal women in our sample were likely to have osteoporosis and similar estimations have been observed in other countries. In previous studies the prevalence of osteoporosis varied widely depending on the type of technology, measurement sites and the cut-off values used for the diagnosis. In 1997, the working group of WHO selected a *t*-score cut off-value of –2.5 to diagnose osteoporosis, somewhat arbitrarily, as it identified 30% of postmenopausal women as having osteoporosis and it captured most patients with osteporotic fractures.[9] A subsequent study in Denmark reported 50% prevalence of osteoporosis among women older than 50 years.[13] Among postmenopausal Thai women, the prevalence of osteoporosis increased from 39% at 60–64 years to 57.7% at 70–74 years.[14] Among Japanese women aged between 50 and 79 years, the prevalence of osteoporosis was found to be 35% in the spine and 12% in the hip.[15] In the same population the prevalence of osteoporosis in the distal radius was 56.8%. In 2006, Jang *et al*. reported 30.6% prevalence of osteoporosis among postmenopausal women aged 45–64 years, 52.5% among women aged 65–64 years and 68.7% in women above 75 years. These figures were based on lumbar spine BMD, measured in 365 postmenopausal women selected from one area in China.[16]

This study has a number of limitations. People were made aware of the study 3–4 days before the scanning day and only women who volunteered to the study were recruited. Hence, selection bias would have occurred. Women who volunteered would have been a health-conscious subgroup with a low prevalence of osteoporosis and this would have led to underestimation of osteoporosis. Also, this would make the study sample not representative of the general population. This was visible in the age distribution where the number of women over the age of 70 was relatively fewer when compared with the other age groups. This too, would have underestimated the prevalence of osteoporosis, as only women who had reasonable mobility were able to attend scan sessions held in various locations and women with marked osteoporosis or fractures were not able to take part in the survey.

The north and east provinces were not included in the data collection due to security reasons. We do not see the non-inclusion of these two provinces as a major drawback in the study as Tamil and Moor ethnic groups

were included from other provinces. Comparison of BMD between peripheral and central sites was done in a small subgroup of randomized women from the southern province. A larger sample, selected from all seven provinces would have given more valid results when calculating sensitivity and specificity figures. Further, two technicians were involved in collecting data. Although they were trained together and followed the same protocol in scanning, interobserver variation in BMD measurements would have occurred.

In summery, this study involving healthy postmenopausal women in Sri Lanka, indicated that 45% of postmenopausal women in our society are likely to have osteoporosis. Although this is relatively high, similar values have been reported from other Asian countries. This information will be useful for health educators in the country when planning preventive measures in osteoporosis. Future studies may use this information to plan their studies. However, this estimation is not based on direct measurements of key skeletal sites such as spine, proximal femur or mid-radius, but calculated using peripheral BMD which tends to overestimate the prevalence of osteoporosis. Hence the actual prevalence of osteoporosis may be different from this estimated value.

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Original Article

Age-Related Trends in Phalangeal Bone Mineral Density in Sri Lankan Men and Women Aged 20 Yr or More

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Abstract

To establish normative reference values and to study the age-related trends in phalangeal bone mineral density (BMD), 4504 male and 5215 female volunteers aged 20 yr or more were recruited from 7 provinces from October 2004 to October 2005. Subjects suffering from diseases and those who were taking medications, which could affect BMD were excluded from the analysis (n = 530). Phalangeal BMD was measured in the nondominant hand using an AccuDXA. Men and women were categorized to age groups of 20−29 (1087 men and 1079 women), 30−39 (1122 men and 1146 women), 40−49 (1148 men and 1455 women), 50−59 (810 men and 1111 women), 60−69 (250 men and 335 women), and 70 yr or more (87 men and 94 women). Mean BMDs (SD) of men in above categories were 0.595 (0.057), 0.603 (0.061), 0.591 (0.066), 0.576 (0.069), 0.558 (0.077), and 0.522 (0.079) g/cm^2, respectively. The corresponding BMDs (SD) in women were 0.495 (0.057), 0.506 (0.062), 0.502 (0.064), 0.462 (0.072), 0.406 (0.072), and 0.340 (0.055) g/cm^2, respectively. Peak BMD was seen in 30−39-age category in both sexes. Women after 50 yr lost BMD at a rate of 0.006 (standard error 0.0003) g/cm^2/yr, whereas the corresponding value in men was 0.002 (standard error 0.0001) g/cm^2/yr. These data provide normative reference data for the calculation of T-score and Z-score for phalangeal BMD in Sri Lankan men and women aged more than 20 yr.

Key Words: AccuDXA; osteoporosis; phalangeal bone mineral density; reference data; Sri Lanka.

Introduction

Osteoporosis has become a major noncommunicable disease and increased incidence of hip fractures is expected, particularly in Asian countries, in future (1). Bone mineral density (BMD) is a major determinant of fractures in old age (2) and it is widely used in identifying high-risk patients. Factors such as genetic composition, social habits, nutrition, physical activities, and gonadal hormones have varying effects on the bone mass (3). As these factors vary in different communities, variations in peak bone mass and the rate of bone loss can be expected in different populations.

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Restricted availability of central-type DXA machines limits the early detection and treatment of subjects with high fracture risk in developing countries. Clinical risk factors of fractures such as previous fractures and maternal history of fractures are being used by clinicians to detect high-risk subjects. Several peripheral-type DXA machines including AccuDXA, have been introduced to Sri Lanka recently. Using 2 energy beams, low and high, AccuDXA measures BMD and bone mineral content (BMC) of the middle phalanx of the middle finger of the nondominant hand, site, which is rich in cortical bone. This portable device has the advantage of easy using in community settings and scan time of 1−2 min. Ohtsuka et al in 2002 found a significant association between phalangeal BMD (PBMD) and incident vertebral fracture (4), whereas Mulder et al found a significant correlation between PBMD and BMDs in central sites (5). However, the lack of reference data on local population and limited knowledge on clinical applications of these devices

has created an uncertainty among clinicians. Although, PBMD is not used to diagnose osteoporosis (6) or to monitor the therapeutic efficacy of antiresorptive drugs (7), its ability to predict fractures has been proven in epidemiological studies (8). Despite limitations in clinical applications, these peripheral devices will remain available for clinicians, as central DXA facility is available only in few major cities in Sri Lanka.

Country-specific normative data provide more accurate estimation of the prevalence of osteoporosis and osteopenia (9). Although some countries have developed local reference data, this is a daunting task for countries with limited resources. In Sri Lanka, no large community-based studies have been done to establish normative reference BMD values and this survey was carried out to study the age-related trends in BMD in a sample of men and women selected from 7 out of 9 provinces in Sri Lanka.

Methods

The Community Osteoporosis Survey in Sri Lanka recruited men and women above 20 yr of age from October 2004 to October 2005; 9719 subjects were included from all provinces except the 2 provinces in North and East, which were not included due to security reasons. A minimum of 2 different residential areas, which represented rural and urban populations, were selected randomly from each province. These areas were identified based on the type of local administration, adhering to the method used by the Department of Census and Statistics during 2001 census (10). Public was informed about the purpose and the nature of the study using public announcing systems 2−3 d prior to the scheduled visit. After explaining the purpose of the study and the procedure involved, subjects were recruited from volunteers who gathered in these scanning centers. All consenting subjects filled a brief questionnaire on health-related information. Weight was checked while wearing light cloths and without foot wear. PBMD and phalangeal BMC (PBMC) of the middle finger of the nondominant hand were measured using AccuDXA (Schick technologists, USA). Two trained technicians filled the questionnaire and performed all scans, while calibration of the machine was performed on each scanning day to ensure the accuracy of BMD measurements. The precision error Coefficient of Variation (CV%) of BMD estimations was calculated by measuring 30 women, aged between 20 and 60 yr, twice on the same day with repositioning between the 2 measurements and was found to be 0.98%.

Statistics

Descriptive data of the study sample are given as mean (SD) or numbers (%) unless stated otherwise. Subjects were categorized to 10-yr age categories; 20−29, 30−39, 40−49, 50−59, and 60−69 yr. Subjects aged 70 yr or above were grouped to 1 category as the number of participants was limited. Mean PBMD and PBMC in different age categories were estimated and compared using ANOVA with Bonferroni correction in post hoc analysis. The association between the PBMD and age was examined using linear regression model with BMD as the dependent and age as the independent variables, initially unadjusted and then adjusted for body weight. Similarly, regression model was fitted as PBMD as the dependent and years since menopause as the independent variables. Correlations between PBMD, current weight (in both men and women), and years since menopause (in postmenopausal women) were examined using Pearson correlation (r). p (2-Tailed) less than 0.05 was taken as the level of statistical significance. SPSS for Windows (version 10) was used for all calculations. Ethical approval for the study was given by the Ethical Review Committee of the Faculty of Medicine, Galle.

Results

Data of subjects with history of epilepsy, inflammatory arthritis, endocrine diseases, recurrent wheezing, malabsorption, chronic renal or liver diseases, vasculitis, and other chronic inflammatory diseases were excluded from the analysis. Similarly, data of subjects who had taken medications such as corticosteroids, anticonvulsants, heparin, vitamin D, hormone replacement therapy, antiresorptive drugs, and pharmacological doses of calcium were excluded (total number of exclusions = 530). Subjects with previous fracture were not excluded from the analysis. After exclusions, 5215 women and 4504 men were eligible for the study and description of these subjects are given in Table 1. Mean (SD) age of women and men were 40.6 (12.7) and 42.1 (12.6) yr, respectively; 1642 (31.5%) women were postmenopausal. The number of children born to married women ranged from 1 to 14 with median (inter quartile range) of 2 (1−4).

BMD showed a positive correlation with current body weight, both in men and women ($r = 0.17$ and 0.27 in men and women, respectively, $p < 0.001$). In postmenopausal

Table 1
Descriptive Data of 4504 Men and 5215 Women Included in the Final Analysis

Measurement	Men (n = 4504)	Women (n = 5215)
Mean (SD) age: yr	42.1 (12.6)	40.6 (12.7)
Mean (SD) body weight: kg	62.3 (19.5)	54.4 (10.6)
Mean* (SD) age at menopause: yr	NA	47.2 (3.1)
Smoking**		
Ever	1150 (43.8%)	4 (0.18%)
Never	1473 (56.2%)	2174 (99.8%)
Alcohol**		
Ever	1767 (67.4%)	4 (0.18%)
Never	856 (32.6%)	2174 (99.8%)

*n = 1642 postmenopausal women.
**n = 2623 men and 2178 women.

Table 2
Mean (SD) Phalangeal BMD and BMC of 4504 Men in Different Age Categories

Age Group (yr)	Number of Subjects	*BMD (SD) (g/cm^2)	*BMC (SD) (g)
20–29	1087	0.595 (0.057)	2.15 (0.341)
30–39	1122	0.603 (0.061)	2.21 (0.356)
40–49	1148	0.591 (0.066)	2.17 (0.385)
50–59	810	0.576 (0.069)	2.13 (0.387)
60–69	250	0.558 (0.077)	2.07 (0.412)
70 and above	87	0.522 (0.079)	1.90 (0.400)

Abbr: BMD, bone mineral density; BMC, bone mineral content.
*$p < 0.001$ for differences in both mean phalangeal BMD and BMC between different age groups (assessed by ANOVA post hoc test with Bonferroni correction).

women, BMD showed a negative correlation (−0.48, $p < 0.001$) with years since menopause.

Phalangeal BMD, BMC, and Age

When compared with the women in the same age categories, men always had a higher PBMD. The highest PBMD and PBMC were seen in 30–39-yr age category in both sexes (Tables 2 and 3). However, men and women in 20–29-yr age category had achieved 98% of the maximum PBMD and the difference of PBMD between 20 and 29 and 30 and 39 age groups was only 2%. Furthermore, no substantial change in PBMD occurred from 30 to 50 yr and PBMD started declining after 50 yr of age. The decline was more rapid in women than in men (Fig. 1).

Although women older than 50 yr, lost BMD at a rate of 0.006 g/cm^2 each year (standard error, 0.0001; $p < 0.001$), men above 50 yr, lost BMD at a lesser rate (0.002 g/cm^2 annually; standard error, 0.0001; $p < 0.001$), and the rate of

Table 3
Mean (SD) Phalangeal BMD and BMC of 5215 Women in Different Age Categories

Age Group (yr)	Number of Subjects	*BMD (SD) (g/cm^2)	*BMC (SD) (g)
20–29	1074	0.495 (0.057)	1.48 (0.279)
30–39	1146	0.506 (0.062)	1.55 (0.308)
40–49	1455	0.502 (0.064)	1.55 (0.308)
50–59	1111	0.462 (0.072)	1.44 (0.325)
60–69	335	0.406 (0.072)	1.27 (0.325)
70 and above	94	0.340 (0.055)	1.04 (0.251)

Abbr: BMD, bone mineral density; BMC, bone mineral content.
*$p < 0.001$ for differences in both mean phalangeal BMD and BMC between different age groups (assessed by ANOVA post hoc test with Bonferroni correction).

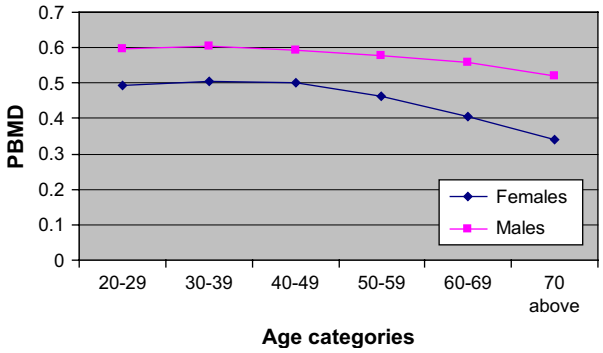

Fig. 1. Age-related changes of phalangeal bone mineral density (BMD) in 4504 men and 5215 women included in the analysis. PBMD = phalangeal BMD in g/cm^2.

BMD loss between the 2 genders was significant ($p < 0.001$). Inclusion of weight in the model did not change these values materially.

Among postmenopausal women, PBMD declined by 0.005 g/cm^2 (standard error 0.0002, $p < 0.001$) for each year since menopause and inclusion of body weight in the model did not affect the results significantly.

Discussion

Our results will provide normative PBMD and PBMC reference data for the calculation of T-score and Z-score for PBMD, measured by AccuDXA in Sri Lankan men and women older than 20 yr. Peak PBMD was seen between 30 and 39 yr in both sexes and compared to women, men had 19% higher peak bone mass (603 vs 506 g/cm^2). Compared to women, men maintained a higher BMD, while the magnitude of the difference was greater in old age. After the age of 50 yr, the annual bone loss was much higher in women than in men.

Mean BMDs of women in age categories of 40–49, 50–59, 60–69, and 70 yr or above were, respectively, 0.9%, 8.6%, 19.7%, and 32.8% below when compared with the peak bone mass of women in the age category of 30–39 yr. Corresponding figures for men were 1.9%, 4.5% 7.5%, and 13.4% in age categories 40–49, 50–59, 60–69, and 70 yr or above, respectively. The annual bone loss in women was 0.006 gm/cm^2, whereas that in men was only 0.002 g/cm^2. This indicates that for each decade after 50 yr, women would lose about 11.9% of their BMD, whereas men would lose only 3.4%.

We were unable to find similar epidemiological studies, which used either AccuDXA or measured PBMD using other device to compare our data. Hence, studies selected for comparisons have measured BMDs in other sites by different devices. In a previous study, a gradual decline of hip BMD was seen in both men and women of all 3 major ethnic groups in the United States (11). Furthermore, in a study involving Turkish women, bone loss amounting to 14.1–32.7% at different skeletal sites was seen in women older than 70 yr when compared with young Turkish women (12). Similarly,

Greek women lost 32% and 29.5% of bone mass between 20 and 70 yr in the femoral neck and spine, respectively. Corresponding figures for men were 29% and 19.5%, lower than those of women (13). Bone loss ranging from 29% to 34.3% has been recoded in the forearm bones in old Chinese women (14). Further Chinese women in Hong Kong lost 10% of their bone mass in each decade from 50 to 79 yr and this compares well with our data. Although no significant bone loss was seen in Hong Kong Chinese men from 40 to 70 yr, we recorded a lesser but still significant, 3.4% bone loss in each decade in men (14).

The age in which peak bone mass is achieved has shown a wide variation according to the study population and the region of interest included in the BMD assessment. In our study, although, the highest BMD was seen in men and women between 30 and 39 yr, subjects in 20−29-age category had gained 98% of their maximum BMD. When the study sample was further divided to 5-yr age categories, the peak PBMD was seen between 30 and 34 yr in both sexes. In the United States, men and women in all 3 major ethnic groups reached the peak hip BMD between 20 and 30 yr (11). However, delays in reaching the peak bone mass in populations outside the United States have been reported. Saudi women reached peak spine BMD around 35 yr but earlier at proximal femur (15). Similarly in Greek women, spinal BMD reached its peak between 30 and 35 yr, whereas at femoral neck the peak BMD was seen between 25 and 30 yr (13). In Chinese, although peak BMD in proximal femur was seen between 20 and 24 yr, the peak BMD in the forearm bones was delayed until 40−44 yr (16). Although the exact reasons for delay in reaching the peak bone mass in certain populations is not known, variations in genetic, social, and nutritional states in different populations may play a role.

It is important to develop country-specific reference data for the accurate estimation of T-score and Z-score. Although NHANES data are used widely in the United States, the validity of such data outside United States has been questioned (9). This becomes an important issue when diagnosing osteoporosis as the prevalence of osteoporosis varies according to the reference data used to calculate T-scores. In Turkish women the prevalence of low BMD in hip, defined as T-score less than 1.0, changed from 60.8% to 14.6% when local reference values were used instead of the NHANES data. Similarly in hip, the prevalence of low BMD changed from 60.8% to 14.6% (17). A wide variation in the prevalence of osteoporosis was witnessed among Austrians when local reference data were used (18).

There were several limitations in our study. BMD measurement in this study was limited to 1 single area in the appendicular skeleton. Hence we have no insight as to how BMD in other sites, particularly in clinically relevant central sites such as spine or proximal femur would vary in different age groups. Furthermore, only the scanning centers were selected randomly but not the subjects. This would have led to selection bias. The North and the East provinces were not included in the study due to security reasons. However, we have 8.5% Tamils and 7.8% Moors included from other provinces and these percentages are roughly equal to the proportions of these ethnic groups seen in the population (10). The brief interview did not allow us to go to the details of their medical history and medications and there was a possibility of including subjects suffering from diseases or taking medications, which could affect bone metabolism. The large sample size, however, would have neutralized some of the bias that occurred at the time of recruitment.

In conclusion, our study provides reference database for the calculation of T-score and Z-score for the PBMD measured by AccuDXA in Sri Lankan men and women aged older than 20 yr. Men and women in the study sample gained 98% of their maximum BMD between 20 and 29 yr and this remained relatively unchanged until 50 yr.

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Chapter 3

Factors affecting bone mineral density measurements

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Original Article

Effect of Hip Flexion on the Measurement of Spinal Bone Mineral Density in the Norland Eclipse XR

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Abstract

It is recommended that the hip joints be flexed to 90° during dual-energy X-ray absorptiometry scanning of the lumbar spine in the anteroposterior projection; however, some patients are unable to maintain this position because of the presence of degenerative changes in lower limb joints. This study examines the effect of a lesser degree of hip flexion on the lumbar spine bone mineral density (BMD) measurement and its interpretation. Fifty women were scanned on the Norland Eclipse XR, initially in the standard position with the hips flexed to 90° and then in the adjusted position after allowing for some degree of hip extension to keep them comfortable (hip flexion of 60°–70°). Higher bone mineral content (BMC), surface area, and BMD values were seen in the standard position compared to the adjusted position, but none of the differences was statistically significant. There were strong correlations for BMC, surface area, and BMD measured in the two positions. In the standard position, 26 women were found to have osteoporosis and 18 had osteopenia. In the adjusted position, osteoporosis was noted in 27 women, and 18 had osteopenia. Four women showed a reduction, whereas 12 women showed an increase in BMD in excess of the least significant change at the 95% confidence level, defined as 2.77 times the precision error (0.008 g/cm^2 × 2.77 = 0.120 g/cm^2). Our study demonstrates that a lesser degree of hip flexion in women who find it difficult to maintain the recommended 90° hip flexion during the lumbar spine BMD measurement would not affect the patient classification based on T-scores recommended by the World Health Organization; however, variation in hip flexion can be a major confounding factor when interpreting a change in BMD over time.

Key Words: Osteoporosis; bone density; lumbar spine; hip flexion; patient positioning.

Introduction

Bone mineral density (BMD) is the yardstick for the clinical diagnosis of osteoporosis in those who have not yet sustained a fragility fracture. BMD of both the lumbar spine and hip are often obtained when evaluating patients for bone mass because they are better predictors of fractures at their own sites *(1)*. Further, relatively good measurement precision observed at these sites makes them suitable sites for monitoring BMD trends *(2)*. Spine and hip fractures are of clinical importance, as they are often associated with significant morbidity and mortality, costly to manage, and associated with increased risk of fractures at other sites *(3)*. The lumbar spine, where trabecular bone contributes to 60% of bone composition, might have an added advantage over other skeletal sites in the monitoring of patients with osteoporosis. As a result of the high surface-to-volume ratio in trabecular bone, the spine is a main site that demonstrates bone mineral decline following primary gonadal failure *(4)*, during corticosteroid therapy *(5),* and in chronic inflammatory diseases *(6)*. Furthermore, the BMD response following antiresorptive or anabolic therapy is greater in the lumbar spine than in the hip *(7)*. The additional advantage of the spine over other sites for BMD measurement can, however, be lost in the presence of degenerative skeletal conditions *(8)*.

Correct positioning of the patient during the measurement of lumbar spine BMD is vital to generate precise values. Patients are kept in the middle of the scanning area in the supine position with upper limbs on either side. To minimize

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the curvature of lumbar spine, which, in turn, allows for the maximum separation of lumbar vertebrae in the scan image, leg blocks provided by the manufacturers are used to maintain hip flexion at 90°. We encountered several practical problems in positioning patients for lumbar spine BMD scanning in routine clinical practice, which prompted us to perform this study. The recommended flexion of the hips to 90° was not achievable in some patients because of the presence of degenerative changes either in the hip or spine. Although adequate flexion was achieved in some patients, they were not comfortable in this position and were unable to maintain it during the entire period of scanning.

Studies examining the effect of hip flexion on the measurement of lumbar spine BMD are limited *(9)*. This study was done to assess the differences in lumbar spine BMD when measured with a lesser degree of hip flexion in a group of women who were uncomfortable in the recommended position during the measurement of spinal BMD.

Materials and Methods

A group of 50 perimenopausal women, selected from patients referred to the Center for Metabolic Bone Diseases in Galle in southern Sri Lanka for the assessment of BMD was included in the study. They were positioned on the scanner table adhering to the Norland's guidelines and using the leg block provided by the manufacturer. The first dual-enrgy X-ray absorptiometry (DXA) scan of the lumber spine from L_2 to L_4 in the anteroposterior projection was done using the Norland Eclipse XR machine (Norland Corp, Ford Atkinson, USA) with the hip joints flexed to 90° as recommended by the manufacturer (standard position). A second scan was done in women who said they were "feeling uncomfortable" during the initial scanning, after allowing some degree of hip extension from the initial position to make them more comfortable (adjusted position). The widest side of the leg block was used in all women. No change in the side of the leg block or other parts of the patient's body was allowed between the two scans. The degree of hip extension from the position of the first scan was measured (to the nearest 5°) using two thin rules: (1) perpendicular to the scan table and (2) along the shaft of the femur from the greater trochanter to the tibial tuberosity. Bone mineral content (BMC), surface area, and BMD of vertebrae L_2, L_3, and L_4, individually and then collectively were taken for analysis.

Statistical Analysis

Bone mineral density, BMC, and the surface area between the standard and adjusted positions were compared using the Student's paired *t*-test. Correlations of measurements in the standard and adjusted positions were examined using the Pearson correlation coefficient. T-Scores were calculated for spine BMD (L_2 to L_4) using the Asian reference data provided by the manufacturer and they were categorized as osteoporotic, osteopenic, or normal based on the World Health Organization's (WHO) criteria *(10)*. This was done in both the standard and adjusted positions and the degree of discrepancy was examined. The precision error for spine BMD (0.008 g/cm^2) was estimated by scanning 30 perimenopausal women twice, and the least significant change (LSC) in spine BMD at the 95% confidence level was taken as 0.020 g/cm^2 (defined as 2.77 times the precision error) *(11)*. The number of women who showed BMD change in excess of 0.020 g/cm^2 from the initial scan was estimated. Statistical significance was defined as two-tailed $p < 0.05$ for all estimations. All analyses were done using the SPSS (version 10) for Windows. Each subject signed a consent form for the second scan, and ethical approval for the study was obtained from the local ethics committee.

Results

The mean (SD) age of 50 women who participated in the study was 56.5 (5.5) yr and 40 of them were postmenopausal. In all of subjects, the initial scan was done in the standard position with the hip flexed to 90°. The second scan was done after allowing some degree of hip extension from the initial position. In 19 subjects, we had to extend the hip by 20° (i.e., hip flexion of 70°); in another 19 subjects, we had to extend the hip by 25° (i.e., hip flexion of 65°); and in the rest, we had to extend the hip by 30° (i.e., hip flexion of 60°).

The means and standard deviations for BMC, BMD, and surface area of vertebrae from L_2 to L_4 individually and collectively in both the standard and adjusted positions and their differences are given in Table 1.

In general, higher BMC, surface area, and BMD values were seen in the standard position compared to the adjusted position, but none of the differences was statistically different from zero at the 5% significance level. There were strong correlations for BMC, surface area, and BMD measured in the two positions.

Table 2 shows the differences in BMD between the two positions expressed as a percentage of the initial value. The greatest variation was seen when the hip joint was flexed by 65°. At 70° and 60° of hip flexion, the variation was less. In the standard position, 26 women were found to have osteoporosis whereas osteopenia was detected in 18 subjects. In the adjusted position, osteoporosis was noted in all who had osteoporosis in the standard position and in one additional woman (total of 27). Eighteen women in the adjusted position had osteopenia in the spine. When examined for the absolute BMD change, four women (8%) showed a decline, whereas 12 (24%) had an increase in BMD beyond the defined level for the LSC.

Discussion

Lumbar spine BMD is useful for clinicians in many ways. Apart from estimating the future fracture risk in postmenopausal women *(1)*, lumbar spine BMD is also used to monitor effects of aging *(4)*, prolonged corticosteroid use *(5)*, chronic inflammatory conditions *(6),* and response to medical therapies *(7)*. The usefulness of lumbar spine BMD, however, diminishes with age *(12)* because, degenerative changes in the lumbar spine and calcification of the abdominal aorta could cause falsely elevated values *(8)*.

Table 1
Mean (SD) BMC, Surface Area, and BMD in the Standard and Adjusted Positions, Their Correlations, and Their Differences

Site	Standard position	Adjusted position	r^a	Mean difference[b]	95% CI for difference	*p*-Value
BMC (g)						
L2	8.17 (2.19)	8.15 (2.27)	0.96	0.020	(–0.165, 0.206)	0.83
L3	9.33 (2.52)	9.15 (2.50)	0.96	0.179	(–0.028, 0.386)	0.09
L4	9.85 (2.50)	9.69 (2.47)	0.94	0.157	(–0.095, 0.409)	0.22
L2–L4	27.35 (6.97)	27.00 (7.05)	0.97	0.355	(–0.143, 0.853)	0.16
Surface area (cm^2)						
L2	11.20 (0.91)	11.22 (0.90)	0.83	–0.017	(–0.170, 0.135)	0.82
L3	12.24 (1.01)	12.13 (0.92)	0.81	0.120	(–0.053, 0.294)	0.17
L4	13.00 (1.20)	12.86 (1.10)	0.74	0.142	(–0.096, 0.380)	0.26
L2–L4	36.44 (2.64)	36.21 (2.49)	0.86	0.225	(–0.165, 0.615)	0.25
BMD (g/cm^2)						
L2	0.728 (0.178)	0.724 (0.184)	0.99	0.005	(–0.005, 0.014)	0.33
L3	0.759 (0.182)	0.752 (0.187)	0.99	0.006	(–0.002, 0.014)	0.11
L4	0.756 (0.171)	0.752 (0.175)	0.98	0.004	(–0.005, 0.013)	0.40
L2–L4	0.748 (0.174)	0.743 (0.178)	0.99	0.006	(–0.001, 0.013)	0.08

[a]Pearson correlation coefficient between standard and adjusted positions ($p < 0.0001$ for all correlations).
[b]Mean of the paired differences (standard–adjusted).

Table 2
Percentage Change of BMD at Different Hip Flexions

	Minimum	Maximum	Mean	SD
Entire group ($n = 50$)	–4.80	10.85	0.90	3.52
At 70° ($n = 19$)	–2.94	7.11	0.61	2.40
At 65° ($n = 19$)	–4.83	10.85	1.95	4.49
At 60° ($n = 12$)	–2.63	8.31	–0.31	3.01

The prevalence of both osteoporosis and osteoarthritis in weight-bearing joints in the lower limbs increases with advancing age and its not unusual for some patients referred for DXA to have reduced mobility in the hip and knee joints, which could make proper positioning of these patients on the scanning table difficult. Attempts to flex the hip joints to 90° as recommended by the manufacturer can cause great discomfort for these patients. This study demonstrates the effect of a lesser degree of hip flexion on the measurement of spinal BMD using the Norland Eclipse XR and its clinical interpretation.

When the diagnosis of either osteoporosis or osteopenia is of interest, a change of hip flexion to the degree that we allowed in our study would not cause any significant impact in the prevalence of these two conditions. In a clinical setting, if a patient is unable to keep the hips flexed to 90° during the estimation of spinal BMD, a slight extension of the hips from the recommended position can be allowed, to keep the patient comfortable without causing a significant impact on the WHO classification of the patient.

When compared to the standard position, the mean BMC, surface area, and BMD values in the adjusted position were relatively higher, except for the surface area of the L_2 vertebra. Although these differences were not statistically significant, their clinical relevance was clearly evident. When the position was adjusted the, BMD change ranged from –4.8 to 10.8%, with a mean of 0.9%. Both mean BMC and the surface area increased when the position was adjusted, but the BMC to a greater extent (–15.4 to 18.6%) than the surface area (–12.8 to 10.7%). This could explain the higher BMD observed in the adjusted position. This pattern was similar when vertebrae were considered both individually and collectively.

When the spine BMD (L_2 to L_4) in the second scan was considered, 23 women (46%) had a reduction, and the rest showed an increase from the initial value. In 16 women, the change in BMD was in excess of the LSC. Thus, in follow-up studies, if attention is not paid to the degree of hip flexion, a difference of hip flexion by about 25° would cause either false elevation or reduction of BMD in about 32% of subjects to a value that could be interpreted as a biologically significant true change. If the initial scan was obtained with a lesser degree of hip flexion, then this must be recorded for future reference and the same degree of hip flexion should be achieved in subsequent scans. This will minimize the false change in BMD because of the variation in hip positioning.

This study has several limitations. The applicability of our results to DXA scanners other than Norland remains unknown. Unlike Hologic and Lunar, Norland does not include L_1 in spinal BMD estimations and we have analyzed only L_2 to L_4 in this study. Similar studies should be performed using Hologic and Lunar central DXA to determine if the principles are broadly applicable. Finally, the degree of hip flexion was measured to the nearest 5° and some patients may have been categorized to the wrong group.

Conclusion

In summary, this study illustrates the effect of hip flexion on the spinal BMD analysis and interpretation. As there should

be a uniform method in positioning patients for spine scans, keeping the thighs perpendicular to the scan table, with the hips flexed to 90°, should be considered the standard method when using Norland central DXA. Leg blocks provided by the manufacturers are helpful to achieve and maintain this position throughout the study. If this is not achievable, a lesser degree of hip flexion can be allowed without altering the diagnosis based on the WHO criteria. The degree of hip flexion achieved should be documented in the patient's notes and the same degree of hip positioning should be maintained in repeat scans.

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Original Article

Measurement of Spinal Bone Mineral Density on a Hologic Discovery DXA Scanner With and Without Leg Elevation

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Abstract

Although it is generally recommended that patients keep their hips flexed by 90° during the measurement of spinal bone mineral density (BMD), there is no uniform agreement among the manufacturers of dual-energy X-ray absorptiometry (DXA) scanners regarding the positioning of legs while scanning the spine. We measured spinal BMD in 54 postmenopausal women, from L1 to L4 in posterior-anterior projection, using a Hologic Discovery scanner, first with their legs elevated as recommended by the manufacturer and then with their legs flat on the scanning table. Differences of bone mineral content (BMC), area of the region of interest (ROI), BMD, and T-score of the total spine between the 2 scans were compared. The mean (SD) age of the women was 54.3 yr (15 yr). Between the 2 scans, BMC, area of the ROI, BMD, and T-scores showed high correlations ($r = 0.98$, 0.94, 0.99, and 0.99, respectively). BMC and the area of the ROI changed significantly between the 2 scans, but the changes of BMD and T-scores were not significant. The percentage changes of BMC and the area of the ROI were similar (2.6% and 2.4%, respectively), whereas T-scores showed no change and change of BMD was only 0.6%. The absolute difference in BMD between the 2 scans was only 0.005 ($p = 0.09$). When spinal BMD was measured with their legs elevated, 31 women were found to have osteoporosis and further 13 were found to have osteopenia. When spinal BMD was measured with their legs flat, 32 women were found to have osteoporosis and further 12 were found to have osteopenia. In conclusion, no clinically or statistically significant difference in the total spinal BMD was found when the BMD in a group of women was measured on a Hologic Discovery DXA scanner with their legs positioned flat.

Key Words: Bone mineral density; leg positioning; precision error.

Introduction

The lumbar spine is one of the key sites used in the clinical evaluation of patients with osteoporosis. Initial bone loss following menopause *(1)* and the maximum therapeutic effects of current therapies of osteoporosis are mainly seen in the lumbar spine *(2)*. The clinical applicability of spinal bone mineral density (BMD) diminishes in old age due to the occurrence of degenerative changes in and around the lumbar spine *(3)*.

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Generally, the patients' hip joints are flexed by 90° to keep their thighs perpendicular to the scanning table while estimating spinal BMD. This reduces the lumbar curvature, allows separation of individual vertebrae, and prevents overlap of bone tissue. However, there is no uniform agreement between the manufacturers of dual-energy X-ray absorptiometry (DXA) scanners regarding the positioning of legs during scanning of spine, and different leg positions are recommended by different DXA scanner manufacturers. Whereas the manufacturers of the Hologic and Norland scanners recommend flexion of hips by 90° while scanning for spinal BMD, the Lunar scanner manufacturer does not recommend such positioning. This study was done to estimate the difference between spinal BMD measured with hip flexion and that measured without hip flexion, using a Hologic DXA scanner.

Table 1
Mean (SD) of BMC, Area of the ROI, and BMD Measured With Patients' Legs Up and Patients' Legs Down and Their Correlations and Mean Differences

Measurement	Legs-up position	Legs-down position	Correlation (*r*)	Mean difference (95% CI)	p^a
BMC (g)	35.66 (9.90)	34.86 (10.04)	0.98*	0.79 (0.19 to 1.40)	0.011
Area of the ROI (cm^2)	47.26 (5.47)	45.99 (5.62)	0.94*	1.27 (0.73 to 1.80)	<0.001
BMD (g/cm^2)	0.746 (0.164)	0.750 (0.168)	0.99*	−0.005 (−0.010 to 0.001)	0.09
T-score	−2.74 (1.49)	−2.70 (1.53)	0.99*	−0.03 (−0.09 to 0.01)	0.153

Abbr: BMC, bone mineral content; BMD, bone mineral density; CI, confidence interval; ROI, region of interest.
[a]*p* contrasts between the 2 DXA measurements taken with patients' legs up and patients' legs down.
*$p < 0.001$ (Pearson correlations for 2 measurements taken with patients' legs up and patients' legs down).

Method

A group of postmenopausal women referred to the Center for Metabolic Bone Diseases in the Faculty of Medicine, Galle, Sri Lanka, was selected for the study. Fifty-four consenting women had their lumbar spine scanned from L1 to L4 in the posterior-anterior projection, using a Hologic Discovery W (Hologic Inc.) scanner. First, the scan was done with their hips flexed, using the leg positioning cushion provided by the manufacturer (legs-up position). Patients were then positioned for routine hip scans using the hip positioning aid provided by the manufacturer, and a second scan of the spine, from L1 to L4 in the posterior-anterior projection, was done while their legs were flat on the bed (legs-down position). Patients were not moved from the scanning table, and only their legs were adjusted between the 2 scans. All scans were done by the same technician who analyzed each scan individually. Ethical approval for the study was obtained by the Ethics Review Committee of the Faculty of Medicine, Galle, and each participant signed a consent form.

Statistics

Data are given as mean (SD) values unless stated otherwise. Only BMC, area of the region of interest (ROI), BMD, and T-scores of the total spine from L1 to L4 were considered for the analysis. Differences in spinal BMC, area of the ROI, BMD, and T-scores between the 2 scans were compared using the paired Student's *t*-test. Correlations of BMC, area, BMD, and T-scores between the 2 scans were examined using linear regression. The women were classified into osteoporosis, osteopenia, or normal groups depending on the WHO cutoff values based on T-scores *(4)*. The agreement of the classification in the 2 positions was compared using kappa statistics. The agreement of BMD, BMC, and area of the ROI, measured in the 2 positions was examined using the Bland-Altman plot. Precision error of spinal BMD was estimated for the leg-up position by scanning 30 perimenopausal women twice, with repositioning between the 2 scans, and was found to be 0.008 g/cm^2 (least significant difference = 0.020 g/cm^2). Thirty-four perimenopausal women were scanned twice on separate occasions in leg-down position with repositioning between the 2 scans to estimate the precision error of spinal BMD estimations in leg-down position, which was found to be 0.009 g/cm^2 (least significant difference = 0.022 g/cm^2).

Table 2
Change of BMC, Area, and BMD Between the 2 Scans

Measurement	Median (%)	IQR (%)
BMC	2.5	0.2 to 5.1
Area	2.6	1.2 to 4.7
BMD	−0.48	−2.3 to 0.9
T-score	0	−3.2 to 6.5

BMC, bone mineral content; BMD, bone mineral density; IQR, inter quartile range.

Results

The mean (SD) age of the women was 54.3 yr (15 yr). High correlations were seen in BMC, area of the ROI, BMD, and T-scores measured in legs-up and legs-down positions. Differences in BMC and the area of the ROI between legs-up and legs-down positions were statistically significant, whereas BMD and T-score differences were not significant (Table 1). The percentage change of BMC, area of the ROI, BMD, and T-score showed a skewed distribution; hence, median and inter quartile range (IQR) values were estimated. Percentage changes of BMC and the area of the ROI were almost similar (2.5% and 2.6%, respectively), whereas no change in T-score and a marginal change in BMD were seen (Table 2).

In regression analysis, BMD measured in the 2 positions showed a very high correlation ($r = 0.99$) (Fig. 1). The Bland-Altman plot drawn to examine the agreement of BMD measured in the 2 positions showed that most of the observations (96%) were within 2 SDs around the mean value of difference between the 2 measurements (i.e., BMD leg up − BMD leg down), indicating good agreement of paired measurements (mean = −0.004 and SD = 0.02 g/cm^2) (Fig. 2). However, more scatter was seen in plots drawn for BMC (mean = 0.799 and SD = 2.21 g) and area of the ROI

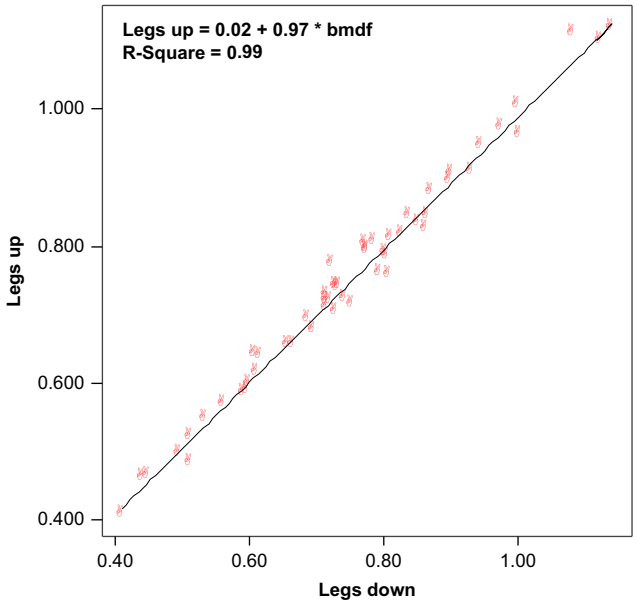

Fig. 1. Regression plot of bone mineral densities measured in the 2 positions.

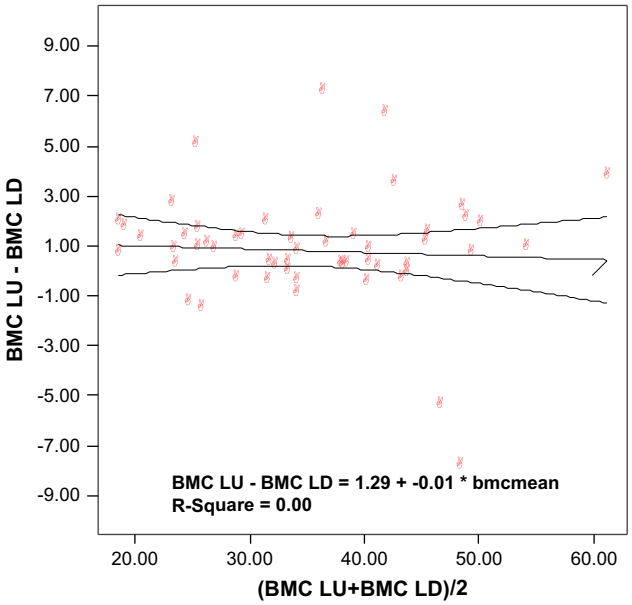

Fig. 3. Bland-Altman plot for bone mineral content (BMC) measurements taken with patients in legs-up (LU) and legs-down (LD) positions.

(mean = 1.27 and SD = 1.96 cm^2), indicating less agreement in those measurements (Figs. 3 and 4). When spinal BMD was measured in the legs-up position, 31 women were found to have osteoporosis and further 13 were found to have osteopenia. With spinal BMD measured in the legs-down position, 32 women were found to have osteoporosis and further 12 women were found to have osteopenia (kappa = 0.84).

Discussion

The results of our study showed no significant difference in the total spinal BMD or T-score measured with hip flexion and that measured without hip flexion. When patients' legs were kept flat, the area of the ROI and BMC, both reduced

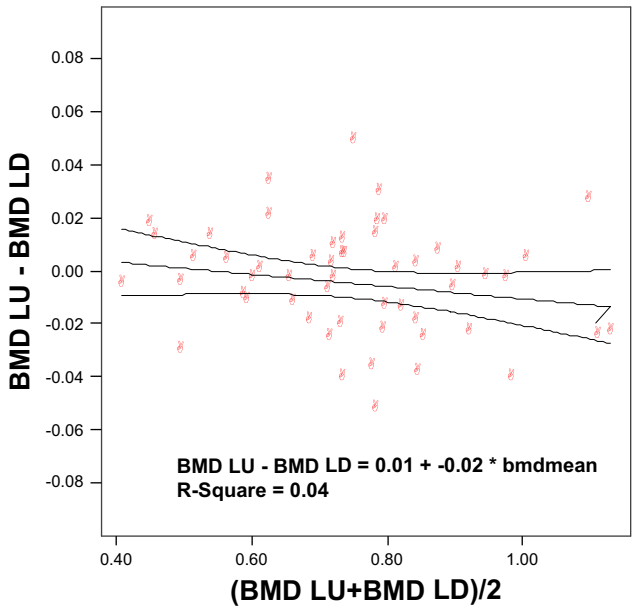

Fig. 2. Bland-Altman plot for bone mineral density (BMD) measurements taken with patients in legs-up (LU) and legs-down (LD) positions.

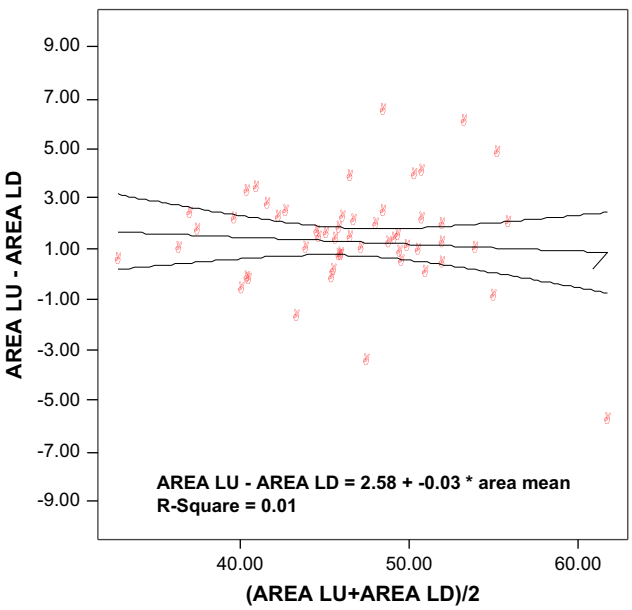

Fig. 4. Bland-Altman plot for area of the region of interest measurements taken with patients in legs-up (LU) and legs-down (LD) positions.

almost to the same extent, and thus, BMD and T-score did not change significantly. BMD and T-score differences remained the same after adjusting for the height of the women, the percentage change in BMC, or the area of the ROI. The change of mean BMD was only 3% when expressed as a percentage of SD of BMD measurements. Change of BMD had only a minor effect on the T-score, resulting in misclassification of one patient with osteopenia as having osteoporosis.

Flexion of legs at the hip joints reduces the lumbar curvature, causing separation of intervertebral spaces. When legs are kept flat, the spine would resume its normal lumbar curvature, resulting in a reduction in the ROI. However, the Hologic analysis software had no difficulty in locating the intervertebral spaces to place horizontal lines to demarcate individual vertebrae and the operator did not have to do this manually.

There is no uniform agreement among manufacturers of DXA scanners on how the legs should be positioned while estimating spinal BMD. The manufacturers of the Hologic and Norland scanners recommend flexion of hips by 90° to keep the thighs perpendicular to the surface of the scanning table. As the current reference data used in most of the systems have been obtained by adhering to this positioning, it is logical to position patients in a similar manner, if those reference data are to be used in patient evaluation.

If BMD of the spine can be measured while the patient is positioned for a hip scan, it will save time and can be less troublesome to the patient. This can be done only if DXA machines have the same accuracy for measuring BMD with or without hip flexion. Further, the high precision we observed in leg-down position would support the adoption of such practice. A previous study using a Lunar Prodigy or Bravo scanner showed results comparable to those of our study *(5)*. In this study involving a group of postmenopausal women, the correlation of BMDs measured with or without leg elevation was similar to the value we observed in our study. Further, in the regression analysis, the slope and intercept values observed were highly comparable to our figures. This study based on Lunar, however, showed a statistically significant and higher difference in BMDs between the 2 positions. The difference in BMDs observed in this study was much higher (0.014 g/cm^2) than the corresponding figure observed in our study (0.005 g/cm^2).

Yang and Jeon, using a Hologic QDR 4500 scanner, demonstrated comparable results *(6)*. Spinal BMDs with and without leg elevation showed a correlation of 0.99, whereas there was no significant difference between the mean BMDs estimated in the 2 positions (0.907 vs 0.922 g/cm^2). Further, there was only a 0.13 SD difference in the mean T-scores between the 2 positions.

This study has a few limitations. We used the same reference data to calculate T-scores in both positions. These reference data have been developed using standard protocols, and their applicability for BMD estimated in a different way is questionable. T-scores obtained in the legs-down position would have been different if we had used reference data developed by scanning subjects with their legs flat. To the best of our knowledge, such reference data do not exist.

Our data would add to the existing body of evidence that the total spinal BMD can be measured while the patient is positioned for a hip scan, without compromising the diagnostic stratification. The high precision and accuracy we observed in this study, in estimating spinal BMD while patients' legs were positioned flat, would support this. The same cannot be said about the BMC and the area of the ROI as there were significant differences in these 2 measures when estimated in the 2 positions. However, BMD is used more often by clinicians and researchers in their decision making, and BMC or area of the ROI is only seldom used.

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Original Article

Effect of Leg Rotation on Hip Bone Mineral Density Measurements

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Abstract

Bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) is widely used in the management of patients with osteoporosis. Factors, which are specific to machine or to operator, can influence the accuracy and precision of BMD estimations. We studied the effect of leg rotation by 10° either internally or externally from the standard position in a group of 50 women (average age 54.9, SD = 11.1 yr) who were free of bone active diseases or medications. External rotation of leg by 10° from the customary position increased the average BMD by 0.005, 0.003, and 0.036 g/cm^2 in the femoral neck, trochanter, and Ward's area (p = 0.119, 0.309, and <0.001), respectively. Internal rotation of leg by 10° from the customary position decreased the average BMD by 0.009, 0.005, and 0.006 g/cm^2 in the femoral neck, trochanter, and Ward's area (p = <0.001, 0.008, and <0.001), respectively. The number of subjects qualified for the diagnosis of osteoporosis based on the *T*-scores (equal to or below –2.5) of the femoral neck and trochanter did not change significantly in three different positions (18% in the customary position and after the external rotation and 14% after the internal rotation). A significant change in the femoral neck BMD (defined as 2.77 × precision error) was seen in 12% of subjects after the internal rotation and 8% after the external rotation. Our data emphasize the need for proper positioning of the hip during DXA scanning. Malrotation of the hip can be an important confounding factor when interpreting serial BMD values.

Key Words: Bone mineral density; leg positioning; leg rotation; osteoporosis.

Introduction

Osteoporosis is defined as "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" *(1).* The diagnosis of osteoporosis is made when bone mineral density (BMD) estimated by dual-energy X-ray absorptiometry (DXA) is lower than 2.5 SD of the young normal reference population *(2).* Further, BMD can quantify the future fracture risk in an individual and is also used to monitor skeletal response to therapeutic interventions *(2).* Although BMDs of both lumbar spine and proximal femur are considered when the diagnosis of osteoporosis is made, the latter is preferred as is it the best site to predict risk of future hip fracture *(3)* and is less affected than lumbar spine by age-related degenerative changes and other artifacts *(4).*

The precision and accuracy of DXA are the key issues when interpreting BMD measurements in

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clinical practice. The annual BMD loss in most postmenopausal women varies from 0.5% to 2%, and the increase in BMD following currently available antiresorptive drugs is only around 1–6% in 3 yr *(5)*. Hence the precision of DXA should be sufficiently low to detect these modest BMD changes seen when monitoring patients.

For accurate estimation of BMD, the axis of the femoral neck should be maintained parallel to the couch and perpendicular to the X-ray beam while scanning, and DXA manufacturers provide different types of positioning aids to achieve this objective. When cadaveric specimens were used, the minimum BMD in the femoral neck was recorded when the femoral neck was parallel to the couch and gradual increase in BMD occurred when the femur was rotated either internally or externally *(6)*. In another study, anteversion of femur by 19.3° from the neutral position was associated with a significant 2.8% increase in femoral neck BMD *(7)*. Girard et al. also found a significant change in femoral neck BMD when the leg was rotated 10–15° from its original position *(8)*.

Most of these studies have used cadaveric specimens and devices for accurate estimation of the degree of neck rotation *(6–8),* which is largely unknown when scanning patients in a clinical setup. Only limited data are available about the effect of leg rotation on hip BMD in living subjects *(9)*. This study examines the effect of leg rotation by 10° either internally or externally on hip BMD in a group of 50 female volunteers recruited from the community.

Materials and Methods

This study was done on 50 female volunteers, who were participating in a large community-based osteoporosis study conducted in Southern Sri Lanka. A pretested questionnaire was used to gather information on current and previous diseases and medications. This was followed by a detailed physical examination. Subjects with history or clinical evidence of diseases that can affect bone metabolism were excluded from the study. Women who had taken drugs that affect bone metabolism were also excluded from the study.

All subjects had their left hip scanned using a Norland Eclipse XR (Norland Corp., Fort Atkinson, USA) scanner. Norland provides a leg separator block to be kept between the patient's heels and a femoral rotating fixture to rotate the leg at the upper thigh level using two Velcro straps. Subjects were first scanned in the routine position (the customary position) using these positioning aids and adhering strictly to the instructions given in the operator's guide. The scan picture obtained in the customary position was accepted regardless of the degree of hip rotation and analyzed to obtain BMD, bone mineral content (BMC), and surface area of the regions of interest (ROI). In order to minimize the variation in the positioning of ROI in the proximal femur, the operator identified the center of the femoral neck the same way in all scans. The degree of leg rotation in the customary position was noted on a scaled arc using the inner border of the foot as the guide. Two further scans were done following rotation of the leg internally by 10° (the internal rotation) and then externally by 10° (the external rotation) from the customary position. In all three positions, the leg was supported manually to maintain the adjusted position during scanning.

Ethical approval for the study was obtained from the local ethics regulatory authority.

Statistical Analysis

Descriptive data of the cohort, BMC, BMD, and surface area values are expressed as mean and standard deviations. Paired *t*-test was used to compare the BMD, BMC, and surface area values obtained after rotations to the customary position. Percentages of patients with osteoporosis in three positions were determined and compared using Wilcoxon's Signed Ranks Test. Diagnosis of osteoporosis was made when *T*-score was found to be below –2.5 (using the Asian reference dataset provided by the manufacturer) either in the femoral neck or in the trochanter. The difference in BMD after rotation was calculated and expressed as an absolute BMD change. A significant change in BMD was defined as a change in excess of 2.77 times of the precision error at each site *(10)* (i.e., either increase or decrease of femoral neck BMD by 0.030 g/cm^2, trochanteric BMD by 0.033 g/cm^2, and Ward's area BMD by 0.096 g/cm^2). The precisian errors of the machine estimated earlier were

Table 1
BMD, BMC, and Surface Area Values in Hip Regions in Three Different Positions

Description	Mean (range)	SD
Femoral neck BMD		
In customary position (g/cm^2)	0.713 (0.429–0.977)	0.123
After internal rotation (g/cm^2)	0.704 (0.427–0.963)	0.120
After external rotation (g/cm^2)	0.717 (0.418–0.962)	0.128
Femoral neck BMC		
In customary position (g)	3.068 (1.583–4.630)	0.650
After internal rotation (g)	3.001 (1.428–4.486)	0.628
After external rotation (g)	3.145 (1.481–4.087)	0.666
Femoral neck area		
In customary position (cm^2)	4.32 (2.82–5.26)	0.55
After internal rotation (cm^2)	4.28 (2.80–5.24)	0.55
After external rotation (cm^2)	4.49 (2.81–7.28)	0.76
Trochanteric BMD		
In customary position (g/cm^2)	0.583 (0.336–0.754)	0.099
After internal rotation (g/cm^2)	0.578 (0.353–0.751)	0.097
After external rotation (g/cm^2)	0.586 (0.361–0.767)	0.099
Trochanteric BMC		
In customary position (g)	5.676 (3.111–7.948)	1.238
After internal rotation (g)	5.800 (3.225–8.213)	1.210
After external rotation (g)	5.438 (2.397–7.745)	1.311
Trochanteric area		
In customary position (cm^2)	9.63 (5.58–11.69)	1.30
After internal rotation (cm^2)	9.94 (6.19–12.23)	1.15
After external rotation (cm^2)	9.17 (5.59–11.72)	1.44
Ward's area BMD and BMC[a]		
In customary position (g/cm^2 or g)	0.518 (0.230–0.830)	0.131
After internal rotation (g/cm^2 or g)	0.512 (0.244–0.761)	0.124
After external rotation (g/cm^2 or g)	0.554 (0.255–0.860)	0.138

[a] In Ward's triangle the surface area is 1 cm^2 and it remains constant in all positions. Hence BMD and BMC have similar values.

0.011, 0.012, and 0.035 g/cm^2 for the femoral neck, trochanter, and Ward's area, respectively.

Results

Mean age of the 50 women in the study was 54.9 (SD = 11.1) yr. Mean weight and height of the subjects were 50 (SD = 10.2) kg and 1.49 (SD = 0.06) m, respectively. The positions of the leg measured as an angle from the surface of the couch to the inner border of the foot were 70.4 (SD = 5.4), 60.4 (SD = 5.4), and 80.4 (SD = 5.3) degrees in the customary position, after external and internal rotations, respectively.

Table 1 shows the mean BMD, BMC, and surface area values in the femoral neck and trochanter in the customary position, after internal and external rotations. Since the surface area of the Ward's triangle remains constant (1 cm^2) in all three positions, both BMD and BMC have the same values and are given together.

Table 2 shows the differences in mean BMD, BMC, and surface area values in hip regions following rotations. The external rotation increased BMD in all three sites, while reduction of BMD was seen after the internal rotation. Significant differences were observed in the femoral neck and trochanteric area

Table 2
Differences in Mean BMD, BMC, and Surface Area in Three Regions After Internal and External Rotations

Comparison	Mean difference	SD	*p*-Value
Femoral neck BMD			
Customary–external rotation	0.005 g/cm^2	0.021	0.119
Customary–internal rotation	–0.009 g/cm^2	0.015	<0.001
Femoral neck BMC			
Customary–external rotation	0.077 g	0.155	0.001
Customary–internal rotation	–0.067 g	0.109	<0.001
Femoral neck area			
Customary–external rotation	0.169 cm^2	0.467	0.012
Customary–internal rotation	–0.044 cm^2	0.105	0.003
Trochanteric BMD			
Customary–external rotation	0.003 g/cm^2	0.021	0.309
Customary–internal rotation	–0.005 g/cm^2	0.013	0.008
Trochanteric BMC			
Customary–external rotation	–0.238 g	0.408	<0.001
Customary–internal rotation	0.124 g	0.267	0.002
Trochanteric area			
Customary–external rotation	–0.465 cm^2	0.760	<0.001
Customary–internal rotation	0.304 cm^2	0.406	<0.001
Ward's area BMD and BMC[a]			
Customary–external rotation	0.036 g/cm^2	0.048	<0.001
Customary–internal rotation	–0.006 g/cm^2	0.043	0.320

[a] In Ward's triangle the surface area is 1 cm^2 and it remains constant in all positions. Hence BMD and BMC have similar values.

after the internal rotation and also in Ward's area after the external rotation.

The external rotation increased BMC in the femoral neck and Ward's area significantly. The internal rotation reduced BMC in these two sites and only the difference in the femoral neck was statistically significant. In the trochanter, BMC decreased after the external rotation and increased after the internal rotation, and both differences were statistically significant.

In the femoral neck, surface area increased after the external rotation and decreased after the internal rotation. In the trochanter, changes in the surface area following rotations were in opposite directions to those observed in the femoral neck. In the trochanter, surface area decreased after the external rotation and increased after the internal rotation.

Nine subjects (18%) were found to have osteoporosis when the hip was scanned in the customary position, and this number remained same after the external rotation. Only seven subjects (14%) were noted to have osteoporosis after the internal rotation. These differences were not statistically significant.

A significant change in femoral neck BMD was found in six (12%) subjects after the internal rotation and in four subjects (8%) after the external rotation. The number of subjects with a significant change in trochanteric and Ward's area BMD after the internal rotation were one (2%) and two (4%), respectively. After the external rotation, the number of women with a significant BMD change in the trochanteric and Ward's area were two (4%) and four (8%), respectively.

Discussion

This study once again highlights the importance of proper positioning of the hip during DXA scan-

ning. According to our results, the effect of malpositioning of the hip during DXA scanning would be more relevant in longitudinal patient monitoring than in cross-sectional BMD analysis.

Previous studies demonstrated an increase in the femoral neck BMD with either internal or external rotation *(6).* However, in our study, mean BMDs in all three hip regions increased after the external rotation and decreased after the internal rotation. Previous studies examining the effect of leg rotation on BMD have used cadaveric specimens and devices such as CT images for accurate positioning of the femoral neck while scanning *(6–8).* Although manufacturers provide positioning aids to maintain the axis of the femoral neck perpendicular to the X-ray beam while scanning, whether this can be achieved in all subjects is questionable. It is unlikely that all subjects had their femoral neck positioned in the ideal way when they were scanned first in the customary position in our study. Increase in BMDs following rotation would have occurred in subjects who had correct positioning of the femoral neck initially, whereas in others, who had rotated femoral neck to begin with, decrease of BMD would have occurred when the neck assumed the correct position after rotation. Change in BMD in different directions could be partly due to variation in acquiring the ideal position in the initial scanning.

When measured repeatedly, change in areal BMD at a particular site can be a result of several reasons. Differences in BMC, surface area in the ROI, or both can change the areal BMD. When measuring BMD in the proximal femur, Norland systems maintain a constant surface area (1 cm^2) for Ward's triangle but not for the other two sites. In our analysis, BMD and BMC changes in Ward's area were similar in both direction and magnitude, indicating that change in BMD in this site was due purely to change in BMC. The same cannot be said about the other two sites, where the surface areas of the ROIs were not kept constant on repeated measurements. In the femoral neck, although the changes in both BMC and surface area were in the same direction, they were of different magnitudes. With the external rotation, femoral neck BMC increased by an average of 2.6% ($p = 0.001$) while surface area increased by 3.8% ($p = 0.012$), and the resultant change in BMD was only marginal ($p = 0.119$). With the internal rotation, femoral neck BMC and surface area decreased by 2.1% ($p < 0.001$) and 1.0% ($p = 0.003$), respectively, and these disproportionate changes finally contributed to a significant decline in femoral neck BMD ($p < 0.001$) with the internal rotation.

After the external rotation, trochanteric BMC and the surface area declined by 4.2% ($p < 0.001$) and 4.8% ($p < 0.001$), respectively, and no appreciable change in BMD occurred at this site ($p = 0.309$). However, with the internal rotation, trochanteric BMC increased by 2.7% ($p = 0.002$) while the surface area increased by 3.5% ($p < 0.001$), resulting in a significant decline in BMD ($p = 0.008$).

The BMD changes after the internal and external rotations showed normal distributions in all three areas. Therefore the real magnitude of the BMD change with rotation is not reflected in the mean differences. A significant change in the femoral neck BMD was seen in 12% of subjects after the internal rotation and in 8% after the external rotation. This indicates that internal rotation of the leg by merely 10° between the first and the second scan can bring about significant BMD changes in 12% of subjects. This degree of variation in patient positioning is possible in a clinical setup with high patient turnover and can be a potential confounding factor when serial measurements are taken to monitor BMD trends with or without interventions. Although not large, the greatest effect of this technical error was seen in the femoral neck, which is a key site in monitoring treatment efficacy *(2).* Effect of leg rotation was less pronounced in the trochanteric and Ward's area in our study. Less change in the trochanteric area following leg rotation was noted in previous studies too, and this appears to be a better site to monitor serial BMD changes *(6,7).*

The significant change of BMD in our study was defined as an increase or decrease of BMD greater than 2.77 times the precision error of the particular site. This was based on the least significant change (LSC), which shows the magnitude of the BMD change required to indicate a real biological difference at a particular skeletal site provided the precision error of the site and the level of statistical confidence required are known *(10).* If one scan was done at the baseline and repeated during follow-up, a change of BMD of more than 2.77 times precision

error would mean a real change at 95% confidence level for a site that has a precision error of 1.0. Although the proportion of subjects who showed a BMD change of this magnitude in our study was relatively small, this should be remembered when interpreting serial scan results of individual patients.

According to the results of our study, the prevalence of osteoporosis based on the *T*-scores of the femoral neck and trochanter was not significantly different in three different positions. BMD in Ward's area is generally not considered in making the diagnosis of osteoporosis *(2),* and this was not included when the prevalence of osteoporosis was determined. Our data suggest that leg rotation by this degree has no major effect on the prevalence of osteoporosis when cross-sectional BMD measurements are analyzed.

In summery, correct positioning of the hip during DXA scanning is vital. Rotation of the hip is a potential confounding factor when serial BMD measurements are taken in a single subject, either to monitor response to treatment or to determine the rate of bone loss over a period of time. Attempts must be made to adhere to the manufacturer's hip positioning protocol, which can minimize the variation between repeated scans. When serial BMD measurements are taken, attempts must be made to acquire similar hip positioning and to define ROIs in similar way in all scans. Part of the lesser trochanter, which is a posterior structure, becomes visible when the hip is rotated, and this can be used to judge adequate rotation of the hip prior to scanning. Further, previous scan images can be recalled and compared with the current scan image to minimize variations in hip rotation and defining regions of interests.

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Chapter 4

Structural properties of the hip and the relation with bone mineral density

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ORIGINAL ARTICLE

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Age-related trends in hip geometry in Sri Lankan women: a cross-sectional study

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Abstract Indices of hip geometry are known to be predictive of hip fractures while sex and ethnic differences in hip geometry have been previously demonstrated. Age-related trends in hip geometry among Asians, however, have not been studied sufficiently. A total of 280 healthy, perimenopausal women, aged between 32 and 97 years, were selected from the Community Study Area of the Faculty of Medicine, Galle, Sri Lanka. Hip DXA images were analyzed further to calculate the hip axis length, neck-shaft angle, and femoral neck width at the narrowest point of the femoral neck. Standard formulae were used to calculate cross-sectional area, cross-sectional moment of inertia, and section modulus in the femoral neck region. Mean (SD) age, weight, height, femoral neck bone mineral density (BMD), hip axis length, neck-shaft angle, neck width, cross-sectional area, and cross-sectional moment of inertia of the study sample were 56.8 (13.0) years, 47.8 (10.1) kg, 1.48 (0.06) m, 0.704 (0.147) g/cm^2, 90.6 (5.6) mm, 123.2 (5.7)°, 2.99 (0.24) cm, 2.00 (0.42) cm^2, and 1.62 (0.47) cm^4, respectively. Height and weight of subjects had positive correlations with most of the indices of hip geometry. Femoral neck BMD, cross-sectional area and section modulus showed a rapid reduction during the postmenopausal period. With advancing age, there was a marginal but statistically nonsignificant expansion of the neck width, increase in the hip axis length, and narrowing of the neck-shaft angle. In conclusion, this study demonstrated a gradual loss of BMD in postmenopausal age, accompanied by thinning of the cortical shell and deterioration of the resistance to bending in the femoral neck of this group of healthy women. The clinical relevance of the marginal changes seen in other indices such as neck-shaft angle, hip axis length, and neck width is not known.

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Introduction

Although bone mineral density (BMD) is widely used in assessing the future risk of hip fracture [1–3], there is a wide overlap of BMD between subjects with and without hip fractures [4,5]. Previous studies have shown certain indices of hip geometry, such as hip axis length, to be predictive of hip fractures [6–8]. Further, indices of hip geometry when considered in combination with age and body proportions improved the sensitivity of BMD in predicting hip fractures [9,10].

Indices of hip geometry vary in different communities, and these variations may partly explain the geographical and ethnic differences in the hip fracture incidence [11,12]. When compared with white women, black women had higher BMD, cross-sectional area, mean cortical thickness, and section modulus both at the femoral neck and the proximal shaft of the femur [13], and these differences may explain the difference in the hip fracture incidence observed in these two populations.

Compared with Europeans, Asians have a low incidence of hip fracture, and what factors protect Asians from hip fracture are not entirely clear. The relatively low incidence of femoral fractures among Asians may have several explanations. The differences in genetic composition, environmental influences, physical activity, and state of nutrition may have a role to play in determining fracture occurrence. Further, Asians in their postmenopausal age may have more favorable structural adaptations in long bones than white women, and hence retain bone integrity in old age [12,14]. Studies on age-related changes in hip geometry among Asians are limited. This study was done to assess the age-related trends in geometry of the femoral neck in a group of randomly selected, community-dwelling women in Southern Sri Lanka.

Materials and methods

Study population

Female volunteers numbering 370, above 20 years of age, were selected using the latest voter registers from the Community Study Area of the Faculty of Medicine, Galle. Houses were selected randomly using a table, and all women over the age of 20 years in the selected households were contacted through the Family Health Worker of the area. Consenting women were invited to the Center for Metabolic Bone Diseases, in the Faculty of Medicine, where present and past health was assessed using a predesigned questionnaire and a complete physical examination was done. Pregnant women and those with a history of diseases such as inflammatory arthritis, inflammatory bowel disease, chronic asthma, hyperthyroidism, Cushing syndrome, type I diabetes, and hyperparathyroidism were excluded from the study. Women who had taken drugs such as oral corticosteroids, thyroxin, vitamin D preparations, pharmacological doses of calcium, and thiazide diuretics were also excluded. Weight of the subjects was measured after emptying the urinary bladder and while wearing light garments, and height was measured without footwear. Ethical approval for the study was obtained from the local Ethical Review Committee of the Faculty of Medicine, Galle, and all participants signed a informed consent form before participation.

Bone densitometry

Bone mineral density (BMD) of the nondominant proximal femur was measured using a Norland Eclipse XR (Norland, Ft. Atkinson, WI, USA) densitometer, adhering to the recommendations of the manufacturer. Hip scan images with clearly visible femoral neck and devoid of artifacts were selected for extraction of structural properties.

Extraction of bone mass and structural properties

Hip axis length (HAL) was defined as the distance from the center of the pelvic acetabulum to the outer edge of the femoral shaft just below the greater trochanter and measured manually by drawing a line between those two points through the center of the femoral neck using the "ruler function" in the Norland software. The built-in Norland software measures the angle between the femoral neck axis and the line orthogonal to the femoral shaft and the neck shaft angle (NSA) was obtained by adding 90° to this value. Femoral neck width (FNW) was estimated by drawing a line between two subperiosteal surfaces of the femoral neck at its narrowest point which was determined visually by the observer.

Cross-sectional area of the femoral neck (CSA) was calculated as:

$$CSA = (\text{femoral neck BMD} \times \text{femorla neck width})/p_m$$

In this formula, p_m is the effective density of bone mineral in fully mineralized bone tissue ($1.05/cm^2$) [15,16].

The cross-sectional moment of inertia (CSMI – cm^4) was calculated using the following formula [15]:

$$CSMI = \pi/4[(FNW/2)^4 - p(ED/2)^4]$$

ED is the estimated endosteal diameter and p is the trabecular porosity.

$$ED = 2\sqrt{[(FNW/2)^2 - f_c(CSA/\pi)]}$$

where f_c is the assumed proportion of cortical mass in the femoral neck, taken as 0.6, and p is the cortical porosity, which is calculated by following formula [15]:

$$P = 1 - [\{(1 - f_c) \cdot CSA\} \div \pi(ED/2)^2]$$

Section modulus was calculated by correcting the CSMI for the neck width:

$$\text{Section modulus} = CSMI/NW$$

The coefficient of variation (CV) of the manually measured HAL and FNW were estimated by measuring them twice in 20 scan images, blinded to the results of the first analysis, and with a 2-week interval between analyses. CV% (calculated as SD/mean*100) for HAL and FNW were 0.8% and 1.2%, respectively.

Statistics

Mean (SD) BMD of the femoral neck and other indices of hip geometry were estimated for different age groups unadjusted and then adjusted for body weight using ANOVA. A linear regression model was fitted to examine the effect of age (as independent variable) on femoral neck BMD and indices of hip geometry (as dependent variables).

Results

Fifty-four women who have taken drugs, or gave a history of diseases that can affect their bone health, were excluded from the study. Thirty-six scan images were unsuitable for the structure analysis because of poor clarity or hazy bone margins. Age of the women in the study ranged from 32 to 97 years, with a mean of 56.8 (SD, 13) years (Table 1). Average FNW was nearly 3 cm, whereas the average HAL and NSA were 9.1 cm and 123°, respectively.

Once adjusted for age, height and weight had positive and significant correlations with most of the indices. However, weight had no significant correlations with either NW or the NSA (Table 2).

There was a sharp decline in femoral neck BMD as age progressed. Both CSA and the Section modulus, also showed changes parallel to BMD trends, indicating the deterioration of the structural properties of the femoral neck as BMD is lost leading to gradually thinning cortical shell (Fig. 1). Although there was a expansion of the neck width, the degree of expansion was not statistically signifi-

cant. Unadjusted NSA showed a gradual narrowing with aging, while adjusted HAL showed a mild degree of lengthening (Table 3).

Discussion

Results of our study showed a sharp decline in femoral neck BMD, CSA, and section modulus after 50 years. After adjusting for body measurements, there was a gradual but nonsignificant expansion of the femoral neck width with advancing age. When women in the third decade were taken as the reference group, women in the fifth decade had 8.6% reduction in BMD, and it was further reduced by 20% in the sixth decade. Although reduction of hip BMD during postmenopausal age is a universal occurrence, more rapid reduction was seen among our subjects. The reason for this rapid BMD decline was not clear. These women, selected from our community study area, had a rural and semiurban background and their living conditions, current and past, would have partly contributed to this rapid BMD decline. CSA, which measures the area of the cortical bone in the neck region, showed parallel changes with neck BMD, indicating gradual thinning of the cortical envelope with aging. These changes were accompanied by the gradual reduction of section modulus, indicating gradual reduction in resistance to bending.

Our data showed a progressive lengthening of the hip axis length and narrowing of the neck shaft angle as age advanced. Whether this was a real biological change or secondary to degenerative changes in the hip joint was not clear. In previous studies, however, longer neck length and wider neck shaft angle were associated with increased fracture risk [6,8].

Age-related BMD loss is a universal phenomenon. This loss eventually reduces the mechanical properties of the bone tissue, making the bone vulnerable to structural breakdown. Expansion of the neck would partly compensate the gradual reduction of mechanical strength by widening the outer diameter of the long bone, which prevents easy buckling under stress [16]. With rapid bone turnover during postmenopausal age, resorption of bone in the endosteal surface leads to the thinning of the cortical envelope and expansion of the medullary cavity, weakening the bone structure [17]. Gradual apposition of bone in the periosteal surface would increase the diameter of the long bones, and this would partly compensate the mechanical failure [17].

Table 1. Descriptive data of 280 women whose hip structure was analyzed

Measurement	Mean	SD
Age (years)	56.8	13.0
Weight (kg)	47.8	10.1
Height (m)	1.48	0.06
Femoral neck bone mineral density (BMD, g/cm^2)	0.704	0.147
Hip axis length (mm)	90.6	5.6
Neck shaft angle (degrees)	123.2	5.7
Neck width (cm)	2.99	0.24
Cross-sectional area (cm^2)	2.00	0.42
Cross-sectional moment of inertia (cm^4)	1.62	0.47

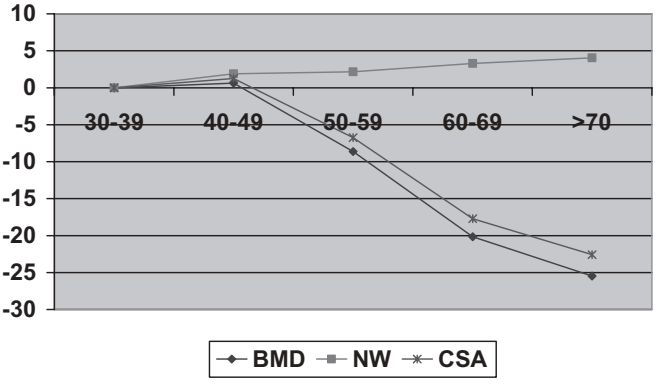

Fig. 1. Percentage changes in bone mineral density (*BMD*), neck width (*NW*), and strength-related indices in different age groups. *CSA*, cross-sectional area of the femoral neck

Table 2. Age-adjusted (partial) correlations between weight, height, BMD, and the indices of hip geometry

	BMD	NW	CSA	Height	Weight	NSA
HAL	0.04 $P = 0.47$	0.41 $P < 0.001$	0.23 $P < 0.001$	0.55 $P < 0.001$	0.27 $P < 0.001$	0.04 $P = 0.47$
BMD	—	–0.14 $P = 0.017$	0.89 $P < 0.001$	0.20 $P = 0.001$	0.57 $P < 0.001$	–0.17 $P = 0.004$
NW	—	—	0.32 $P < 0.001$	0.39 $P < 0.001$	0.05 $P = 0.32$	0.25 $P < 0.001$
CSA	—	—	—	0.36 $P < 0.001$	0.57 $P < 0.001$	–0.06 $P = 0.32$
Height	—	—	—	—	0.33 $P < 0.001$	0.20 $P = 0.001$
Weight	—	—	—	—	—	0.008 $P = 0.89$

HAL, hip axis length; NW, neck width; CSA, cross-sectional area; NSA, neck shaft angle; BMD, femoral neck bone mineral density

Table 3. The crude and weight- and height-adjusted mean (SD) values of BMD and indices of hip geometry according to age groups

	Less than 40 (n = 36)	40–49 years (n = 67)	50–59 years (n = 71)	60–69 years (n = 82)	70 and above (n = 60)	P value
Femoral neck BMD						
*	0.808 (0.111)	0.807 (0.139)	0.739 (0.104)	0.614 (0.092)	0.550 (0.088)	<0.001
*	0.789 (0.016)	0.784 (0.011)	0.720 (0.011)	0.629 (0.012)	0.587 (0.012)	<0.001
Hip axis length						
*	90.8 (5.3)	91.3 (5.6)	90.6 (5.7)	90.4 (5.6)	89.9 (5.9)	0.697
**	88.5 (0.84)	90.0 (0.59)	90.0 (0.57)	91.5 (0.54)	91.9 (0.65)	0.012
Neck shaft angle						
*	125.2 (4.59)	124.8 (5.79)	123.7 (5.13)	122.1 (5.82)	121.9 (5.92)	0.003
**	124.3 (927)	124.5 (679)	123.7 (660)	122.5 (618)	122.5 (718)	0.158
Neck width						
*	2.70 (0.21)	2.72 (0.19)	2.70 (0.18)	2.70 (0.24)	2.70 (0.20)	0.963
**	2.63 (0.033)	2.69 (0.024)	2.70 (0.023)	2.73 (0.022)	2.75 (0.026)	0.111
Cross-sectional area						
*	2.07 (0.29)	2.09 (0.37)	1.909 (0.29)	1.58 (0.27)	1.42 (0.24)	<0.001
**	1.98 (0.041)	2.01 (0.030)	1.85 (0.029)	1.63 (0.027)	1.54 (0.033)	<0.001
Section modulus	0.969 (0.172)	0.983 (0.191)	0.905 (0.167)	0.771 (0.172)	0.697 (0.139)	<0001
	0.911 (0.025)	0.940 (0.018)	0.881 (0.017)	0.803 (0.016)	0.764 (0.020)	<0001

*Crude; **weight- and height adjusted

These compensatory mechanisms can only be partly effective, and bone strength finally deteriorates, as indicated by falling section modulus [18]. Further, the widening of the femoral neck associated with aging has shown gender differences in that men showed more favorable changes than women [15]. These differences in hip geometry are believed to explain, partly, the gender differences observed in hip fracture incidence [15,17].

Compared with Caucasian women, Asian women are shown to have different hip structural properties, partly because of differences in height and weight measurements [14]. Firm conclusions, however, cannot be made as hip structure data in Asian populations are limited. In a study by Wang et al., Chinese women in young adulthood were observed to have 0.85 SD narrower femoral neck, 0.79 SD shorter femoral neck axis length, and 0.47 SD thinner cortex when compared with Caucasian women of the same age group [19].

Results comparable to ours have been noted in previous cross-sectional studies examining the age-related trends in the indices of hip geometry. In the National Health and Nutrition Examination Survey (NHANES) study, a gradual expansion of the femoral neck width was seen while BMD and cross-sectional area of the femoral neck continued to decline [16]. There was a gradual decline in strength-related indices such as the cross-sectional moment of inertia and section modulus whereas expansion of the neck partly offset the decline [16]. Similar trends were observed in our study, too.

Our study has several limitations. CSA calculated in our study represented the area of the cortical bone within the femoral neck envelope. This value was calculated assuming that the femoral neck is a circular structure and the cortical shell has an even thickness in the entire rim. Further, the hip axis length was measured from the inner surface of the acetabulum through a midline up to a point in the outer margin of the femoral shaft. This value is different from the femoral neck length measured in other methods, which exclude the hip joint, and therefore is not affected by changes in the hip joint. The neck width was measured between the two periosteal surfaces in the narrowest part of the neck, determined visually by the investigator. All measurements were done by the same investigator, and they showed an acceptable measurement precision. This study has a cross-sectional design, which has its own limitations when studying age-related changes. Also, the sample size was relatively small.

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Infant Growth Influences Proximal Femoral Geometry in Adulthood

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ABSTRACT: The relationship between early growth and adult femoral geometry has not been studied previously. In 333 adults, we were able to show that infant weight predicts femoral width and cross-sectional moment of inertia but not femoral neck length. These results support the hypothesis that growth in early life leads to persisting differences in proximal femoral geometry.

Introduction: Both femoral geometry and bone mass have been shown independently to predict both hip strength and fracture risk. Whereas growth during intrauterine and early postnatal life has been shown to influence adult bone mass, the relationship between growth in early life and adult femoral geometry has not been described previously.
Materials and Methods: We studied the relationship between growth during early life, adult hip geometry, and proximal femur bone mass in a sample of 333 men and women (60–75 years of age), for whom birth weight and weight at 1 year of age were recorded. Hip geometry was derived using Hip Structure Analysis software from proximal femur DXA scans (Hologic QDR 1000).
Results: There were significant ($p < 0.002$) relationships between weight at age 1 year and measures of femoral width as well as intertrochanteric (IT) cross-sectional moment of inertia (CSMI), but not with femoral neck length. The relationships with measures of femoral width but not CSMI remained after adjusting for adult body weight and were independent of proximal femoral BMC.
Conclusions: These results support the hypothesis that different patterns of growth in utero and during the first year of life lead to persisting differences in proximal femoral geometry, thereby mediating in part the effects of early growth on risk of hip fracture in adulthood.
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Key words: osteoporosis, programming, bone mass, epidemiology, developmental origins

INTRODUCTION

Osteoporosis is a major cause of morbidity and mortality through its association with fragility fractures. Of the estimated £1.7 billion cost each year incurred by patients with osteoporotic fractures in England and Wales, 80% are caused by hip fracture.[1] Whereas BMD is well recognized as a risk factor for hip fracture,[2] the distribution of bone mineral within the proximal femur seems to be an independent determinant of proximal femoral strength. Among measures of femoral geometry, hip axis length[3] and femoral width[4] have been shown to determine hip fracture risk. These can be used to derive the cross-sectional moment of inertia (CSMI), a biomechanical measure of the bending strength of bone.[5]

Among determinants of osteoporotic fracture, there is a growing body of evidence to suggest that poor growth during intrauterine and early postnatal life might be associated with an increased likelihood of both low bone mass[6] and fracture[7] in later adulthood. However, observed differences in bone mass attributable to poor intrauterine and infant growth do not seem to account for the documented increase in risk of hip fracture in late adulthood. We therefore used a British cohort, which included data on birth weight, growth in infancy, and adult skeletal status (the Hertfordshire Cohort Study), to test the hypothesis that poor growth during early life influences femoral geometry some seven decades later.

MATERIALS AND METHODS

We studied 333 healthy subjects (178 men and 155 women), 60–75 years of age, included in the skeletal component of the Hertfordshire Cohort Study.[8] The subjects were born and still reside in the county of Hertfordshire, UK, and are known to be representative of elderly men and women in the country, with regard to body build, cigarette smoking, and other lifestyle determinants of bone mass.

The authors state that they have no conflicts of interest.

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The birth weight and weight at 1 year of age of each individual had been recorded in a ledger by a team of midwives and health visitors who had attended each birth in Hertfordshire and had visited the child's home at intervals during the first year of life. After obtaining written permission from each person's general practitioner, we approached each subject by letter asking whether they would be willing to be contacted by one of our research nurses.

At interview, each subject completed a questionnaire including information on previous medical history, current medications, alcohol intake, cigarette smoking, physical activity, and dietary calcium intake. In addition, measurements were made of height (using a stadiometer) and weight (using calibrated electronic scales). BMD was measured in each subject by DXA at the lumbar spine and femoral neck, using a Hologic QDR 1000 instrument. Bone area, BMC, and BMD were obtained directly from the scans. Measurement precision, expressed as the CV, was 1.55% for lumbar spine BMD, 1.45% for total femur BMD, and 1.83% for femoral neck BMD.

DXA scan images were first converted into bone mass images using the automated Hip Structure Analysis (HAS) program.[5] A single operator manually placed four cursers to define the limits of the femoral neck. The software automatically demarcated the linear axes of the neck and shaft as well as three cross-sectional analysis regions: the narrowest width of the femoral neck; the intertrochanteric region; and the femoral shaft. For each of these regions, cross-sectional measurements were derived from the distribution of bone mass across the bone using the method described by Martin and Burr.[9] Reproducibility of the technique in this study was assessed in 50 replicate scans; the CV was derived for the femoral neck length (5.1%), femoral width (0.83%), and CSMI (1.7%).

Data were double entered and analyzed using STATA v 7.0. Variables with a skewed distribution were normalized by an appropriate transformation where necessary. The relationships between birth weight, weight at 1 year, and adult proximal femoral geometry were explored using linear regression. Partial correlation coefficients after adjustment for body size were tested for statistical significance. Potential confounding variables, for example, smoking, were examined using multiple regression. Early growth was further characterized by calculating sex-specific SD scores for birth weight, weight at 1 year, and infant growth conditional on birth weight.[10] This conditional infant growth SD score was free of the artefactual effects of regression to the mean and could be included in analyses simultaneously with birth weight without multicolinearity problems. Use of a conditional characterization of postnatal growth enabled the independent effects of growth in the first year of life on femoral geometry to be separated from the effects of birth weight.

RESULTS

Table 1 shows the anthropometric characteristics of the 333 subjects. Whereas men and women were of similar age and current BMI, the men were significantly taller ($p < 0.001$) and heavier ($p < 0.001$) than the women; as infants, males weighed significantly more than females at 1 year ($p < 0.001$). At the proximal femur, men had greater BMD than women ($p < 0.001$). Femoral geometry measurements also differed by sex; men had significantly ($p < 0.001$) greater femoral neck length and width than women. CSMI at the narrow neck, intertrochanteric (IT), and femoral shaft was also greater in the men ($p < 0.001$). In both men and women, current height was significantly related to neck length (men, $r = 0.28$, $p = 0.0002$; women, $r = 0.30$, $p = 0.0001$), IT width (men, $r = 0.44$, $p < 0.0001$; women, $r = 0.51$, $p < 0.0001$), and IT CSMI (men, $r = 0.46$, $p < 0.0001$; women, $r = 0.51$, $p < 0.0001$). Current height was also significantly ($p < 0.001$) associated with width and CSMI at the narrow neck and femoral shaft sites.

Table 1. Descriptive Characteristics and Proximal Femoral BMD and Geometric Measurements of 333 Adults for Whom Weight at Birth and 1 Year of Age Were Recorded

	Men (n = 178)	*Women (n = 155)*	*p*
Age (years)	66 (3.2)	66 (2.8)	0.41
Height (m)	1.7 (0.07)	1.6 (0.06)	<0.001
Weight (kg)*	78.8 (1.2)	67.9 (1.2)	<0.001
BMI (kg/m^2)*	26.5 (1.1)	26.5 (1.2)	0.88
Birth weight (kg)	3.6 (0.5)	3.5 (0.5)	0.02
Weight at 1 year (kg)	10.3 (1.2)	9.7 (1.1)	<0.001
Proximal femoral bone mass and geometry			
BMD (g/cm^2)	0.81 (0.1)	0.71 (0.1)	<0.001
Neck length (cm)	4.9 (0.6)	4.5 (0.5)	<0.001
Neck width (cm)	3.7 (0.3)	3.2 (0.2)	<0.001
Neck CSMI (mm^4)*	3.5 (1.3)	1.9 (1.2)	<0.001
IT width (cm)	6.2 (0.4)	5.5 (0.3)	<0.001
IT CSMI (mm^4)*	19.0 (1.3)	11.7 (1.3)	<0.001

Values are means (SD).
p values contrast men and women.
* Geometric mean and SD.
CSMI, cross-sectional moment of inertia; IT, intertrochanteric.

Figure 1 and Table 2 show the relationship between femoral geometry and birth weight, weight at 1 year, and conditional infant growth in men and women. In both sexes, a 1-kg increase in weight at 1 year was associated with an increase in IT width by 0.11 cm (0.25 SD of IT width in men and 0.33 SD in women). These relationships persisted even after adjusting for lifestyle determinants of BMD (exercise, dietary calcium intake, cigarette smoking, and alcohol consumption), as well as current height and weight. Weight at 1 year also predicted IT CSMI in men and women and IT cortical buckling ratio in men (Fig. 1). The association between infant weight and IT cortical buckling ratio in the women was also positive but just failed to attain statistical significance ($r = 0.14$, $p = 0.08$). Whereas the relationship between IT CSMI and weight at 1 year did not remain statistically significant after adjusting for adult weight and height, weight at 1 year predicted IT cortical buckling ratio even after adjustment for both current height ($r = 0.22$, $p = 0.008$) and weight ($r = 0.26$, $p < 0.01$). Similar positive associations were found between weight at 1 year and

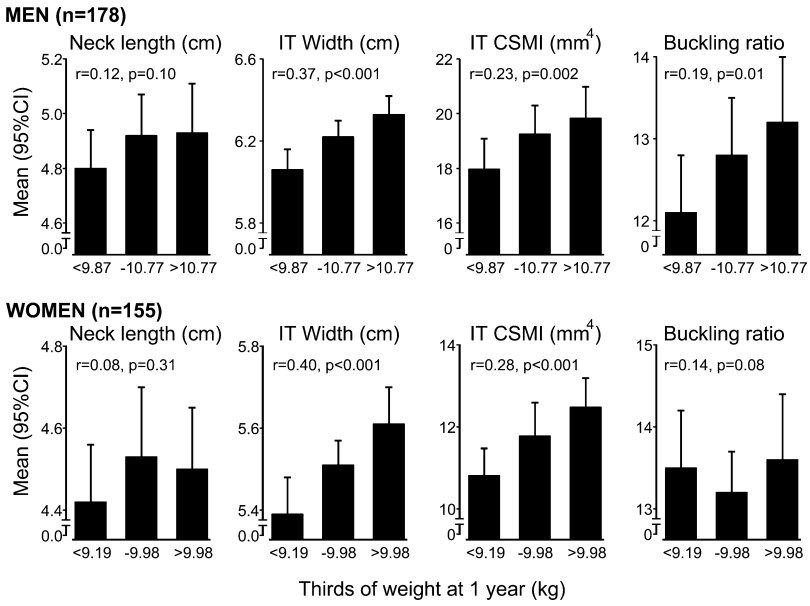

FIG. 1. Relationship between infant weight and femoral neck length, intertrochanteric (IT) width, cross-sectional moment of inertia (CSMI), and cortical buckling ratio.

TABLE 2. RELATIONSHIPS BETWEEN BIRTH WEIGHT, WEIGHT AT 1 YEAR, CONDITIONAL INFANT GROWTH, AND FEMORAL GEOMETRY

	Birth weight	*Weight at 1 year*	*Conditional infant growth*
Men			
Neck length (cm)	–0.03 ($p = 0.68$)	0.12 ($p = 0.10$)	0.14 ($p = 0.05$)
Neck width (cm)	0.15 ($p = 0.05$)	0.23 ($p = 0.002$)	0.19 ($p = 0.01$)
Neck CSMI (mm4)	0.10 ($p = 0.17$)	0.14 ($p = 0.07$)	0.10 ($p = 0.16$)
IT width (cm)	0.22 ($p = 0.003$)	0.37 ($p < 0.0001$)	0.30 ($p < 0.0001$)
IT CSMI (mm4)	0.14 ($p = 0.06$)	0.23 ($p = 0.002$)	0.19 ($p = 0.01$)
Buckling ratio	0.14 ($p = 0.06$)	0.19 ($p = 0.01$)	0.14 ($p = 0.06$)
Women			
Neck length (cm)	0.05 ($p = 0.50$)	0.08 ($p = 0.31$)	0.06 ($p = 0.44$)
Neck width (cm)	0.18 ($p = 0.03$)	0.27 ($p = 0.0007$)	0.21 ($p = 0.009$)
Neck CSMI (mm4)	0.19 ($p = 0.02$)	0.26 ($p = 0.001$)	0.19 ($p = 0.02$)
IT width (cm)	0.19 ($p = 0.02$)	0.40 ($p < 0.0001$)	0.34 ($p < 0.0001$)
IT CSMI (mm4)	0.19 ($p = 0.02$)	0.28 ($p = 0.0004$)	0.21 ($p = 0.007$)
Buckling ratio	0.02 ($p = 0.85$)	0.14 ($p = 0.08$)	0.14 ($p = 0.08$)

Values are Pearson r (p).

femoral width, CSMI, and buckling ratio at the narrow neck and femoral shaft. Weaker associations were observed between birth weight and measures of femoral width (Table 2); adult CSMI was not, however, significantly associated with birthweight (Table 2).

Weight at 1 year was also significantly ($p < 0.01$) associated with bone mass (BMC) at the proximal femur. We therefore evaluated the independent relationship between weight at 1 year, adult proximal femoral BMC, and proximal femoral geometry. The data relating each of these determinants to proximal femoral cross-sectional moment of inertia are shown in Fig. 2. Figure 2 shows that each third of weight at 1 year and proximal femoral BMC were independent predictors of adult proximal femoral CSMI ($p < 0.001$). The relationships between femoral geometry and conditional infant growth were strikingly similar to those between femoral geometry and weight at 1 year (Table 2), showing that postnatal growth was related to IT width and CSMI in men and women and buckling ratio in men, independently of size at birth.

Eighteen men and 16 women had sustained fractures after age 45 years. Twenty-eight of these 34 fractures were at the wrist, with the remainder at the shoulder, hip, and spine. Measures of proximal femoral geometry did not show significant associations with fracture history, but analyses of relationships with hip fracture were not possible because of limited statistical power.

DISCUSSION

The results of this study suggest that poor growth in infancy is associated with disproportion of the proximal femur in later adult life and a possible corresponding reduction in the mechanical strength of this region. The selective association between weight in infancy and reduced width of

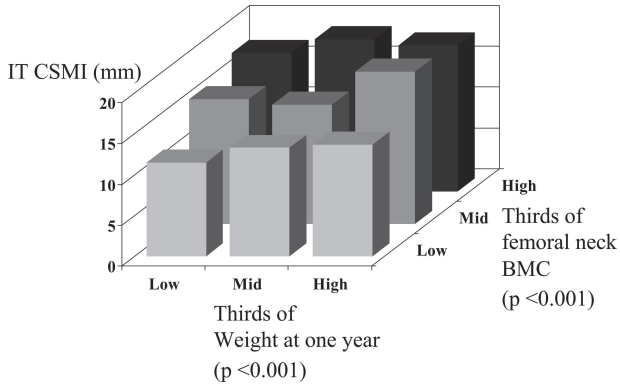

FIG. 2. Relationship between infant weight, proximal femoral bone mass, and intertrochanteric cross-sectional moment of inertia in 333 Hertfordshire men and women.

the femoral neck, with relative preservation of femoral neck length, may contribute to the previously observed relationship between poor growth in utero and during infancy, with the later risk of hip fracture.

Proximal femoral geometry is an independent determinant of hip fracture risk.[3,11] Whereas hip axis length is important in determining fracture risk, mechanical models suggest that other measures of femoral geometry, such as femoral width and cross-sectional moment of inertia, are also important contributors to strength. Hip structure analysis permits dissection between these various structural components; previous cadaveric studies have suggested that the mechanical characteristics of the proximal femur are more closely assessed by these measures than by BMD measurement alone.[5]

This study adds to the growing body of evidence for the developmental origins of osteoporosis. Programming is the term used to describe lasting changes in structure and function caused by environmental stimuli acting at critical periods during early development.[12] Several epidemiological studies have shown an association between growth in infancy and both adult bone mass[6] as well as hip fracture.[7] Mother-offspring cohort studies have delineated maternal environmental characteristics, such as nutrition, smoking, and physical activity, which alter the trajectory of mineral accrual in the fetal skeleton.[13] However, most studies to date have evaluated the influence of these early environmental characteristics on BMC rather than on femoral geometry. Our study suggests that an adverse intrauterine environment might influence fracture risk not only through reduced bone mass, but also by an alteration in proximal femoral shape and structure. The underlying mechanism for this specific effect of poor intrauterine and early postnatal growth on femoral shape is not known. Poor growth in early life may alter subperiosteal apposition at the proximal femur either during infancy or by altering the trajectory of growth in subsequent years. The timing of this effect might be determined in future studies by assessment of proximal femoral geometry during childhood and adolescence.

Our study has several limitations. These include the use of the DXA images for assessment of proximal femoral geometry. Although these images were not designed for this purpose, the hip structure analysis software has been well validated and limitations in the system described previously.[14] The degree of anteversion of the femoral neck would also alter estimation of neck length and neck shaft angle; such bias would act conservatively in our study. Furthermore, previous studies have shown that at least 15° of anteversion is required before significantly modifying proximal femoral measurements.[15] We found that the CV for femoral neck length was higher than that for femoral width and CSMI. This is because the former measurement is determined as the distance between the center of the femoral head and the intersection of the neck and shaft axes. The latter is automated, but the former is strongly dependent on the user correctly placing the circle on the head. We were unable to measure muscle strength around the hip joint in this study. Although adult grip strength, a measure of muscle strength at a distant site that is moderately well correlated with quadriceps strength, was significantly associated with femoral neck width, the relationship was no longer apparent after adjustment for adult height. Finally, the Hertfordshire Cohort Study does not include detailed information on gestational age at birth or maternal lifestyle (e.g., cigarette smoking). During the period covered by the cohort, it is likely that almost all babies were term births, and we were able to explore relationships between weight in infancy and proximal femoral geometry among subsets in the lowest and highest 10ths of the sex-specific birthweight distribution. These relationships were constant in these two subsamples, suggesting that they act across the population distribution of birth weight rather than being subject to a threshold by gestation. Although information on maternal smoking was not available, we were also able to analyze the relationships between proximal femoral geometry and smoking during adult life among women. No significant relationships were found between any of the geometric parameters and smoking status in adulthood.

In conclusion, the results of this study show that low weight in infancy is associated with reduced femoral neck width, but with relative preservation of femoral neck length. This disproportion results in reduced CSMI and might account for reduced proximal femoral strength several decades later. The association seems independent of that between poor early growth and adult bone mass; it may explain, in part, the developmental origins of hip fracture.

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Chapter 5

Body composition and chronic diseases in relation to bone mineral density

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ORIGINAL ARTICLE

Association between bone mineral density, lean mass, and fat mass among healthy middle-aged premenopausal women: a cross-sectional study in southern Sri Lanka

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Abstract Associations between lean mass, fat mass, and bone mass have been reported earlier; however, most of those studies have been done in Caucasian populations, and data from Asian countries, especially those in South Asia, are limited. We examined the associations between lean mass, fat mass, bone mineral density (BMD), and bone mineral content (BMC), determined by dual-energy X-ray absorptiometry technology, in a group of healthy, middle-aged, premenopausal female volunteers. The mean (SD) age of the women (n = 106) was 42.1 (6.1) years and the mean (SD) body mass index was 24.3 (3.6) kg/m^2. Total body BMD, total body BMC, and BMD in total spine, total hip, and femoral neck showed statistically significant partial correlations (adjusted for age) with total fat mass ($r = 0.19$–0.43, $P < 0.05$) and lean body mass ($r = 0.28$–0.54, $P < 0.05$). Truncal fat mass correlated positively with total body BMC and BMD at total hip and femoral neck ($r = 0.33$–0.40, $P < 0.001$). When a stepwise regression model was fitted, lean mass remained the strongest predictor of total body BMD, total body BMC, and total spine BMD (regression coefficients = 0.004–0.008 g/cm^2 per 1-kg change in lean mass, $P < 0.001$). Similarly, crude BMD and BMC increased across the tertiles of lean mass (P trend < 0.05). We show that lean mass is the strongest predictor of total body BMC and BMD at different sites, although positive correlations with fat mass also exist.

Keywords Lean mass · Fat mass · Bone mineral density · Premenopausal women · Sri Lanka

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Introduction

Although there are various ways to estimate body composition, dual-energy X-ray absorptiometry (DXA) is widely used in research and clinical settings [1]. DXA uses two X-ray beams of different energies; high and low, which are attenuated preferentially while passing through different body compartments. The low-energy beam is attenuated by the soft and bone tissues; the high-energy beam is attenuated only by the bone tissue. The degree of attenuation of the two beams is used to estimate bone mineral content (BMC), bone mineral density (BMD), and fat mass and lean mass. BMD and BMC, which are highly correlated with bone mass [2], are used to determine the fracture risk of an individual with low bone mass [3].

Previous studies have demonstrated significant associations between different body compartments, and some of these associations were age specific [4–7]. In young and premenopausal women, lean mass was the main predictor of BMD [4, 5], whereas in old or postmenopausal women, fat mass predicted BMD better than lean mass [6, 7]. These studies would help in understanding age-related trends in body composition in different populations. Increased fat mass and reduced bone mass have clear clinical consequences, and this information would help in

understating the comorbidity associated with osteoporosis or hyperlipidemia.

Studies on body composition among South Asian women are scarce, which may reflect the restricted availability of facilities of estimating body composition in these countries. Women in South Asia can be expected to have associations different from those already reported from Western countries as South Asian women have a different lifestyle, which is associated with a high level of physical activity, marginal nutrition, multiparity, less smoking, and low alcohol consumption. This study was conducted in southern Sri Lanka using a group of healthy, middle-aged, premenopausal volunteers to examine the associations between lean mass, fat mass, and BMD, and also to determine the strongest predictor of BMD at various sites.

Materials and methods

A group of healthy premenopausal female volunteers, aged 30 years or older and living in the neighborhood of the Faculty of Medicine, Galle, Sri Lanka, was included in the study. These volunteers responded to an open invitation displayed in public places within 1 km distance from the faculty. After a brief interview and physical examination, women with history of diabetes, hypertension, chronic renal or liver disease, hyperlipidemia, ischemic heart disease, endocrine diseases, or prolonged inflammatory conditions were excluded from the study. Women using bone-active medications such as systemic corticosteroids, heparin, vitamin D, or pharmacological doses of calcium were also excluded, and 113 women were selected for the study.

All consenting women completed a health-related questionnaire and underwent a detailed physical examination conducted at the Center for Lipid Disorders in the Faculty of Medicine, Galle, during which body measurements such as weight, height, and hip and waist circumference were recorded. All measurements were taken by the same technician, adhering to the standard protocols of defining these measurements. Weight was measured while wearing light clothes and after emptying the urinary bladder. Height was measured using a stadiometer.

A total body DXA scan was performed for all subjects using a Hologic Discovery scanner (Hologic, Bedford, MA, USA). DXA scanning was also performed over the lumbar spine and proximal femur of the nondominant side to estimate BMD in the total spine from L1 to L4 in the anteroposterior projection, total hip, and femoral neck region. The coefficient of variation of BMD measurements in the same machine has been published earlier [8].

Analytical software provided by the DXA manufacturer was used to analyze body composition. All scans were analyzed by the same technician, adhering to the guidelines provided by the manufacturer, and total body bone mineral density, total body bone mineral content, and lean body mass were estimated. Furthermore, total fat mass and the regional fat mass over the abdomen, truncal fat mass, were measured using the same analytical software. Ethical approval for the study was obtained from the local Ethics Review Committee of the Faculty of Medicine, Galle, and all participants signed a consent form at the beginning of the study.

Statistics

Descriptive data of the sample are given as mean (SD) values. Associations between lean body mass, fat mass, BMC, and BMD were examined by partial correlations, after controlling for age. The regression model was fitted with BMD or BMC as the dependent variable and body mass index (BMI), waist–hip ratio, age, lean body mass, and total fat mass as independent variables; weaker variables were excluded in stepwise fashion to find the strongest predictor of BMC or BMD at different sites. Mean BMD across the tertiles of lean body mass, which emerged as the strongest predictor of BMD in the regression model, were compared using analysis of variance (ANOVA), initially unadjusted, and then adjusted for age and BMI. Data were not adjusted for smoking habits or alcohol consumption as only five women had consumed alcohol in the past. No subjects in the study group reported smoking. Two-tailed $P < 0.05$ was taken as the level of statistical significance. The SPSS version 10 for Windows was used for all statistical analyzes.

Results

Fifteen women were excluded and 113 subjects were recruited to the study. Seven DXA images were unsuitable for body composition measurements, and data of 106 women were included in the final analysis. Age of the women in the sample ranged from 30 to 54 years, with a mean of 42.1 (SD 6.1) years. Mean (SD) BMI and waist–hip ratio (WHR) were 24.3 (3.6) kg/m^2 and 0.87 (0.06), respectively (Table 1). When controlled for age, both lean mass and total fat mass showed positive and significant partial correlations with total body BMC and all BMD measurements. Furthermore, truncal fat mass correlated positively with total body BMC and BMD at total hip and femoral neck (r varied from 0.33 to 0.40; $P < 0.001$) (Table 2).

In the regression analysis, lean body mass remained the strongest predictor of total body BMC, total body BMD,

and spine BMD. During this process, the model excluded the weak predictors such as age, BMI, waist–hip ratio, and total fat mass. However, BMD in the total hip and femoral neck showed less strong associations with the lean body mass, and in these sites BMI was the strongest determinant.

Independent of age, BMI, and total fat mass, a change of lean body mass by 1 kg was associated with change in total body BMD and spine BMD by 0.004 and 0.008 g/cm^2, respectively (SE 0.002; $P < 0.05$). Regression coefficients between lean body mass and BMD at proximal femur sites were relatively smaller and nonsignificant (Table 3).

When mean total body BMC and BMD were compared across the tertiles of lean body mass, the lowest BMD or BMC were seen among women in the lowest tertile of lean mass, whereas the highest BMC or BMD were seen among women in the highest tertile. When these values were corrected for age and BMI, except for the total body, total hip, and lumbar spine BMD, the pattern remained the same (Table 4).

Although fat mass showed significant partial correlations with BMC and BMD (see Table 2), in the regression analysis it did not predict BMC or BMD as strongly as lean mass. The regression model excluded weaker associations such as age, BMI, waist–hip ratio, and total fat mass in stepwise fashion while identifying the lean mass as the strongest predictor of BMD or BMC. In support of this finding, age- and BMI-adjusted BMC or BMD in the tertiles of the total fat mass were not significantly different (data not shown).

Table 1 Descriptive data of 106 women who participated in the study

Measurement	Mean	Standard deviation
Age (years)	42.1	6.1
BMI (kg/m^2)	24.3	3.6
Waist–hip ratio	0.87	0.06
Total body BMD (g/cm^2)	1.065	0.086
Total body BMC (g)	1782.6	226.9
Total fat mass (kg)	20.25	5.2
Lean body mass (kg)	36.11	5.4
Total spine BMD (g/cm^2)	0.923	0.136
Total hip BMD (g/cm^2)	0.922	0.099
Femoral neck BMD (g/cm^2)	0.764	0.097

BMI body mass index, *BMD* bone mineral density

Table 3 Regression coefficients of lean mass with BMD or BMC where lean mass was taken as the independent variable and BMD or BMC was taken as the dependent variable

	Regression coefficients[a]	Standard error	*P* value[b]
Whole-body BMD	0.004	0.002	0.013
Whole-body BMC	22.88	3.89	<0.001
Total spine BMD	0.008	0.002	0.001
Total hip BMD	0.002	0.002	0.4
Femoral neck BMD	0.004	0.002	0.056

[a] Data are adjusted for age, BMI, and truncal and total fat mass

[b] *P* values indicate statistical significance of regression coefficients

Table 2 Age-adjusted partial correlations between bone mineral density (BMD), bone mineral content (BMC), lean body mass, and total fat mass in 106 women included in the analysis

	Total body BMC	Total spine BMD	Total hip BMD	Femoral neck BMD	Total fat mass	Lean body mass	Truncal fat mass
Total body BMD	0.87 ($P < 0.001$)	0.63 ($P < 0.001$)	0.72 ($P < 0.001$)	0.68 ($P < 0.001$)	0.19 ($P = 0.047$)	0.28 ($P = 0.004$)	0.17 (0.080)
Total body BMC	–	0.61 ($P < 0.001$)	0.66 ($P < 0.001$)	0.68 ($P < 0.001$)	0.41 ($P < 0.001$)	0.54 ($P < 0.001$)	0.33 (<0.001)
Total spine BMD	–	–	0.49 ($P < 0.001$)	0.52 ($P < 0.001$)	0.21 ($P = 0.032$)	0.22 ($P = 0.02$)	0.17 (0.085)
Total hip BMD	–	–	–	0.83 ($P < 0.001$)	0.43 ($P < 0.001$)	0.37 ($P < 0.001$)	0.038 (<0.001)
Femoral neck BMD	–	–	–	–	0.43 ($P < 0.001$)	0.40 ($P < 0.001$)	0.40 (<0.001)
Total fat mass	–	–	–	–	–	0.69 ($P < 0.001$)	0.84 (<0.001)
Lean body mass							0.58 (<0.001)

Table 4 Crude and adjusted (age, BMI) mean (SD) BMC and BMDs in the tertiles of the lean body mass

	The lower third of lean mass ($n = 35$)	The middle third of lean mass ($n = 36$)	The upper third of lean mass ($n = 35$)	P^a
Age (years)	42.6 (1.03)	41.3 (1.02)	42.6 (1.03)	0.62
Lean mass (g)	31466 (601.7)	35484 (593.3)	41407 (601.7)	<0.001
TBBMD[b]	1.024 (0.014)	1.082 (0.014)	1.088 (0.014)	0.002
TBBMD[c]	1.030 (0.018)	1.086 (0.016)	1.081 (0.018)	0.054
TBBMC[b]	1628.15 (33.33)	1812.77 (32.86)	1906.13 (33.33)	<0.001
TBBMC[c]	1636.13 (42.63)	1823.48 (38.27)	1885.24 (42.65)	0.001
TSBMD[b]	0.876 (0.023)	0.943 (0.022)	0.950 (0.023)	0.04
TSBMD[c]	0.884 (0.023)	0.956 (0.021)	0.939 (0.023)	0.065
THBMD[b]	0.862 (0.015)	0.941 (0.015)	0.962 (0.015)	<0.001
THBMD[c]	0.891 (0.018)	0.952 (0.016)	0.928 (0.018)	0.039
FNBMD[b]	0.701 (0.015)	0.784 (0.015)	0.805 (0.015)	<0.001
FNBMD[c]	0.730 (0.018)	0.785 (0.016)	0.787 (0.018)	0.04

TBBMD total body BMD, *TBBMC* total body BMC, *TSBMD* total spine BMD, *THBMD* total hip BMD, *FNBMD* femoral neck BMD

[a] *P* contrasts mean differences between the three groups and estimation by analysis of variance (ANOVA)

[b] Crude values

[c] Age- and BMI-adjusted values expressed in g/cm^2

Discussion

In the current study, we observed positive and significant correlations between lean mass, fat mass, BMC, and BMD measured at various sites. Lean mass emerged as the strongest predictor of total body BMC, total body BMD, and spine BMD. The categorical analysis showed a pattern in which the highest BMC and BMD were seen among women with higher lean mass and the lowest BMC and BMD were seen among women with lower lean mass; all these associations were independent of age and BMI.

Generally, BMI is considered a surrogate of the global adiposity or total fat mass. However, both lean mass and total BMC contribute to the weight of the person, which is used in calculating BMI. Therefore, BMI partly reflects the changes in lean mass and total BMC. In our study sample, BMI was more representative of total fat mass ($r = 0.89$) than either lean mass ($r = 0.66$) or total BMC ($r = 0.66$). We believe that when results were adjusted for BMI, it actually tested the effect of total fat mass on the analysis. In support of this, we did not see a change in the results when the categorical analysis was adjusted for the total fat mass.

A similar association between BMD and lean mass has been demonstrated among young or premenopausal women [4, 5], and it has been observed among healthy women [4–7] as well as in women with rheumatoid arthritis [9]. In contrast, fat mass showed a stronger association with BMD in postmenopausal or older women [6, 7].

Although current literature demonstrates an association between lean mass and BMD or BMC, especially among young women, the exact mechanism underlying this association is not clear. The role of insulin-like growth factors and circulating adiponectin has been discussed [10, 11]. Physical activity appears to be the most plausible link between these measures. Physical activity has a positive influence on both BMD and lean mass [12, 13]. Compared to less physically active women, women who were more active had a stronger association between lean mass and BMD [14]. Less physical activity in old age may disrupt this association, allowing the fat mass to be the main predictor of bone density in postmenopausal women. If physical activity is the underlying mechanism between lean mass and bone density, the association can be expected to be more prominent among males. However, studies involving men are limited [15].

In our data collection, we had categorized our subjects as "very active," "moderately active," or "less active" depending on their current physical activities. Most of the women (80 subjects) were found to be in the "moderately active" group, and the data did not change materially when adjusted for their physical activity. This, we believe, is the result of inadequacy of recording the physical activity of our subjects.

Aromatization of estrogen precursors in the peripheral adipose tissue and skin is the main source of estrogen in postmenopausal women. The concentration of circulating estrogens in postmenopausal women increases according to body weight and age [16]. Common biallelic polymorphism of the aromatase gene was found to be associated with significant differences in bone mass and fracture occurrence [17]. Therefore, women with higher fat mass are likely to have higher circulating estrogen levels and

higher BMD. This mechanism may explain the association between BMD and fat mass in postmenopausal women.

The role of vitamin D in the association between lean mass and BMD should be examined. Although association between serum vitamin D level and BMD or fracture occurrence is well established [18], it is also known that vitamin D polymorphism is associated with strength of major skeletal muscles such as the quadriceps and hamstrings in premenopausal women [19]. Hypovitaminosis D leading to low BMD and low lean mass is a possible link between these two measures. Vitamin D deficiency or insufficiency is prevalent in many countries in Europe as well as in Asia [18].

The link between lean body mass and BMD has several clinical applications. When low BMD is associated with low muscle mass, the risk of facture is relatively higher as sarcopenia would increase the risk of falls. This association has been shown in epidemiological studies where low BMI appeared as a risk factor for fractures, and low BMI in these patients may represent the combination of low bone and muscle mass [20]. As BMD and lean mass are positively related, interventions meant to improve muscle mass would simultaneously improve BMD. The association between physical activities and fractures has been shown previously [21]. Various forms of forces, such as torsion and traction, applied by muscles during physical activities would facilitate the accumulation of bone materials under the periosteum, leading to increased cortical thickness. Bradney et al. [22] found more cortical thickness and increased section modulus in the proximal femur in growing subjects allocated to moderate exercise program.

In our study, a change of 1 kg in lean mass was associated with a change of 0.004–0.008 g/cm^2 in BMD in different sites. An increase of lean mass by 5 kg would result in a 0.04 g/cm^2 increase in total spine BMD, which would represent a 4.3% difference when expressed as a percentage of the mean total spine BMD of the sample. Further, this would approximate to one-third of the SD of lumbar spine BMD of the study sample. This degree of BMD difference could be clinically important. In epidemiological studies, a 1 SD decrease of lumbar spine BMD doubled the risk of vertebral fractures [3]. In a previous analysis, although a 10% loss of bone mass in the vertebrae doubled the risk of vertebral fractures, a 10% loss of bone mass in the hip increased the risk of hip fracture by 2.5-fold [23]. Hence, the 4.3% change in spine BMD associated with a 5-kg change in lean mass would be clinically relevant.

The current study has a few limitations. Our sample size was relatively small, and selection bias could have occurred at the time of recruitment. Most of the women belonged to the working class, engaged in sedentary office work, and would not represent the normal community. This factor was evident in our results, as they mostly belonged to the "moderately physically active" category. We had no detailed estimation of their current and past activities to adjust our data for physical activities.

In summary, results of our study showed a positive correlation between lean mass, fat mass, and bone mass in these healthy, middle-aged, premenopausal female volunteers. Of all the measurements examined, lean mass was the strongest predictor of BMD or BMC, and this association was independent of age and BMI. Physical activity and vitamin D status appear to be the most plausible explanations of this association. This finding is clinically relevant as women with low BMD would have an added risk of fracture because of associated sarcopenia leading to falls. Interventions such as physical activity may simultaneously modify both these risk factors.

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Original Article

Osteoporosis and Cardiovascular Risk Among Premenopausal Women in Sri Lanka

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Abstract

We examined the association between bone mineral density (BMD) and cardiovascular risk in a group of premenopausal women selected from the Southern province of Sri Lanka. One hundred six previously healthy premenopausal volunteers (aged 30−54 yr) were recruited by open invitations. Subjects with previous history of diabetes, hypertension, epilepsy, chronic renal or liver disease, hyperlipidemia, ischemic heart disease, endocrine diseases, or prolonged inflammatory conditions were excluded. Subjects who were taking medications that can affect bone density, blood sugar, serum lipids, or blood pressure (BP) were also excluded. Women with the history of previous fractures were not excluded. BMDs in the spine, hip, and total body (TB) were measured using a Hologic Discovery scanner (Hologic Inc, Bedford, MA). BP, fasting glucose, and fasting lipids were also measured. Independent of body mass index (BMI) and age, TB bone mineral content (BMC) and spine BMD showed inverse and significant correlations with total cholesterol (TC), low density cholesterol, and the ratio between TC and high density lipoprotein cholesterol (r ranged from -0.24 to -0.27, $p < 0.05$ for all). The highest mean lipid levels were seen among the women in the lowest third of spine BMD, whereas women in the upper third of spine BMD had the lowest lipid levels. The number of women with metabolic syndrome in the 3 tirtiles of spine BMD was not significantly different. Fasting glucose or BP had no association with either BMD or BMC. In conclusion, our data demonstrates an association, independent of age and BMI, between BMD and BMC or lipid levels among previously healthy, premenopausal women. This may explain the high cardiovascular risk seen in women with osteoporosis in old age.

Key Words: Blood pressure; fasting glucose; lipids; osteoporosis; Sri Lanka.

Introduction

Epidemiological studies have shown a high occurrence of acute myocardial infarctions among patients with osteoporosis, suggesting a possible link between the 2 major noncommunicable diseases affecting women *(1)*. An inverse association between bone mineral density (BMD) and calcification of aorta, which is a surrogate marker of cardiovascular disease, has also been documented *(2,3)*. Among postmenopausal women, an association has been seen between BMD and serum lipids, in which, women with low BMD had a lipid profile that promotes atherosclerosis *(4,5)*. This association, however, was not consistently seen in other studies *(6,7)*. In 1999, Cappuccio et al, found an inverse association between femoral neck BMD and diastolic blood pressure (DBP) among postmenopausal women and this association was independent of age, body measurements, and other confounders *(8)*.

The clinical consequences of low BMD and high lipids are well established. Although BMD shows a continuous association with the risk of osteoporosis-related fractures in postmenopausal women *(9)*, a similar relationship is observed between

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cardiovascular disease and elevated total cholesterol (TC) or low density lipoprotein (LDL) cholesterol levels *(10,11)*.

Most of the studies examining the association between bone health and cardiovascular health have used postmenopausal female populations who have a relatively higher risk for both osteoporosis and cardiovascular diseases when compared with premenopausal women. The association between osteoporosis and cardiovascular diseases among premenopausal women has not been well documented. Although data from older women would help clinicians to recognize the cardiovascular risk among women with osteoporosis, and vice versa, data from younger patients would help to identify the origin of this association. Furthermore, most of the studies have been done in Caucasian populations and data from South Asian populations are limited.

The current study was performed in a group of previously healthy, middle-aged, premenopausal women selected from the Southern province of Sri Lanka to study the association between BMD and conventional cardiovascular risk factors—serum lipids, fasting blood sugar, and BP.

Materials and Methods

Previously healthy, premenopausal women, aged 30 or more, were invited to participate in a research related to bone and cardiovascular health conducted by the Center for Metabolic Bone Diseases in Galle, Sri Lanka. Open invitations were sent to the nearby institutions and they included a government primary school, 2 hospitals, and a university. Posters were also displayed in public places, such as bus stops and religious places inviting middle-aged healthy female volunteers for the study. All volunteers who responded to our invitation (n = 163) had a brief interview and a physical examination and women with the history of diabetes, hypertension, epilepsy, chronic renal or liver disease, hyperlipidemia, ischemic heart disease, endocrine diseases, or prolonged inflammatory conditions were excluded. Women who had taken drugs, such as systemic corticosteroids, heparin, vitamin D, antiresoptives, lipid-lowering therapy, hypoglycemic agents, antihypertensives, hormonal contraceptives, or pharmacological doses of calcium were also excluded (total number of exclusions = 46). Although women younger than 30 yr (n = 4) were excluded from the study, those who had previous traumatic fractures (n = 8) were not excluded. Further, 7 subjects had no lipid reports and finally 106 women were selected for the study.

All women included in the study signed an informed consent form, filled a health-related questionnaire, and underwent a detailed physical examination during which 2 mL of venous whole blood was collected with a minimum of 12 h overnight fasting. Weight was measured while wearing light cloths and after emptying the urinary bladder. Height was measured without footware using a stadiometer (Nagata, Tainan, Taiwan). All body measurements were taken by one technician, adhering to the standard protocols of defining these measurements. After 15 min of resting, systolic BP (SBP) and DBP were measured, twice, with 15-min interval between the measurements and average BPs were considered for the analysis.

Serum TC, high density lipoprotein (HDL), triglyceride (TG), and plasma glucose concentrations were measured using Humalyzer 2000 (Wiesbaden Human, Germany). Concentration of LDL was calculated using the Friedewald formula. None of the subjects had TG level that would make the application of this formula invalid.

All subjects had total body (TB) dual-energy X-ray absorptiometry (DXA) performed using Hologic Discovery scanner (Hologic Inc, Bedford, MA) to measure TBBMD and TB bone mineral content (TBBMC). DXA was also performed over the lumber spine and left proximal femur to measure total spine BMD (TSBMD) from L1 to L4 in the anteroposterior projection, total hip BMD (THBMD), and femoral neck BMD (FNBMD). All scans were performed and analyzed by one technician. Precision errors of BMD estimations in the same machine were checked by measuring 30 postmenopausal women, twice on the same day, with repositioning between scans and found to be 0.008, 0.001, and 0.002 g/cm^2 for the TS, FN, and TH, respectively *(12)*. Ethical approval for the study was obtained from the local Ethics Review Committee of the Faculty of Medicine, Galle.

Statistical Analyses

The characteristics of the 106 women included in the analysis are given as mean and standard deviation (SD) (Table 1). Correlations between age, body mass index (BMI), BMDs, lipid levels, BPs, and plasma glucose level were examined first and

Table 1
Descriptive Data of 106 Premenopausal Women Included in the Analysis

Measure	Mean (SD)
Age (yr)	42.0 (6.0)
Weight (kg)	57.6 (8.9)
Height (m)	1.54 (0.06)
BMI (kg/m^2)	24.4 (3.6)
Waist circumference (cm)	84.9 (9.2)
Hip circumference (cm)	96.9 (7.5)
Waist hip ratio	0.87 (0.06)
TC (mg/dL)	201.7 (32.9)
LDL cholesterol (mg/dL)	129.2 (31.5)
HDL cholesterol (mg/dL)	44.7 (6.4)
TG (mg/dL)	137.9 (33.8)
TG/HDL ratio	4.5 (0.94)
TBBMD (g/cm^2)	1.065 (0.086)
TBBMC (g)	1782.63 (226.9)
TSBMD (g/cm^2)	0.923 (0.136)
THBMD (g/cm^2)	0.922 (0.099)
FNBMD (g/cm^2)	0.764 (0.097)

Abbr: SD, standard deviation; BMI, body mass index; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglyceride; TBBMD, total body bone mineral density; BMC, bone mineral content; TBBMC, total body bone mineral content; TSBMD, total spine bone mineral density; THBMD, total hip bone mineral density; FNBMD, femoral neck bone mineral density.

partial correlations between the TBBMC, BMDs, lipids, BPs, and fasting glucose were examined after adjusting for age and BMI. Using analysis of variance (ANOVA), mean levels of lipids, blood sugar, and BPs in the thirds of the TSBMD were estimated and compared, initially unadjusted and then adjusted for age and BMI. Homogeneity of variance of the model was checked using Levene test and interactions between BMD, BMC, and indices of cardiovascular risk were also checked. TSBMD was selected for the above analysis as it showed the highest correlation with lipid levels. Women were diagnosed to have metabolic syndrome if they had waist circumference 80 cm or more and 2 other abnormalities—HDL cholesterol less than 50 mg/dL, TG more than 150 mg/dL, fasting glucose more than 100 mg/dL, or BP greater than 130/85 mm Hg. The mean TBBMC, TBBMD, and regional BMDs in women with and without metabolic syndrome were estimated and compared, using unpaired Student's *t*-test, initially unadjusted and then adjusted for age. Statistical Package For the Social Sciences (SPSS Inc., Chicago) for Windows version 10 was used for all analyses and 2-tailed p less than 0.05 was taken as the level of statistical significance.

Results

Age of the women ranged from 30 to 54 with mean (SD) of 42.0 (6.0) yr. None of the subjects had ever smoked, whereas only 5 (4.7%) women had taken alcohol previously. Ninety-three (87.7%) of them were married and the median (Interquartile range) number of children was 2 *(2,3)*. Eight (7.5%) women had suffered traumatic fractures but none had suffered fragility fractures.

Age showed no significant correlations with BMI, BMD, or lipid levels, whereas BMI showed significant correlations with spine and hip BMDs ($r = 0.31-0.41$, $p < 0.05$) but not with lipids. When adjusted for age and BMI, the TC, LDL cholesterol and the ratio between TC and HDL (TC/HDL) showed negative correlations with the TBBMC and all BMD values. Of these correlations, only the correlations seen with the TBBMC and TSBMD were statistically significant. Although not statistically significant, TG showed negative associations with BMDs and TBBMC. HDL cholesterol showed positive correlations with BMDs and TBBMC but these associations too were not statistically significant (Table 2).

When adjusted for age and BMI, fasting glucose, DBP, and SBP showed no statistically significant correlations with the TBBMC or BMDs measured at various sites.

The highest mean TC, LDL cholesterol, and TC/HDL ratio were seen among women in the lower third of TSBMD, whereas the lowest mean lipid levels were seen among women in the upper third of spinal BMD. These differences were statistically significant and were independent of age and BMI. Mean values of HDL cholesterol, TG, fasting glucose, SBP, or DBP were not statistically different in the tirtiles of the TSBMD (Tables 3 and 4).

Fifty-seven (53.8%) women in the study sample had waist circumference either equal or greater than 80 cm and 47 (44.3%) of them had 2 other criteria of metabolic syndrome—HDL less than 50 mg/dL, TG greater than 150 mg/dL, fasting glucose greater than 100 mg/dL or BP more than 130/85, and they were diagnosed to have metabolic syndrome. Independent of age, women with metabolic syndrome had lower BMC and BMD, but only the difference in the TH

Table 2
Age and BMI Adjusted Partial Correlations Between BMD, BMC, and Lipids

Variable	TC	LDL cholesterol	TGs	HDL cholesterol	TC/HDL ratio
TBBMD	−0.13	−0.14	−0.01	0.05	−0.15
	(−0.31 to 0.06)	(−0.31 to 0.05)	(−0.20 to 0.18)	(−0.14 to 0.24)	(−0.33 to 0.04)
	$p = 0.25$	$p = 0.19$	$p = 0.95$	$p = 0.64$	$p = 0.19$
TBBMC	−0.25	−0.25	−0.12	0.08	−0.26
	(−0.43 to −0.06)	(−0.43 to −0.06)	(−0.31 to 0.07)	(−0.11 to 0.27)	(−0.43 to −0.06)
	$p = 0.03$	$p = 0.03$	$p = 0.30$	$p = 0.49$	$p = 0.02$
TSBMD	−0.26	−0.26	−0.05	0.13	−0.27
	(−0.43 to −0.06)	(−0.43 to −0.06)	(−0.24 to 0.14)	(−0.06 to 0.31)	(−0.44 to −0.08)
	$p = 0.03$	$p = 0.018$	$p = 0.64$	$p = 0.25$	$p = 0.02$
THBMD	−0.04	−0.07	0.03	0.12	−0.10
	(−0.23 to 0.15)	(−0.26 to 0.12)	(−0.16 to 0.22)	(−0.07 to 0.31)	(−0.29 to 0.09)
	$p = 0.74$	$p = 0.54$	$p = 0.78$	$p = 0.28$	$p = 0.34$
FNBMD	−0.18	−0.21	−0.06	0.14	−0.23
	(−0.37 to 0.01)	(−0.39 to −0.02)	(−0.25 to 0.13)	(−0.05 to 0.32)	(−0.41 to −0.04)
	$p = 0.11$	$p = 0.06$	$p = 0.57$	$p = 0.21$	$p = 0.05$

Abbr: BMI, body mass index; BMD, bone mineral density; BMC, bone mineral content; TC, total cholesterol; LDL, low density lipoprotein; TGs, triglycerides; HDL, high density lipoprotein; TBBMD, total body BMD; TBBMC, total body BMC; TSBMD, total spine BMD; THBMD, total hip BMD; FNBMD, femoral neck BMD.

Given in cells are r, 95% confidence intervals (within brackets) and p values examined by partial correlation, adjusted for age and BMI.

Table 3
Mean (SEM) Lipids, Fasting Blood Glucose, and BPs in the Thirds of the TSBMD of 106 Premenopausal Women

Variable	Lower third of spinal BMD	Middle third of spinal BMD	Upper third of spinal BMD	*p* Value*
TC				
Crude	210.8 (6.0)	207.8 (6.2)	188.4 (6.3)	0.026
Age and BMI adjusted	210.9 (6.1)	208.1 (6.3)	187.9 (6.6)	0.029
LDL cholesterol				
Crude	138.4 (5.8)	136.1 (6.0)	115.1 (6.1)	0.013
Age and BMI adjusted	138.8 (5.9)	135.6 (6.1)	115.3 (6.3)	0.021
HDL cholesterol				
Crude	44.5 (1.2)	43.4 (1.2)	46.0 (1.2)	0.32
Age and BMI adjusted	44.2 (1.2)	43.6 (1.2)	46.2 (1.3)	0.33
TG				
Crude	139.9 (6.5)	140.4 (6.7)	135.6 (6.8)	0.86
Age and BMI adjusted	140.9 (6.3)	143.3 (6.5)	131.4 (6.7)	0.42
TC/HDL				
Crude	4.8 (0.18)	4.8 (0.18)	4.1 (0.19)	0.021
Age and BMI adjusted	4.8 (0.18)	4.8 (0.18)	4.1 (0.19)	0.017
Fasting glucose				
Crude	83.5 (2.6)	84.8 (2.7)	83.1 (2.8)	0.90
Age and BMI adjusted	82.9 (2.7)	84.9 (2.8)	83.6 (2.9)	0.88
SBP				
Crude	109.3 (2.0)	111.3 (2.0)	112.5 (2.1)	0.53
Age and BMI adjusted	109.1 (1.8)	112.7 (1.9)	111.3 (2.0)	0.39
DBP				
Crude	72.3 (1.4)	71.9 (1.5)	75.0 (1.5)	0.29
Age and BMI adjusted	72.2 (1.3)	72.8 (1.4)	74.2 (1.4)	0.60

Abbr: SEM, the standard error of the mean; BPs, blood pressures; BMD, bone mineral density; TSBMD, total spine BMD; TC, total cholesterol; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure.

**p* Value contrasts differences in mean values in 3 columns and calculated using post-hoc analysis of variance with Bonferroni correction.

was statistically significant. Further, the percentages of women with metabolic syndrome in the lower, middle, and upper thirds of the TSBMD were 40.7%, 50%, and 38.5%, respectively, and this difference was not statically significant ($p = 0.67$).

Discussion

Osteoporosis-related fractures and cardiovascular diseases are 2 major noncommunicable diseases seen among postmenopausal women. Moreover, there is substantial mortality, morbidity, and loss of productivity associated with these diseases. Early detection and treatment are the main measures adopted by current health care systems to reduce the burden of these 2 diseases.

Results of the current study demonstrate an association between measures of bone health and lipid levels among these previously healthy, middle-aged, premenopausal females. In this analysis, TC, LDL cholesterol and TC/HDL ratio inversely and significantly correlated with the TBBMC and TSBMD. In contrast to women with high TSBMD, women with low TSBMD had high TC, LDL cholesterol, and TC/HDL ratio. Furthermore, women with metabolic syndrome had lower BMD and BMC, but only the difference observed in the TH was significantly different. Although there was an inverse correlation between TG and BMD among our subjects, the association was not statistically significant and not in keeping with previous reports *(13)*. In general, results of the current study indicate a coexistence of low bone mass and dyslipidemia in these middle-aged women.

In previous studies, women with low bone mass had high cardiovascular mortality *(1)*, calcification of aorta *(2,3)* and lipid abnormalities that would promote atherosclerosis *(4,5)*. In contrast, Adami et al and Brownbill et al, found a positive association between BMD and lipids levels where women with higher BMD had elevated lipid levels *(5,7)*. An association between BMD and BP has been observed among postmenopausal women. In one study, the group of women with low BMD and high BP had high urinary calcium excretion, suggesting a possible mechanism of this association *(8)*. We did not find an association between BP and BMD or BMC and our results are consistent with a large epidemiological study conducted

Table 4
Mean (SEM) BMC and BMD Values Among Women With and Without Metabolic Syndrome

Variable	With metabolic syndrome (n = 45)	Without metabolic syndrome (n = 34)	*p* Value*
TBBMD			
Crude	1.061 (0.013)	1.080 (0.015)	0.33
Age and BMI adjusted	1.061 (0.013)	1.078 (0.015)	0.39
TBBMC			
Crude	1782 (33)	1823 (38)	0.41
Age and BMI adjusted	1783 (33)	1820 (38)	0.47
TSBMD			
Crude	0.931 (0.017)	0.950 (0.020)	0.90
Age and BMI adjusted	0.931 (0.017)	0.935 (0.020)	0.87
THBMD			
Crude	0.905 (0.014)	0.950 (0.016)	0.036
Age and BMI adjusted	0.906 (0.014)	0.948 (0.016)	0.046
FNBMD			
Crude	0.757 (0.013)	0.785 (0.015)	0.18
Age and BMI adjusted	0.758 (0.013)	0.784 (0.015)	0.21

Abbr: SEM, the standard error of the mean; BMC, bone mineral content; BMD, bone mineral density; TBBMD, total body BMD; BMI, body mass index; TBBMC, total body BMC; TSBMD, total spine BMD; THBMD, total hip BMD; FNBMD, femoral neck BMD.

**p* Value contrasts differences in mean values in 2 columns and calculated using Student's *t*-test (unpaired) with Bonferroni correction.

using 2738 nationally representing group of women where no association between BMD and hypertension was found *(14)*. Similarly there was no significant association between blood sugar and BMD or BMC among our women and this is keeping with the data seen previously *(15)*.

Coexistence of osteoporosis and dyslipidemia has not been proven yet. Hence, current practice guidelines do not recommend routine testing of lipids in women with osteoporosis. If further studies confirm this coexistence, it can have several clinical implications. Once a woman is detected to have one abnormality, clinician will be required to search for the other and then attempt to reverse both conditions. Non-pharmacological measures such as enhanced physical activity and limiting the intake of alcohol can reverse dyslipidemia while influencing BMD positively *(16)*. Furthermore, cessation of smoking would help both conditions. Therapy with selective estrogen receptor modulators *(17)* or bisphosphonates *(18)* in postmenopausal women led to reversal of dyslipidemia. Therapy with statins in women with high lipids resulted in increasing BMD *(19)*. This indicates the existence of shared metabolic pathway in bone and lipid metabolism.

The exact mechanism involving regulation of bone mass and cardiovascular risk in humans is not known. Some observational studies have indicated that atherosclerosis could lead to local bone loss. Finding of low BMD and aortic calcification among women with intermittent claudication of legs would support this hypothesis *(2)*. Also obstructing atheromas were found in the small and large arteries supplying the hip region in women with osteoporotic hip fractures *(20,21)*.

The role of lipids, especially in oxidized form, in the causation of atherosclerosis and mineralization of vascular wall and bone tissue has been discussed. In 1999, a study involving mice, showed that minimally-oxidized LDL (MM-LDL) is capable of promoting adipogenic differentiation of marrow stromal cells while inhibiting their osteoblastic differentiation *(22)*. Parhami et al in 1997 reported that MM-LDL and other oxidized lipoproteins could promote mineralization of vascular cells while inhibiting mineralization of bone cells *(23)*. Brodeur et al (2008) demonstrated the influence of oxidized LDL in reducing the viability of osteoblasts, mediated through lysosomal membrane damage *(24)*. Bagger et al examining the role of lipids in the link between bone and cardiovascular heath were unable to find a significant association between lipids and bone health. In this observational study the presence of apolipoprotein E ε4 allele had significant impact on lipid profile but not on BMD measurements *(25)*. Osteoprotegerin, receptor activator of nuclear factor κB (RANK), and RANK-ligand, the well-established cytokinin network in bone metabolism, has been linked to cardiovascular disease. Studies have established links between this pathway and vascular calcification, advanced atherosclerosis, plaque destabilization, and heart failure indicating its role in the pathophysiology of cardiovascular disease *(26)*.

The current study has many limitations. Women participated in this study were volunteers who responded to our open invitation. As they were not selected on random basis, selection bias would have occurred. Thirty-five of them were used in sedentary type of jobs and others were mainly housewives. Although these subjects would not be representative of the normal middle-aged female population of the country, we were able to draw a sample, which had employment ratio roughly equal to the normal population of the country. Small sample size probably contributed to inconclusive results in many analyses. Although uniform patterns were seen in TG and HDL cholesterol, the differences were not statistically significant, probably, because of small sample size. It can be argued that BMD decline associated with estrogen deficiency may have already begun in perimenopausal women included in this study and this may have contributed to the results. We examined the correlations between age, BMI, BMDs, and lipids among women older than 50 yr (n = 7) and then women older than 45 yr (n = 35) and found no association between these variables. Hence this is an unlikely possibility.

In summary this study, involving a selected group of premenopausal healthy women, showed an inverse association, independent of age and BMI, between BMD and BMC or TC,

LDL cholesterol, or TC/HDL ratio. Fasting sugar, TG, HDL cholesterol, and BP were not found to have significant associations with BMD or BMC. Finding this association in premenopausal age would support the idea that association between lipids and bone health is established early in life, predisposing them to long-term complications in old age. If further studies generate similar associations, clinicians will be required to adopt a holistic approach in evaluating patients with abnormal lipids or low BMD to assess overall mortality and morbidity.

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Original Article

An Association Between Respiratory Function and Bone Mineral Density in Women from the General Community: A Cross Sectional Study

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Abstract. Respiratory function has been associated with bone mineral density (BMD) in patients with respiratory diseases. We examined the relationship between bone density measured at the hip and respiratory function in women from the general community. A total of 4830 women aged 45–76 years were recruited from general practice age – sex registers in Cambridge between 1991 and 1995. At baseline survey, data collection included health questionnaires, measures of anthropometry, respiratory function, as well as bone mineral density BMD measured using dual energy X ray absorptiometry. BMD at total hip, femoral neck and trochanter significantly and positively correlated with FEV_1. This association was independent of age, weight, height, smoking habit, history of respiratory diseases, corticosteroids and use of hormone replacement therapy. After adjustment for these factors, an increase in FEV_1 of 1 l/s was associated with 0.026, 0.021 and 0.026g/cm^2 increase in bone mineral density at total hip, femoral neck and trochanter respectively. The association was consistent and similar in magnitude among current smokers and current non-smokers and across all age groups. The magnitude of the association was comparable to that associated with an age difference of 6 years or weight difference of 5 kg. Women in the bottom compared to top quartile of respiratory function had about double the risk of low bone density independent of other factors. Respiratory function measured using FEV_1 is positively and independently related to BMD in these middle-aged and older women across the whole normal distribution of these physiologic measures. This may reflect underlying common determinants such as physical activity. Even in healthy women, respiratory function may be a marker for women at increased risk of osteoporosis and associated fractures.

Keywords: Bone density; Community; Forced expiratory volume; Osteoporosis; Respiratory function; Women

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Introduction

Osteoporosis and fragility fractures not only have considerable current medical and economic impact but are projected to increase exponentially world wide[1,2]. Bone mineral density (BMD) and fragility fractures in adults have been associated with numerous genetic, nutritional and environmental factors [3,4]. These include physical activity [5], alcohol intake [6], smoking habit [7], milk consumption [8] and parity [9] as well as early life factors such as weight and length at birth or at one year [3,4]. Some of these factors may help to explain the wide geographic variations and secular changes in bone health and fracture occurrence [10].

In clinical studies in patients with respiratory diseases such as cystic fibrosis and bronchial asthma, measures of respiratory function have correlated with bone mineral density [11,12]. In addition to compromised lung function, patients with these conditions are exposed to a variety of other factors that might impair their bone health. For example, cystic fibrosis is associated with pancreatic malabsorption and bronchial asthma is often treated with long-term corticosteroids. Conversely, in patients who have spinal osteoporotic fractures, reduced

pulmonary function is related to the severity of spinal deformity [13] where, again, there are obvious reasons for the association.

It is, therefore, not clear whether the observed association between respiratory function and BMD is simply restricted to patients with respiratory or other diseases or whether it occurs across the whole normal range of respiratory function.

In the current study we examined the relationship between respiratory function and bone mineral density in a population-based cross-sectional study of women living in the community.

Methods

The Cambridge General Practice Health Study invited women aged 45–76 years, resident in the community and identified using general practice age-sex registers, to participate in a health survey between 1991 and 1995. About 50% of those mailed agreed to participate. All those consenting completed a health and lifestyle questionnaire, which included questions on past medical history and social habits. They then attended for a health examination at Addenbrooke's Hospital, Cambridge.

At the health examination, height and weight was measured in light clothing without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Bone mineral density was measured at the total hip, femoral neck and trochanter by dual energy X-ray absorptiometry (DEXA), using the Hologic QDR –1000 densitometer (Hologic Inc., Waltham, MA, USA). The coefficient of variation for hip BMD measurement was 1.6% for femoral neck, 1.5% for trochanter and 3.0% for Ward's triangle [14]. In these analyses, results for total hip, femoral neck and trochanteric area are presented. Current smokers were defined as those who reported 'Yes' to the question 'Do you smoke cigarettes now?' Steroid users were defined as those who reported 'Yes' to the question 'Have you ever taken steroid tablets or injections for three months or more?' Women taking hormone replacement therapy (HRT) were defined as those who reported 'Yes' to the question 'Are you currently receiving any hormone replacement therapy (HRT)?'

Respiratory function was assessed by forced expiratory volume in 1 second, FEV_1, which was measured twice using a portable spirometer (Micromedical, UK) [15]. The higher reading of the two measurements was used in the analyses. Pulse rate was assessed as the average of two readings after the participant had been sitting resting for five minutes.

Statistical Analyses

Women were divided into quartiles according to respiratory function. Descriptive data are expressed as mean (SD) or percentages (number) in FEV_1 quartiles. Differences in BMD between FEV_1 quartiles were compared unadjusted and then adjusted for possible covariates using analysis of variance (ANOVA). Since FEV_1 and BMD are related to weight and height in different ways, we used weight and height independently in the models rather than the BMI. However, using BMI in place of height and weight in the analytical model did not change the salient findings. A linear regression model was fitted with BMD as the dependent variable and FEV_1 as independent variable with and without other covariates in the model. This analysis was repeated in women who had no previous history of respiratory (chronic obstructive airways disease or asthma), cardiovascular disease or cancer and had not taken steroids or hormone replacement therapy.

We arbitrarily defined low bone density as women in the bottom quintile of the bone density distribution (bottom quintile threshold points for total hip were $<=0.771$ g/cm^2 (estimated *T*-score -1.70), neck $<=0.634$ g/cm^2 and trochanter $<=0.570$ g/cm^2). We examined the prevalence of women with low bone density by quartile of respiratory function in the whole cohort and after excluding all women taking steroids, HRT or current smokers. Data were analyzed using SPSS software, version 10.0 for Windows. All significance tests were two sided.

Results

Descriptive Data

The baseline characteristics for 4830 women aged 45–76 years according to quartile of FEV_1 are shown in Table 1. Compared to the highest quartile of FEV_1, women in the lowest quartile were older, shorter and had lower bone mineral density. They were more likely to have taken steroids and report past history of respiratory disease, cardiovascular disease or cancer. Women in the lowest quartile were less likely to be current users of HRT compared to those in the highest quartile.

Association between BMD and FEV_1

Bone mineral density was continuously related with FEV_1, with mean bone mineral density increasing with increasing quartile of FEV_1 (Table 2). This association was apparent in all three sites, and remained significant after adjusting for age, weight, height, current smoking, and past history of disease, HRT and steroid use.

Table 3 shows the relationship between BMD and FEV_1 as continuous variables using multiple regression adjusted for age, weight, height, current smoking, current HRT, steroid use, past history of respiratory disease, cardiovascular disease or cancer.

We also analyzed the relationship in subgroups stratified by age (45–54 years, *n*=2047; 55–64 years, *n*=1588; and 65+ years, *n*=1195) adjusting for weight and height and stratified by smoking status (623 current

Table 1. Characteristics of 4830 women aged 45–76 years according to FEV_1 quartiles in the Cambridge General Practice Study

	Quartile 1 (0.51–1.98 l/s) *n*=1216 Mean (SD)	Quartile 2 (1.99–2.32 l/s) *n*=1167 Mean (SD)	Quartile 3 (2.33–2.67 l/s) *n*=1232 Mean (SD)	Quartile 4 (2.68–4.11 l/s) *n*=1215 Mean (SD)	Unadjusted *p* value
FEV_1	1.7 (0.28)	2.2 (0.10)	2.5 (0.10)	2.9 (0.23)	<0.001
Age (years)	64.4 (7.2)	59.7 (7.6)	54.8 (7.1)	51.5 (5.8)	<0.001
Height (cm)	157.9 (6.3)	159.9 (5.3)	161.8 (5.5)	161.5 (6.4)	<0.001
Weight (kg)	65.8 (11.8)	66.8 (11.8)	66.7 (11.9)	66.9 (9.8)	0.056
BMI (kg/m^2)	26.5 (4.5)	26.1 (4.4)	25.5 (4.3)	24.4 (3.3)	<0.001
Pulse (beats/min)	75.2 (12.4)	75.1 (11.7)	74.7 (14.1)	75.1 (11.8)	0.713
Total hip BMD (g/cm^2)	0.829 (0.136)	0.879 (0.139)	0.911 (0.133)	0.932 (0.123)	<0.001
Femoral neck BMD (g/cm^2)	0.686 (0.118)	0.728 (0.124)	0.763 (0.127)	0.791 (0.121)	<0.001
Trochanter BMD (g/cm^2)	0.616 (0.112)	0.656 (0.108)	0.681 (0.103)	0.703 (0.101)	<0.001
	Number (%)	Number (%)	Number (%)	Number (%)	
COAD/asthma	377 (31%)	250 (21.4%)	263 (21.3%)	208 (17.1%)	<0.001
History of cancer	96 (7.9%)	75 (6.4%)	60 (4.9%)	50 (4.1%)	<0.001
History of CVD	56 (4.6%)	27 (2.3%)	18 (1.5%)	2 (0.2%)	<0.001
Current HRT	118 (9.7%)	210 (17.9%)	317 (25.7%)	317 (26.1%)	<0.001
Ever taken steroid	80 (6.6%)	39 (3.3%)	47 (3.8%)	32 (2.6%)	<0.001
Current smoking	119 (9.8%)	150 (12.9%)	156 (12.7%)	118 (9.7%)	<0.001

FEV_1,Forced expiratory volume; BMD, Bone mineral density; COAD, chronic obstructive airway disease; CVD, cardiovascular disease; HRT, hormone replacement therapy.

Table 2. Crude and adjusted mean BMD values in FEV_1 quartiles in 4830 women aged 45–76 years in the Cambridge General Practice Study

		Quartile 1 (0.51–1.98 l/s) *n*=1216 Mean (SD)	Quartile 2 (1.99–2.32 l/s) *n*=1167 Mean (SD)	Quartile 3 (2.33–2.67 l/s) *n*=1232 Mean (SD)	Quartile 4 (2.68–4.11 l/s) *n*=1215 Mean (SD)	*p* value
Total hip BMD (g/cm^2)	*	0.829 (0.136)	0.879 (0.139)	0.911 (0.133)	0.932 (0.123)	<0.001
	**	0.865 (0.278)	0.888 (0.208)	0.896 (0.208)	0.904 (0.278)	<0.001
	***	0.854 (0.556)	0.873 (0.556)	0.879 (0.556)	0.887 (0.625)	<0.001
Femoral neck BMD (g/cm^2)	*	0.686 (0.118)	0.728 (0.124)	0.763 (0.127)	0.791 (0.121)	<0.001
	**	0.726 (0.278)	0.739 (0.208)	0.746 (0.208)	0.757 (0.278)	<0.001
	***	0.721 (0.556)	0.731 (0.556)	0.737 (0.556)	0.748 (0.556)	<0.001
TrochanterBMD (g/cm^2)	*	0.616 (0.112)	0.656 (0.108)	0.681 (0.103)	0.703 (0.101)	<0.001
	**	0.643 (0.208)	0.663 (0.208)	0.671 (0.208)	0.681 (0.208)	<0.001
	***	0.629 (0.486)	0.645 (0.486)	0.652 (0.486)	0.661 (0.486)	<0.001

FEV_1 = Forced expiratory volume, BMD=Bone mineral density
* Crude; ** Adjusted for age, height and weight; *** Adjusted for age, height, weight, smoking, hormone replacement therapy and steroid use, chronic obstructive airway disease, /asthma, cancer and cardiovascular disease.

smokers and 4207 current non-smokers) adjusting for age, weight and height. Finally we examined the relationship between bone mineral density and FEV_1 in 2692 women after excluding all women with a history of respiratory diseases, cancer, cardiovascular disease and steroid use, as well as women who were current HRT users, adjusting for age, weight and height in the model.

A unit increase in FEV_1 (1 l/s) was associated with an increase of 0.065–0.075 g/cm^2 ($p<0.001$) in BMD across three sites in the hip. After adjusting for age, weight and height the magnitude of relationship was reduced to between 0.023 and 0.03 g/cm^2 though still significant ($p<0.001$). The relationship remained significant after adjusting for other covariates including smoking, medication use and existing diseases. The gradients of the relationship between bone mineral density and FEV_1 were comparable not only across different age groups but also between current smokers and current non-smokers. Results were similar in women with no past history of diseases and those not taking steroids or HRT.

Table 4 shows the prevalence of women with low bone density (bottom quintile of BMD distribution) increased with decreasing quartile of respiratory function, with about three times the prevalence in the lowest compared to the highest quartile. Findings were similar

Table 3. Relationship of FEV1 and BMD in multiple regression analysis: Regression coefficients of BMD with FEV1 quartiles in the Cambridge General Practice Study

			Coefficient (per one 1 l/s)	SE	*p* value
Entire group	Total hip	*	0.026	0.004	<0.001
(*n*=4830)	Femoral neck	*	0.021	0.004	<0.001
	Trochanter	*	0.026	0.004	<0.001
Age 45–54	Total hip	**	0.034	0.006	<0.001
(*n*= 2047)	Femoral neck	**	0.031	0.007	<0.001
	Trochanter	**	0.033	0.006	<0.001
Age 55–64	Total hip	**	0.039	0.007	<0.001
(*n*=1588)	Femoral neck	**	0.032	0.007	<0.001
	Trochanter	**	0.032	0.006	<0.001
Age 65+	Total hip	**	0.039	0.008	<0.001
(*n*=1195)	Femoral neck	**	0.029	0.008	<0.001
	Trochanter	**	0.040	0.007	<0.001
Current smokers	Total hip	***	0.036	0.012	0.002
	Femoral neck	***	0.031	0.011	0.004
(*n*=620)	Trochanter	***	0.023	0.010	0.028
Current nonsmokers	Total hip	***	0.029	0.005	<0.001
	Femoral neck	***	0.021	0.004	<0.001
(*n*=4210)	Trochanter	***	0.030	0.004	<0.001
Excluding diseases	Total hip	***	0.029	0.006	<0.001
and drugs (*n*=2692)	Femoral neck	***	0.023	0.006	<0.001
	Trochanter	***	0.031	0.005	<0.001

FEV_1 = Forced expiratory volume, BMD=Bone mineral density.
* FEV_1 adjusted for age, height, weight, smoking, hormone replacement therapy, steroid use, chronic obstructive airways disease/asthma, cancer and cardiovascular diseases.
** FEV_1 adjusted for height and weight.
*** FEV_1 adjusted for age, height and weight.

Table 4. Risk of low bone density according to respiratory function in 4830 women aged 45–76 years in the Cambridge General Practice Study

Prevalence of low bone density[a] *n* (%)					Adjusted[b] odds ratio of low bone density in FEV_1 quartile 1 vs quartile 4 (95% CI)	*p* value
Quartile of FEV_1	Quartile 1 (0.51–1.98 l/s) *n*=1216	Quartile 2 (1.99–2.32 l/s) *n*=1167	Quartile 3 (2.33–2.67 l/s) *n*=1232	Quartile 4 (2.68–4.11 l/s) *n*=1215		
Total hip BMD	428 (35.2)	256 (21.9)	173 (14.0)	111 (9.1)	2.14 (1.57–2.92)	<0.001
Femoral neck BMD	429 (35.3)	271 (23.2)	165 (13.4)	100 (8.2)	1.83 (1.34–2.51)	<0.001
Trochanter BMD	434 (35.7)	253 (21.7)	170 (13.8)	104 (8.6)	2.22 (1.64–3.01)	<0.001

FEV_1=Forced expiratory volume; BMD, Bone mineral density.
[a]Low bone density = bottom quintile of bone density distribution.
[b]Adjusted for age, height, weight, pulse rate, smoking, hormone replacement therapy, steroid use, chronic obstructive airways disease/asthma, cancer and cardiovascular diseases.

for 2361 women with no past history of diseases, not taking steroids or HRT and were non-smokers. Table 4 also shows that women in the bottom compared to the top quartile of respiratory function had about double the risk of low bone density even after adjusting for covariates age, weight, height, pulse rate, smoking, medication use and past history of respiratory and cardiovascular disease or cancer.

Discussion

We found a positive and continuous relationship between FEV_1 and bone mineral density at the hip across the whole normal range of respiratory function in women in the community. After adjusting for possible confounding factors, the mean hip bone mineral density in women in the highest FEV_1 quartile was 3%–5%

higher than the mean BMD in women in the lowest quartile (Table 2). In multiple regression analyses, a unit change in FEV_1 (1 l/s) was associated with about 0.030 g/cm^2 change in total hip BMD independent of other covariates. Despite the differences in composition of bone in different skeletal sites, there was little variation in the BMD FEV_1 relationship at different sites. Within this study group, the magnitude of this relationship was comparable to a difference of 6 years in age or difference of 5 kg in weight on total hip bone mineral density. Random measurement errors in both FEV_1 and bone mineral density are likely to underestimate the magnitude of the relationship.

In our study population, both BMD and FEV_1 were positively related to weight and height. The age-adjusted partial correlation coefficients between BMD and weight at total hip, femoral neck and trochanter were $r = 0.46$, 0.37 and 0.36 ($p < 0.001$ for all), respectively. Partial correlations between bone mineral density and height at same sites were $r = 0.09$, 0.10 and 0.13, respectively ($p < 0.001$ for all). FEV_1 related more strongly to height ($r = 0.43$, $p < 0.001$) than weight ($r = 0.05$, $p < 0.001$). However, the correlation seen between BMD and FEV_1 remained significant even after adjusting for the effect of height and weight and the association appeared to be independent of these two measurements.

FEV_1, a commonly used lung function test in clinical practice, is reduced in both obstructive and restrictive lung diseases. Low BMD has been shown to occur in both obstructive and restrictive lung diseases [11,12]. Although the exact etiology of this is unclear, in patients with these respiratory diseases, chronic ill health, poor nutrition or medication such as steroid use could affect BMD. However, in the current cohort, the association between BMD and FEV_1 was apparent across the normal range of respiratory function even after excluding women with any history of respiratory disease.

The reason for this relationship is not clear. Cigarette smoking habit might plausibly explain the association. Smoking has a negative effect on bone metabolism [7] and is also a major cause of chronic obstructive airway disease resulting in impaired FEV_1 [16]. However, a similar correlation was observed in this cohort of women in both current smokers and current non-smokers; 68% of the latter group consisted of people who never smoked during their life. Smoking is therefore unlikely to explain this association.

Hypoxia has negative effects on bone mineralization [17] but whether the association is mediated through the degree of arterial oxygen saturation is unknown. Patients with chronic airflow limitation tend to be symptomatic by the time they develop chronic hypoxia and are not likely to remain undiagnosed. Patients with interstitial lung diseases tend to develop chronic hypoxia early and they can remain asymptomatic and undiagnosed for a variable period of time. Nevertheless, the low prevalence of interstitial lung diseases in the community [18] is unlikely to explain the above findings.

Low vitamin D levels have been documented among patients with cystic fibrosis, in whom the FEV_1 was correlated with bone mineral density [11]. Poor nutrition, limited sun exposure and pancreatic malabsorption can all contribute to hypovitaminosis D in these patients. Chronic hypovitaminosis D and resulting secondary hyperparathyroidism is known to impair bone mineralization [19]. Hypovitaminosis D is also known to be associated with skeletal muscle weakness [20] although the effect on respiratory muscles has not been documented. Whether low vitamin D status might contribute to the observed association remains to be established.

Physical activity is known to have a positive influence on bone mineral density [21]. FEV_1 depends on the strength of respiratory musculature and vital capacity, both of which are likely to improve with physical activity. Adjusting for self-reported physical activity did not change the findings (results not shown), but it is likely that we were unable to adjust adequately for physical activity in the statistical analysis, since our measurements of physical activity were crude. We used pulse rate as a surrogate marker of physical fitness but its inclusion in the regression model together with other covariates did not change the magnitude of the observed association.

The observed 3–5% difference in mean hip bone mineral density between top and bottom FEV_1 quartiles seen in this study may be of clinical and public health relevance. A difference in bone mineral density of similar magnitude was found when women reporting most frequent milk consumers were compared with least frequent milk consumers [8] and tea drinkers were compared with non-tea drinkers [22]. Tea drinking appears to be associated with lower hip fracture rates in both men and women in Europe [23,24]. Bone mineral density change of similar magnitude occurs following long-term HRT therapy, which has been shown to reduce the incidence of vertebral fractures by nearly 50%.

Although BMD is a major known determinant of future fracture risk of an individual, and pharmacologic interventions such as the bisphosphonates have been shown to reduce fracture risk, other factors which may influence the absolute risk of fracture are taken into consideration when making therapeutic decisions. Women in the bottom quartile of distribution for respiratory function had double the risk of low bone density. It would be of interest to know if respiratory function is an independent predictor of fracture risk. Among the patients with low BMD, the subgroup with poor respiratory function may form a special risk group for future fractures. Both low BMD and low FEV_1 have been shown to predict mortality in men and women [25–27].

The significant association between respiratory function and hip bone mineral density, found across all age groups in women living in the general community has, not to our knowledge, been previously reported. This relationship was independent of age, weight, height, smoking habit, medication use and clinical respiratory or bone diseases. The exact mechanism of this association is unclear but is likely to reflect some common

etiological factor or factors such as physical activity or nutritional status which need to be explored in future studies. In the interim, poor respiratory function may be a useful indicator of women at increased risk of osteoporosis.

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ORIGINAL ARTICLE

An association between respiratory function and hip bone mineral density in older men: a cross-sectional study

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Abstract The association between respiratory function and bone mineral density (BMD) among women living in the community has been reported previously. We examined the association between forced expiratory volume in 1 s (FEV_1) and BMD measured at hip using dual-energy X-ray absorptiometry in a group of 947 men (aged 65 to 76 years) recruited from general practice age-sex registers in Cambridge between 1991 and 1995. A positive and significant correlation was seen between FEV_1 and BMD measured at total hip, femoral neck, and trochanter. A unit change (1 l) in FEV_1 was associated with a change of BMD by 0.019, 0.017, and 0.026 g/cm^2 in the total hip, femoral neck, and tochanteric region, respectively. These associations were independent of possible confounding factors such as age, height, weight, smoking habit, major disease prevalence, and medications, which might affect bone metabolism. In categorical analyses, the highest BMD was seen in the highest FEV_1 quartile, while the lowest BMD was seen in the lowest FEV_1 quartile. This pattern was seen in all three skeletal sites and was independent of covariates listed above. Compared with the bottom FEV_1 quartile, mean hip BMDs in the top quartile were 2–3.5% higher. The exact mechanism of this association is not clear to us. One plausible explanation is that respiratory function and bone health both reflect common but as yet unknown determinants.

Keywords Bone density · Community · Forced expiratory volume · Men · Osteoporosis · Respiratory function

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Introduction

The association between respiratory function and bone mineral density among patients with chronic respiratory diseases has been reported previously [1]. Further, higher risk of osteoporosis among subjects with airflow limitation has been demonstrated in a recent study [2]. We have previously reported a positive and continuous association between forced expiratory volume in 1 s (FEV_1) and bone mineral density (BMD) of the proximal femur in women living in the general community in the UK [3]. This association was independent of age, height, weight, smoking habit, medication use, and presence of chronic diseases, which can affect bone metabolism. We wished to examine the association between respiratory function FEV_1 and hip BMD in a group of older men living in the community.

Methods

This study involved men who participated in the Cambridge General Practice Health Study, which invited men aged 65 or above, resident in the community, and identified using general practice age and sex match registers between 1991 and 1995. Those who consented for the health survey completed the health and lifestyle questionnaire, which gathered information on their current and past medical history. Height and weight were measured in light clothing without shoes during the physical examination by trained personnel at Addenbrooke's Hospital, Cambridge. History of cancer, heart disease, stroke, and respiratory disease, were assessed using self-completed questionnaires. The use of systemic corticosteroids was recorded as "never" or "ever," while participants were categorized into three groups on their smoking habits: "current smokers," "past smokers," and "never smoked." BMD of the nondominant proximal femur was measured using the Hologic QDR 1000 densitometer (Hologic, Waltham, MA, USA). The

Table 1 Descriptive data of 947 men aged 65–76 years, according to FEV_1 quartiles in the Cambridge General Practice Study

Parameter	Quartile 1 ($n=234$)	Quartile 2 ($n=234$)	Quartile 3 ($n=240$)	Quartile 4 ($n=236$)	p Value
Characteristics	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age, years	69.9 (2.8)	69.5 (2.8)	69.1 (2.7)	68.4 (2.5)	< 0.001
Height, cm	169.9 (6.5)	177.7 (6.2)	172.3 (6.4)	175.5 (6.1)	< 0.001
Weight, kg	76.2 (11.9)	77.3 (10.5)	78.5 (11.5)	79.4 (9.7)	0.009
BMI, kg/m^2	26.3 (3.8)	26.5 (3.2)	26.4 (3.2)	25.7 (2.6)	0.008
FEV_1, liter	1.79 (0.31)	2.45 (0.12)	2.83 (0.11)	3.37 (0.28)	< 0.001
Total hip BMD, g/cm^2	0.935 (0.151)	0.959 (0.141)	0.963 (0.146)	0.982 (0.133)	0.004
Femoral neck BMD, g/cm^2	0.759 (0.133)	0.778 (0.117)	0.782 (0.126)	0.803 (0.121)	0.003
Trochanter BMD, g/cm^2	0.712 (0.124)	0.746 (0.123)	0.751 (0.131)	0.766 (0.119)	< 0.001
Percentage of men with	Number (%)	Number (%)	Number (%)	Number (%)	
COAD/asthma	88 (37.6)	42 (17.7)	31 (12.9)	22 (9.3)	< 0.001
Cancer	14 (6.0)	11 (4.6)	12 (5.0)	14 (5.9)	0.890
Cardiovascular disease	43 (18.4)	37 (16.0)	24 (10.0)	28 (11.9)	0.035
Current smoking habit	41 (17.5)	27 (11.4)	13 (5.4)	9 (3.8)	< 0.001
Steroid use	20 (8.5)	5 (2.1)	12 (5.0)	4 (1.7)	0.001

coefficient of variance for hip BMD measurements in our unit was 1.6% for the femoral neck, 1.5% for the trochanter, and 3.0% for Ward's triangle [4].

Forced expiratory volume in the 1st second (FEV_1) was measured twice using a portable spirometer (Micromedical, UK) [5]. The higher reading of the two measurements was used in the analysis.

Statistical analyses

Men were divided into quartiles according to FEV_1, and descriptive data of each quartile were given as mean (SD) or percentages (number). Correlations between hip BMD, age, weight, height, and FEV_1 as continuous variables were examined using Pearson correlation coefficients. Mean BMDs at total hip, femoral neck, and trochanter were compared using multivariate analysis of variance, initially adjusted for age, height, and weight, and then additionally for possible confounders such as respiratory disease, cardiovascular disease, and smoking habit. A linear regression model was fitted to examine the relationship of FEV_1 (independent variable) on BMD (dependent variable) with and without covariates in the model. Data were analyzed using SPSS software, version 10 for Windows.

Results

Descriptive data

The descriptive data of 947 men aged 65 to 76 years (mean 69.2 years, SD = 2.8) are shown in Table 1. Compared with men in the highest quartile of FEV_1, men in the lowest quartile were older, shorter, and lighter, and had lower average BMDs in all hip regions. The percentage of current smokers, corticosteroid users, and men with history of cardiovascular disease and respiratory disease were significantly higher in the lowest FEV_1 quartile when compared with the highest.

Association between FEV_1 and BMD

Significant and positive correlations were observed between FEV_1 and BMD measured in all three hip sites. Age, weight, and height also showed significant correlations with both BMD and FEV_1 (Table 2).

Table 2 Correlations between age, weight, height, hip BMD, and FEV_1. All variables were entered as continuous measures

	Weight	Height	Total hip BMD	Femoral neck BMD	Trochanteric BMD	FEV_1
Age	−0.124	−0.087	−0.106	−0.105	−0.073	−0.198
	< 0.001	0.007	0.001	0.001	0.026	< 0.001
Weight	-	0.482	0.441	0.376	0.339	0.128
	-	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Height	-	-	0.208	0.192	0.233	0.301
	-	-	< 0.001	< 0.001	< 0.001	< 0.001
Total hip BMD	-	-	-	0.854	0.910	0.137
	-	-	-	< 0.001	< 0.001	< 0.001
Femoral neck BMD	-	-	-	-	0.781	0.132
	-	-	-	-	< 0.001	< 0.001
Trochanteric BMD	-	-	-	-	-	0.167
	-	-	-	-	-	< 0.001

Table 3 Adjusted mean (SD) BMD values in FEV_1 quartiles in men aged 65–76 years, in the Cambridge General Practice Study. *Fem neck BMD* femoral neck BMD, *Troch BMD* trochanteric BMD

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* Value
Total Hip BMD[a]	0.945 (0.012)	0.963 (0.012)	0.959 (0.012)	0.973 (0.012)	0.18
Total Hip BMD[b]	0.950 (0.012)	0.963 (0.012)	0.957 (0.012)	0.970 (0.012)	0.45
Fem neck BMD[a]	0.768 (0.012)	0.781 (0.012)	0.779 (0.012)	0.795 (0.012)	0.15
Fem neck BMD[b]	0.773 (0.012)	0.782 (0.012)	0.777 (0.012)	0.792 (0.012)	0.41
Troch BMD[a]	0.721 (0.012)	0.748 (0.012)	0.749 (0.012)	0.756 (0.012)	0.01
Troch BMD[b]	0.725 (0.012)	0.74 (0.012)	0.748 (0.012)	0.752 (0.012)	0.09

[a]Adjusted for age, weight, and height
[b]Adjusted for age, weight, height, respiratory diseases, cardiovascular diseases, smoking, and steroid use

Mean (and SD) BMDs of total hip, femoral neck, and trochanter in FEV_1 quartiles are shown in Table 3. After adjusting for possible confounding factors, the highest BMDs were observed in the highest FEV_1 quartile, while the lowest BMDs were seen in the lowest FEV_1 quartile, and this pattern was seen in all three hip regions. Mean BMDs generally showed an upward trend with increasing FEV_1.

Results of the regression analysis are shown in Table 4. A significant and positive relationship, independent of the effects of age, height, weight, smoking habits, prevalent disease, or steroid medication was observed between FEV_1 and hip BMD. A unit change in FEV_1 (1 l) was associated with a statistically significant 0.031, 0.027, and 0.034 g/cm^2 change in BMD in total hip, femoral neck, and trochanter, respectively. Including the potential confounding factors in the model attenuated these associations but they still remained significant. Excluding current smokers or steroid users in the regression model did not materially alter the regression slopes (data not shown).

Discussion

We previously reported a continuous and positive association between FEV_1 and hip BMD among community-living women who participated in the same study. These women were recruited from the same community and were assessed by the same team in the same manner. The association seen in these women was independent of age, body mass index, smoking habit, and history of diseases or medications which might influence bone metabolism [3]. The association was evident in young, middle, and older age groups almost to the same extent. Although the exact mechanism of this association was not clear, a common underlying determinant, such as physical activity was a plausible explanation.

Table 4 Regression coefficients of BMD with FEV_1 in men aged 65–76 years, in the Cambridge General Practice Study

	Coefficient (per 1 l/s)	SE	*p* Value
Total hip BMD, unadjusted	0.031	0.008	< 0.001
Total hip BMD, adjusted[a]	0.019	0.007	0.006
Femoral neck BMD, unadjusted	0.027	0.007	< 0.001
Femoral neck BMD, adjusted[a]	0.017	0.006	0.005
Trochanter BMD, unadjusted	0.034	0.008	< 0.001
Trochanter BMD, adjusted[a]	0.026	0.006	< 0.001

[a]Adjusted for age, weight, height, respiratory diseases, cardiovascular diseases, smoking, and steroid use

In the current study, a positive correlation was seen between respiratory function measured by FEV_1 and hip BMD measured at total hip, femoral neck, and trochanter in men aged 65–76 years. The association was independent of age, weight, height, smoking habits, steroid use, and prevalent diseases, which might affect bone metabolism. After adjusting for above potential confounding factors, mean hip BMD of men in the highest FEV_1 quartile was approximately 2.0–3.5% higher when compared with mean BMD in those in the lowest quartile. This is somewhat less than what was seen in women previously [3]. BMD in all three hip regions showed a general upward trend from the lowest to the highest FEV_1. In contrast to women, the mean differences in BMD in FEV_1 quartiles were not statistically significant except in the trochanteric area. However, more sensitive regression analyses showed statistically significant relationships.

In the regression analysis, the magnitude of the association seen between respiratory function and BMD in men was weaker than that seen in the subgroup analysis of women over 65 years [3]. In older women ($n = 1{,}195$), a unit (1 l) change in FEV_1 was associated with a change in BMD of 0.039, 0.029, and 0.040 g/cm^2 in total hip, femoral neck, and trochanter, respectively. In the current study involving men of a similar age group, corresponding figures were 0.019, 0.017, and 0.026 g/cm^2. Nevertheless, while these differences were small, and observed mean BMDs for men did not reach osteoporosis or osteopenia thresholds in the lowest quartiles, they may still be of interest in terms of understanding the mechanisms involved in bone loss.

The differences we observed in the association between respiratory function and BMD between men and women could partly be due to differences in sample sizes and, hence, lack of power, although a real gender difference cannot be excluded. Gender differences were observed in both BMD and hip geometry [6, 7]. Gender differences in BMD were observed early in life, between

prepubertal men and women [8] and also in forearm bones among Japanese [9]. If physical activity is the link between BMD and respiratory function, the association might be expected to be greater among men, who are more physically active than women. Other possible factors such as smoking, alcohol consumption, prevalence of diseases, and use of drugs which can affect bone metabolism may also differ in men and women. Although recruited from the same community, considerable differences in the prevalence of current smokers and in the number of patients with a history of cancers and other relevant diseases were seen between men in the current study and women in our previous study [3], reflecting the well-recognized sex differences in health.

Our study has several limitations. Selection bias is unlikely to explain the relationship unless nonresponders differed from responders with respect to the relationship between respiratory function and BMD. That is, that nonresponders were more likely to have good respiratory function and low BMD or vice versa, which does not seem plausible. There are measurement errors in assessment of BMD and respiratory function, but random measurement error would attenuate any relationship. We did not quantify smoking and corticosteroid use, and they were used as categorical variables in the analysis. The effects of smoking and corticosteroids both on BMD and lung functions are dose related, so we may not have adjusted adequately for smoking and steroid use. Nevertheless, regression analyses after excluding steroid users and current smokers found similar relationships between respiratory function and BMD. We did not include spine BMD in the analysis, since spine BMD is influenced by the presence of degenerative changes and vertebral fractures. Vertebral fractures reduce lung function, and the extent of this problem was not known to us in this study.

The association between respiratory function and BMD seen in these studies need further exploration. Whether respiratory function has a direct influence on BMD or both measures reflect a common predisposing factor is unknown. Elucidating the nature of the relationship may help in the understanding of the determinants and prevention of bone loss in later life.

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Chapter 6

General Discussion

Discussion

Osteoporosis-related fractures create a substantial economic burden on current health-care systems [1] and many countries have adopted measures at different levels to lessen the burden. Despite the predictions that increased number of hip fractures would occur in Asia [2], South Asian countries are not considering osteoporosis a health priority[3]. Lack of epidemiological data in these countries has partly contributed to the low priority given to the disease, currently.

Prevalence of postmenopausal osteoporosis

Our study showed that nearly 45% of Sri Lankan women in postmenopausal age are likely to develope osteoporosis [4]. This observation is based on phalangeal BMD measured in a community survey conducted in seven out of nine provinces of the country. This survey is the largest bone-related health survey conducted in Sri Lanka. Although we were unable to draw subjects from the North and East provinces which are largely inhabited by Tamils and Sri Lankan Moors, we were able to include these ethnic groups from other provinces, roughly to the same proportions they exist in the country's population. In general, the participants of this survey were volunteers who gathered to the community screening centers and were not selected on a random basis. Since only the screening centers were randomized we cannot exclude the possibility of selection (health) bias that might have influenced the results, and most importantly this consideration needs to be contemplated in the interpretation of these figures.

As our estimation is based on phalangeal BMD, it is likely that, the prevalence we observed could be materially different if a central site such as spine or hip was studied. Discordance of T scores as well as the prevalence of osteoporosis between skeletal sites is well documented. El Maghraoui *et al* reported discordance of WHO diagnostic category between spine and hip in every 4 in 10 patients[5]. Mulder *et al* showed that estimation of osteoporosis prevalence, based on a single skeletal site, can lead to a substantial variation. They observed the prevalence of osteoporosis to vary, widely, when BMDs were estimated in multiple sites including phalanx, forearm, spine and proximal femur [6]. Hence the prevalence figure we observed in our analysis could be different from the true disease prevalence. Further studies using

central-type DXA are needed in Sri Lanka to check the reproducibility of our data. This is a daunting task in a country which has only three central-type densitometers for the entire population. Until such a study is conducted, our prevalence data can be used as a platform for future studies and to infer the health status of the Sri Lankan population.

Further, we believe that, our prevalence data can be used to convince health policy makers about the high prevalence of osteoporosis in our society. It is also likely that our figure is somewhat closer to the true value as similar prevalence figures have been reported from neighboring countries. Cheng *et al* found 31% prevalence of osteoporosis, either in the spine or proximal femur, in Chinese women older than 50 years [7]. Among postmenopausal Thai women, the prevalence of osteoporosis was 39% between 60-64 years and 57.7% between 70-74 years [8-10]. Among Japanese women aged between 50 and 79 years, the prevalence of osteoporosis was 35% in the spine, 12% in the hip, and 56.8% in the forearm [11]. Among Chinese women, Jang *et al* reported 30.6% prevalence of osteoporosis between 45-64 years, 52.5% between 65- 64 years and 68.7% above 75 years [12]. The prevalence we reported is comparable with above figures.

Peak bone mass (PBM)

We found the phalangeal BMD among our subjects to reach the peak value between 30-40 years. Previous studies found a variation of the timing of PBM accrual based on ethnicity and skeletal site [13-15,16]. Peripheral sites such as phalanx and forearm showed a delay in achieving PBM when compared with central sites such as spine or proximal femur which most of the time, reached a peak between 20-30 years [14]. It is possible, therefore, the maximum BMDs of spine and proximal femur to occur earlier in our subjects, perhaps between 20-30 years of age. In support of this assumption, our subjects achieved nearly 96% of maximum phalangeal BMD between 20-30 years, and individuals between 20-30 and 31-40 years did not have significantly different BMD levels. Although further studies can be performed to ascertain the timing of skeletal maturation of different skeletal sites, they are unlikely to provide additional clinically relevant information. For practical purposes we could consider

that nearly 96% of PBM is achieved by 20-30 years and all measures to improve bone health should be focused on younger age groups. However, further 4-6% of BMD increment is still feasible when the desired BMD level has not been achieved by the age of 30 years.

There are many determinants of PBM. Factors such as protein-energy nutrition, calcium intake, vitamin D status and physical activity are proven to be associated with PBM [17-19]. These factors are potentially modifiable and can be incorporated at primary care level when designing preventive measures. As most of these determinants have their maximum influence on growing skeleton than on the mature skeleton, the “window of opportunity” can be determined based on the timing of PBM in the population. Health promoters in Sri Lanka should encourage measures that promote achieving higher PBM for people below 40 years knowing that certain parts of the skeleton can potentially be modified until that age.

There are many life-style modifications that are proven to influence bone health. Hind and Burrows, in a systematic review of clinical trials on exercise, found a positive association between exercise and bone mineral accrual in children and adolescents [19]. Exercise has other health benefits as well. A school-based, high-impact exercise intervention implemented three times a week for 12 minutes showed positive effects both on lean mass and indices of hip geometry [20].

Nutrients at different periods in life are known to influence BMD. Intake of calcium and vitamin D in childhood positively influences BMD. School girls who were supplemented with high calcium milk for a period of two years were able to maintain higher sitting height than their controls after one year of withdrawing the supplements [21]. Apart from calcium, other nutrients such as protein have positive influence on bone mineral content (BMC) and overall growth [22].

Health policy makers in Sri Lanka should use this information to design a health promotional package consisted of life-style modifications for people under 40 years. Apart from other health benefits associated with physical activity inculcated early in life, this will allow them to acquire a higher PBM which in turn helps to maintain a higher BMD during old age.

Accuracy, precision and patient positioning

Hip BMD measurement is routinely included in the evaluation of postmenopausal osteoporosis as hip BMD is the best predictor of hip fracture [23]. All DXA manufacturers use hip positioning aids to rotate femur internally, to counteract the automatic anteversion of the hip joint. We highlight the importance of maintaining the same degree of leg rotation in replicate DXA scans. Our data show that internal rotation of femur by 10 degrees between two scans is associated with a change in BMD, in excess of the Least Significant Change (LSC) in 24% of subjects while external rotation by the same degree is associated with a significant change in BMD in 16% of subjects [24]. Although malrotation of leg, either internally or externally, did not compromise the diagnostic classification, a significant effect on the precision of BMD estimations was evident. This indicates that technician should achieve the correct rotation of femur to maintain the accuracy of BMD estimation and then achieve the same degree of rotation in all subsequent scans in order to maintain the precision. Technician will not have an insight to the degree of femur rotation as it cannot be determined externally. As a crude and qualitative guide, the lesser trochanter of the femur can be used to estimate the degree of femur rotation. The lesser trochanter which is a posterior structure should be just visible at the upper inner border of the femoral shaft to indicate adequate retroversion of femur [25]. Technicians should routinely check for this bony landmark to make sure that the same degree of hip rotation has been achieved in all scans. Two other studies examining the effect of leg rotation on hip BMD have generated similar results and support our findings [26,27].

Leg elevation and spine BMD

We examined whether the same accuracy of spine BMD can be obtained on a Hologic machine, when patients keep their legs flat while scanning. When 54 postmenopausal women were measured with their legs flat or elevated, we found the accuracy of the spine BMD estimations to be similar [28]. Furthermore, there was a very high degree of correlation between the BMD values measured in the two positions and the regression intercept was close to zero (0.02). These data indicate that keeping legs flat on the table or elevated on the leg block, while measuring spine BMD, does not

essentially affect the accuracy of data. Although there are no published data, Norland manufacturer would have examined the difference in spine BMD when measured with legs elevated or legs flat and decided to maintain the state of quo. A study based on Lunar scanner showed similar results to ours. Simonelli *et al* in their study, found high correlations of BMDs measured with and without leg elevation. Furthermore, in the regression analysis, the slope and intercept values they observed are highly comparable to ours [29]. Similar to our analysis, Yang *et al*, using a Hologic QDR 4500 scanner estimated spine BMDs with or without leg elevation[30]. In this study, there was no significant difference between the mean BMDs estimated in the two positions (0.907 vs 0.922 g/cm^2) and only 0.13 SD difference in the mean T scores was noted.

In our study, although BMD remained unchanged, there was a significant change in the region of interest (ROI) and BMC between scans obtained in the two positions. This is understandable as positioning of legs would determine the degree of lumbar lordosis, and subsequently the bone image [31]. However, we have shown that BMD values remain unchanged as BMC and the ROI both changed to the same extent and in the same direction.

It is interesting to see whether all DXA manufacturers would come to a uniform agreement about leg positioning while scanning the lumbar spine. With growing evidence manufacturers should agree on a uniform recommendation regarding the use of the leg cushion. As we showed, scanning legs flat will allow technicians to perform both spine and hip scans in the same setting, thus reducing the scanning time and avoiding the inconvenience caused by leg positioning without compromising the accuracy or precision of the measurement.

It can be argued that as the reference datasets which are in current use have been developed using leg elevation, it is logical to maintain the same position when patients are evaluated using these datasets. However, we will not be able to sustain such argument as new datasets based on current Lunar machines, which use leg-flat position, are added to public domain. It is interesting to see whether one will have to select the reference dataset to suit the leg positioning when analyzing patients in future. Our data shows that no difference is made to the WHO categorization of

subjects or T score calculation when subjects are scanned legs flat and analyzed in reference to currently available datasets which have been acquired using conventional leg positioning. However, our sample size was limited to 54 individuals, not allowing us to evaluate this, and should be tested in a larger sample.

Although, osteoarthritis is associated with obesity and osteoporosis with low BMI, the coexistence of the two diseases; osteoporosis and osteoarthritis has been documented[32]. Patients with osteoarthritic changes in lower limb joints may experience difficulty in keeping their legs elevated during scanning. This practical limitation would be more applicable to DXA machines using a pencil-beam as they take a relatively longer time to complete a scan when compared to a fan-beam scanner. Pencil-beam scanners are still in use and all Norland machines use this technology.

The lumbar spine is an important site when making clinical decisions in osteoporosis. Owing to its higher content of trabecular bone, spine shows a greater BMD change than hip in response to metabolic bone diseases [33]; thus all attempts should be taken to include it in routine patient scanning. Furthermore, spine has a better ability to monitor therapy given for osteoporosis [33]. However, when a patient with limited hip mobility is referred for DXA scanning on a machine which requires leg positing, spine may be overlooked due to practical reasons.

Our data show that if a subject has a difficulty in maintaining 90 degree hip flexion during spine scan, he can be allowed to maintain a lesser degree of hip flexion without compromising the accuracy of BMD estimations or WHO categorization [28]. However, the effect of varying degree of hip flexion on the precision of the BMD estimation was evident as variation of 20-30 degrees of hip flexion was associated with change in BMD, in excess of the LSC, in 32% subjects. This means that a variation in hip flexion by 20-30 degrees between two scans could cause an erroneous change in BMD which could be interpreted as a real and significant change in 32% of subjects. Even though a lesser degree hip flexion does not compromise the WHO diagnostic category, the technician should clearly state the change made to the positioning and recommends that same position be maintained in future scanning to avoid systematic errors in precision.

When replicate BMD estimations are made, the technician should procure assessing previous images to maintain consistency in patient positioning and in defining the ROIs. However, it will be difficult to assess if a difference in hip flexion was made in the previous scan. A clear record should be made in case notes if a difference was made to hip flexion and previous records should be perused when performing repeat scans.

Hip geometry

In a group of women, selected randomly from our university study area in the Galle district, we observed a gradual and significant decline in some measures of hip geometry such as femoral neck BMD, cross-sectional area (CSA), and section modulus (SM)[34]. In the same group of women there was a non-significant expansion of the femoral neck width, adjusted for height and weight. Our results are similar with those by Beck *et al* who observed a similar behavior of hip geometry indices among women in the NHANES cohort [35]. Among women in the NHANES cohort, a significant reduction in narrow-neck BMD, CSA, and SM was evident while narrow-neck width expanded gradually. Limited studies exist in other populations which evaluate the patterns of variation in hip geometry indices.

Some indices of hip geometry such as the hip axis length (HAL) can predict fractures independent of BMD [36]. When combining the HAL with BMD, they predict fractures better than BMD alone [37] which is not the case for other hip geometry indices [38, 39]. Age-related changes in hip geometry provide an insight to the mechanism of structural failure of different ROIs. According to the data of Beck *et al,* [35]and ours[34], femoral neck BMD and CSA which represents the cortical bone equivalent of the ROI, decline with advancing age.

Although expansion of subperiosteal diameter of the neck could possibly offset the structural failure induced by declining BMD, the degree of expansion observed in these studies is not sufficient to prevent the mechanical failure entirely. While subperiosteeal bone apposition leads to neck expansion, endosteal bone resorption causes thinning of the cortical envelop and expansion of the medullary cavity[40] .

As the rate of endosteal bone resorption exceeds that of bone apposition, especially in old age, the cortical envelop becomes critically thin making it more susceptible for buckling [41] which is probably the most predicting property picked up by the BMD measurement [39].

There is a paucity of studies examining age trends in hip geometry in other populations. Current literature on hip geometry is largely limited to case-control and comparison studies where two groups of different characteristics have been compared. Compared to Caucasian women, women of African descent have greater cortical thickness, shorter neck length and smaller inter-trochanteric width [42]. Furthermore, Japanese women have shorter femoral neck length and narrower neck-shaft angle when compared to white Americans [43]. Differences in hip geometry have also been shown in three ethnic groups in Singapore. These differences possibly account for the differential fracture risk seen across ethnic groups [44].

Age-related decline in BMD is the plausible explanation for the increased fracture risk seen in old age [45]. As BMD gradually declines with advancing age, osteoporosis-related fracture risk rises, exponentially [46]. BMD differences alone, however, are unable to explain the geographical and ethnic variation in fracture incidence reported earlier [47]. Furthermore, Asians, despite having lower BMD compared to Europeans, experience less fracture incidence [48]. The reasons for this paradoxical phenomenon are not entirely clear and age-related changes in hip geometry may help to explain this disparity. It may be that the bending rigidity of proximal femur is preserved to a greater extent in Asians than Europeans, thus protecting them from fractures in old age.

There is no sufficient data, however, to compare the behavior of hip geometry indices between Asians and other races. Our data [34] do not support the theory that Asian women have preserved hip geometry in old age. Our study sample is not representative of the country’s population as they were drawn from a selected area. More studies should be done using representative samples from the local population and also from other Asian countries to examine this possibility.

Using a UK cohort we were able to demonstrate that growth in early life influences mechanical strength of proximal femur later in adult life [49]. People who were shorter in early life as assessed by different body measurements had poorer mechanical strength in the proximal femur during adult life, independent of their adult body measurements. This suggests that events in early life have long lasing effects on the adult skeleton. This may partly account for the relationship previously observed between hip fracture risk and poor intrauterine or infant growth [50].

Genetic factors and influences in early period of life may play a role in the associations observed. It appears that most of the risk factors of non-communicable diseases have undergone programming in early life. Similarly, it has been shown that adult BMD and risk of hip fracture may have undergone similar programming [50,51]. We were able to demonstrate that certain indices of hip geometry are, possibly, programmed in early period of life. According to our data [49], poor growth in early years has lasting effects on femoral shape and reduces mechanical strength of the proximal femur in adult life.

Many feel that there are "critical periods" during mammalian development which determine the normal development of a particular anatomical structure or its function [52]. Environmental stimuli operating at these critical periods can have lasting effect on these bodily functions. Gale *et al* previously showed an association between adult whole body BMC, lean mass and birth weight among men and women, aged 70-75 years and still living in Sheffield in the UK [51]. This positive association between adult BMC and birth weight was independent of adult height, sex, age, smoking habits, alcohol consumption, calcium intake and physical activity indicating that BMC in adult life is partly determined in early age [51]. Our data would add to the existing body of evidence that adult BMD, indices of hip geometry and fracture risk in adult--hood are programmed in early life.

Further, similar to BMD and the indices of hip geometry, lean mass is also possibly programmed in early age [51]. Among Indians, Sachdev *et al* showed that birth weight or BMI gain in infancy are related to adult lean mass [53]. Hediger *et al* showed that infants of shorter gestation period remained smaller and infants of longer

gestation period remained larger in their early childhood but these differences in weight were mostly attributable to fat mass variation [54].

BMD and associations

We observed that BMD is associated with diverse, still clinically relevant variables [55-58]. In a group of community-dwelling men and women selected from a community in the UK, BMD showed a positive association with FEV1 and this association was independent of smoking habits, alcohol intake, disease prevalence and drug usage [55,56]. Furthermore, BMD showed a positive correlation with the lean mass and an inverse association with serum lipids in a group of pre-menopausal women selected from the Galle district in Sri Lanka [57,58].

Although nearly 70% of BMD variation is genetically determined [59,60], individual contributions made by non-genetic factors such as physical activity and nutrition to the remaining 30% variation are not clear. In our data, a unit increase in FEV1 (1L per second) was associated with an increase of BMD by 0.066 to 0.076 g/cm^2 in the hip [55, 56]. In a different population, a change of lean body mass by 1 kg was associated with change in BMD between 0.004 and 0.008 g/cm^2 [57]. In contrast to both lean mass and FEV1 which showed positive association with BMD, serum LDL showed a negative correlation with BMD [58]. Furthermore, we also described a gender difference in the strength of the association between BMD and FEV1 [55,56].

Previous studies have shown gender differences in many osteoporosis-related health issues. Hip fractures are predominantly seen in women and only about 20-25% of hip fractures occur in men [61]. The overall mortality following hip fracture is about 20% in the first 12 months and is higher in men than in women [62]. Gender differences appear to extend beyond BMD and fracture. Nieves *et al* reported gender differences in hip geometry where males had significantly greater tibial BMC, volumetric BMD, cortical area and cortical thickness compared with females. After controlling for lean mass, males still had 8% higher hip BMD and 5.3% higher total tibial BMD than women [63].

The associations observed between BMD with other functional measurements of different body systems can have many explanations. It is possible that several organs or metabolic pathways could be subjected to same group of stimuli during intrauterine or early postnatal period and undergo programming together, thus allowing them to be inter-related in old age. Similar to BMD, BMC and lean mass, respiratory functions and lipid metabolism may have undergone programming, perhaps simultaneously, to maintain a relationship between them in adult age.

The association between hip BMD and FEV1 could be indirect and mediated through a third factor. Although hypoxia is known to have negative influence on BMD [64], it is an unlikely explanation for the observed association as the association was independent of disease prevalence and seen at normal FEV1 range, which is unlikely to be associated with hypoxia.

Physical activity is a more plausible explanation for most of the associations we observed. There are many studies to support that physical activity may be the link between BMD, lean mass and lipid levels. Morris *et al* reported high impact physical activities in young age to have positive effects both on BMD and lean mass [65]. When compared with a control group, subjects in the exercise group gained significantly more lean mass, less body fat content, greater shoulder, knee and grip strength, and greater BMDs in total body, lumbar spine and femoral neck [65]. In multiple regression analysis, change in lean mass was the primary determinant of BMD accrual. Further, Carels *et al* reported the beneficial effects of increased physical activity on cardio-respiratory fitness, body weight, fat mass, both systolic and diastolic blood pressures, total cholesterol, triglycerides, and LDL cholesterol [66]. Beneficial effects of physical activity have also been reported in Asian populations. In 1996, Suzuki *et al* reported a positive effect of long-term physical training of moderate intensity on body composition, cardiovascular function and serum lipids in mildly obese middle-aged Japanese men and women [67].

Apart from physical activity, vitamin D may play an intermediate role in these associations. Vitamin D is required for bone health and proper functioning of skeletal muscles. As lean mass is directly related to respiratory functions [68, 69], the link between BMD and FEV1 could operate through differences in vitamin D levels. An

association has been described between vitamin D level and respiratory functions, previously [70]. Although vitamin D levels in the community are determined by genetic and environmental factors [71], genetic factors are more likely to make interpersonal variations in vitamin D levels [72] than seasonal variations which would have similar effects on all subjects within the community.

In support of vitamin D theory, Black *et al*, in 2005 demonstrated a strong relationship between serum concentrations of 25-hydroxy vitamin D, FEV1, and FVC [70]. When compared with subjects in the lowest quintile of 25-hydroxy vitamin D, those in the highest quintile had significantly higher FEV1 and FVC and this difference was independent of age, gender, height, body mass index, ethnicity, and smoking history. Furthermore, adjusting data for physical activity, intake of vitamin D supplements, milk intake, and the level of serum antioxidants did not essentially change the results indicating that the association observed between serum vitamin D levels and respiratory functions is independent of physical activities and other confounders [70].

The association observed between BMD and lipids may also operate via vitamin D status. Recent studies have shown an association between vitamin D level and cardiovascular risk factors [73,74]. In 2007, Martins *et al* demonstrated that, in comparison to the highest quartile of serum 25-hydroxy vitamin D, those in the lowest quartile had significantly higher prevalence of hypertension (odds ratio=1.30), diabetes mellitus (odd ratio= 1.98), obesity (odd ratio=2.29), and high serum triglyceride levels (odd ratio= 1.47) [73]. Furthermore, in the US general population, an independent inverse association was found between vitamin D levels and insulin resistance [74]. These data support the theory that vitamin D status is a plausible link between BMD, respiratory functions, lean mass and lipid levels.

Although physical activity and nutrition appear to have positive effects on BMD [75] and skeletal muscles [76], thereby establishing a positive association between BMD and lean mass, this association may breakdown in old age due to various factors. As discussed above, physical activity [76] and vitamin D nutrition [77] are crucial factors in maintaining lean mass and both these may become critical in old age. Studies have shown vitamin D deficiency to be prevalent among elderly in many communities [78].

Lack of physical activity and hypovitaminosis D in old age may disrupt the association observed between lean mass and BMD in middle age. In support of this, previous studies have shown a stronger correlation between BMD and fat mass in older subjects [79,80]. Also in our results, the association between BMD and FEV1 which indirectly reflects lean mass was much stronger in young women than in older subjects [55,56].

The coexistence of low BMD and high cardiovascular risk has many clinical and epidemiological implications. Clinician will have to make a holistic approach and assess both cardiovascular and fracture risk in a given patient before interventions. When advising on life-style modifications, such as physical activity and cessation of smoking, benefits on both cardiac and skeletal systems must be considered. Furthermore, when prescribing drugs, clinicians should consider secondary benefits such as skeletal effects of lipid lowering therapy [81] and lipid lowering properties of antiresorptive agents [82]. At community level, information can be used to motivate people to engage in life-style modifications, such as proper nutrition and physical activity which have positive cardiac and skeletal effects.

Summary

In this thesis, many aspects related to bone health are discussed. They span from osteoporosis prevalence, operational factors, determinants of BMD and co-morbidity in osteoporosis. Although the information has been generated using different populations, the conclusions are broadly generalizable.

The community study conducted in seven provinces in Sri Lanka provides an insight to BMD changes with advancing age in this South Asian population. Although the study has limitations due to inclusion of one solitary skeletal site and possible selection bias, information gathered from this study can be used in designing health promotion programs to reduce fracture burden in the future. Our data would indicate the time frame available to apply community based interventions to optimize the bone mass in this population. The true prevalence of postmenopausal osteoporosis in Sri Lankan community could be materially different from what we have reported from

this study and more studies are needed to estimate the prevalence in more clinically relevant sites such as the lumbar spine or the proximal femur. Until such studies are done, our data can be used to convince health policy makers about the high prevalence of the disease among Sri Lankan women. Also, these findings could be a platform for launching future larger studies of prospective nature and long follow-up.

Precision and accuracy are the key issues when measuring BMD using DXA technology and technicians should take all precautions to ensure them. Although recommendations are made by the manufacturers of DXA regarding patient positioning during routine DXA scanning, they are to date not evidence-based. This is highlighted by the varying recommendations given by different manufacturers of DXA. Our results indicate that specific leg positioning during lumbar spine BMD measurements can be avoided without compromising the accuracy of the measurements. Our data will add to the growing body of evidence that leg positioning during spine scanning is essentially not required. If hip positioning is considered to be essential, then less degree of hip flexion can be allowed in people with poor mobility of lower limb joints. Although, the lesser degree of hip flexion, we allowed, did not alter the accuracy of BMD estimations, the effect on long-term precision was evident. Hence, it is important to maintain the same degree of hip flexion in subsequent scans. Similarly, our data showed that leg rotation has clear clinical implications when repeated BMD measurements are made. To minimize these systematic errors, technicians should ensure that repeated scans also have the same patient positioning as the previous scans. Recall of previous scan images would help specially in hip scans while changes made during lumbar spine scan should be clearly documented.

The indices of hip geometry among our study subjects, selected from a local area, followed similar patterns as those described in American women. As ours is the first study examining age trends in hip geometry among South Asians, more studies are needed to replicate our findings.

We observed an association between BMD, respiratory function, lean mass and cardiovascular risk factors. Also there is an association between the indices of hip geometry and measurements in the postnatal period. Disease prevalence and drug

usage are unlikely to be the underlying cause of these associations as they were mostly observed in healthy subjects. Smoking habits and alcohol use are also unlikely explanations as these associations were independent of such substance use. Nutrition, physical activity, vitamin D status and simultaneous programming are the most plausible underlying mechanism for these associations.

Some of these findings may interest clinicians when evaluating their patients. When assessing a patient with osteoporosis, clinicians should be aware of the mortality or morbidity associated to co-existing diseases and detailed examination should be pursued to assess them. Similarly, when a patient presents with cardiovascular or respiratory illness, the likelihood of having low BMD and the risk of future fracture should be analyzed. This holistic approach in patient care would allow clinician to estimate the overall risk of future major non-communicable diseases and measures can be implemented to mitigate them. Physical activity and cessation of smoking could be beneficial for many such diseases. In selecting drugs, attention should be paid to their multiple effects on co-morbid diseases. Furthermore, the role of vitamin D and calcium as a mediator of these associations should be further studied. In conclusion, this thesis has assessed operational factors surrounding the BMD measurement, etiological relationships of skeletal parameters and the intricate relationship between bone health with functional parameters of the cardiovascular and respiratory system. Overall, the knowledge derived from this thesis has targeted the improvement of medical attention of patients with osteoporosis in Sri Lanka and worldwide.

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Summary

This thesis addresses factors that are related to validity of BMD measurements in the detection of osteoporosis or fracture risk. Studies in this area are scarce and many questions still remain unanswered. Based on DXA images, we assessed the hip geometry indices and examined how they vary with age and also according to measurements in early period of life.

In addition, recent studies indicate that BMD is related to functions of other vital organs or bodily systems in humans. Associations with extra-skeletal outcomes would help to understand the variations in BMD and co-morbidity seen among patients with osteoporosis. In this thesis the associations between BMD and indices of cardiovascular health and respiratory function were also assessed.

Data related to the prevalence of osteoporosis or women at risk of fracture are paramount important for a country to initiate preventive strategies and to plan future health care facilities. Furthermore, the time at which peak BMD is achieved has a direct impact on fracture risk. This information is particularly relevant in recognizing age groups that should be targeted by population or community-based preventive programs.

In Chapter 2.1 we report 44.9% prevalence of osteoporosis among postmenopausal women in the Sri Lankan community. This was estimated extrapolating central DXA findings on a larger community sample selected to represent a wider population of Sri Lanka. Although our figures are similar to those reported in neighboring countries, the true prevalence could be different considering that we did not measure BMD in key skeletal sites such as spine and hip in all subjects and that selection bias could have occurred when we recruited subjects for this study. Despite these limitations this estimation can be used as a ball park figure of the prevalence of osteoporosis in the country and could provide a platform to design future studies and apply country-wide interventions.

In Chapter 2.2 we found both men and women to achieve the peak BMD around 30-40 years of age. This was based on phalangeal BMD estimations and peak BMD acquisition can be different in more clinically relevant sites such as the lumbar spine or the proximal

femur. In addition, previous studies have shown wide ethnic and geographical variation in peak BMD acquisition. Although a large USA based study showed that peak BMD is reached between 20-30 years, studies done in other countries have shown a substantial delay in BMD accrual. In our survey, nearly 95% of peak BMD acquisition occurred in 20-30 year age group and only further 5% increase occurred during the next 10 years.

Operational properties of the BMD measurement are important to be considered in the context of the clinical applications discussed above. According to our observations in Chapters 3.1 and 3.2, the accuracy of spine BMD estimations is not affected by the degree of hip flexion. The effect was seen more in the interpretation of replicate BMD estimations where a significant change in spine BMD could occur purely due to variation in positioning. The same degree of accuracy can be obtained by maintaining a lesser degree of hip flexion facilitating the measurement in patients with difficulties in keeping legs flexed (e.g. elderly or disabled people). Nevertheless, the technician performing DXA scan should procure that subsequent scans use the same degree of hip flexion. Hence, we suggest that the amount of hip flexion maintained during scanning should clearly be documented in the patient notes.

In Chapter 3.3 we confirmed that the leg of the measured side should be rotated internally to maintain the correct positioning of the proximal femur during hip scanning. We found that variation of leg rotation by10^0 (either internally or externally) can cause a major impact on the BMD measurements. The effect was seen more in precision of BMD estimations. If the same degree of leg rotation is not maintained during repeated DXA measurements, a change of BMD could be considered significant while it being purely the consequence of differences in leg positioning. Similar to the recommendation for hip flexion in lumbar spine scans, technicians performing DXA measurements of the hip should be aware of this technical limitation and try to achieve the same degree of leg rotation in all repeated scans. We also suggest using the lesser trochanter as a guide to the degree of leg rotation in previous scans.

Similar to BMD, indices of hip geometry show age-related trends. In Chapter 4.1 we found that indices of bone strength such as cross sectional area (CSA), cross-sectional moment of inertia (CSMI) and section modulus (SM) show gradual decline with advancing age in women in Sri Lanka. While CSA measures the cortical bone equivalent

in the cross section of the bone, both CSMI and SM are indicative of the bending strength of the bone. We also observed tendency (not statistically significant) for expansion of the femoral neck width in postmenopausal women during old age. These patterns of geometrical change help understanding the underlying mechanism leading to structural failure of the femoral neck and increased risk of fracture at advanced ages. Based on these findings we confirm that the expanding femoral neck is a structural adaptation to counteract the decrease in bone strength consequence to reduction in the CSA and thinning of the cortical envelop.

In Chapter 4.2 we found that ‘unfavorable” indices of hip geometry in men and women during adulthood were associated with smaller body size at 1 year, suggesting potential early life programming for the vulnerability to sustain hip fractures later in life. These findings support the existing body of evidence that many organs and bodily functions are programmed in early period of life and clinical outcomes such as fracture or myocardial infarction may be determined early in life.

In Chapter 5.1 we report an association between BMD and lean mass among a group of premenopausal women selected from the community in Sri Lanka. Furthermore, in Chapter 5.2, in the same group of women we report an association between BMD and lipids. In our study population, women with lower BMD had higher total and LDL lipid levels. Recent evidence suggests that bone metabolism is not an isolated series of events but it has cross linking with other metabolic pathways such as lipids. This observation has diverse potential clinical implications. It may help to understand the higher cardiovascular mortality and morbidity seen in women with osteoporosis or suffering from fractures. Also, based on them we can recommend clinicians to take a holistic approach when evaluating patients to estimate the total risk profile of their patients involving several systems. Physical exercises as a non-pharmacological intervention may be beneficial in these patients presenting with co-morbidities. Additional data especially arising from interventional trials are required to evaluate the benefits of improving muscle mass in these patients.

In Chapters 5.3 and 5.4 we report a positive association between BMD of the proximal femur and FEV1 which is a measure of pulmonary function. This association was seen in young, middle aged and old women but to a lesser extent in men. The association seen

between FEV1 and BMD was independent of diseases prevalence, drug usage, body proportions and smoking habits. These findings postulate the co-existence of compromised lung function (low FEV1) and osteoporosis (low hip BMD) in the same person indicating the possibility of a link between these two conditions. Although the underlying mechanism of this association was not clear, physical activity and vitamin D status appear as the most plausible explanations.

Finally, in the general discussion in Chapter 5 general aspects of these operational characteristics and disease associations are discussed in the context of clinical practice. Further, the findings reported on this thesis are placed in perspective of future research and clinical applications involving the measurement of BMD.

Samenvatting

Deze thesis richt zich voornamelijk op factoren die betrekking hebben op de geldigheid van BMD metingen in de opsporing van risico van osteoporose of breuk. Studies op dit gebied zijn schaars en vele vragen nog onbeantwoord. Op basis van MB4 beelden, beoordeelden we de indicatoren van de heup geometrie en onderzochten hoe ze verschillen met leeftijd en ook volgens metingen in de vroege periode van het leven.

Uit recente studies blijkt bovendien dat BMD gerelateerd is aan de functies van andere vitale organen of lichaamssystemen bij de mens. Vergelijking met extra- skeletale resultaten zou helpen om de variaties in BMD en comorbiditeit die gezien wordt bij patiënten met osteoporose te begrijpen. In deze thesis werden ook de associaties tussen BMD en indexcijfers van de cardiovasculaire gezondheid en ademhalingsfunctie beoordeeld. Gegevens met betrekking tot de prevalentie van osteoporose bij vrouwen met het risico van breuk zijn essentieel, en zijn buitengewoon belangrijk om preventieve strategieën te initiëren en bij het ontwerpen en maken van plannen voor toekomstige instellingen voor landelijke gezondheidszorg. Bovendien, de tijd op welke het hoogtepunt van BMD is bereikt heeft een rechtstreekse invloed op risico's van breuk.

Deze informatie is bijzonder relevant met betrekking tot het herkennen van de leeftijdsgroepen waarop bijzondere aandacht moet worden gericht onder de, op de bevolking of, gemeenschap gebaseerde preventieve programma's.

In hoofdstuk 2.1 rapporteren we 44,9% prevalentie van osteoporose bij postmenopauzale vrouwen in de Sri Lankaanse Gemeenschap. Dit werd bereikt door het extrapoleren van centrale MB4 bevindingen door middel van een steekproef onder een grotere onderzoeksgroep die geselecteerd werd om een brede bevolkingsgroep van Sri Lanka te vertegenwoordigen. Hoewel onze cijfers vergelijkbaar zijn met cijfers die in naburige landen gemeld zijn, kunnen er werkelijke prevalentie verschillen gezien worden die anders zijn, omdat we niet BMD in belangrijke skeletal sites zoals rug en heup in alle personen gemeten hebben en dat selectie bias kon hebben plaatsgevonden toen we de personen voor deze studie hebben aangeworven. Ondanks deze beperkingen kan deze schatting worden gebruikt als een basis figuur van de prevalentie van osteoporose in het land en gebruikt worden als een

platform voor het ontwerpen van toekomstige studies en zouden voor interventies op nationaal nivo van toepassing kunnen zijn.

In hoofdstuk 2.2 vonden we dat zowel mannen als vrouwen de piek BMD bereiken in de leeftijdsgroep van ongeveer 30-40 jaar oud. Dit was gebaseerd op phalangeale BMD schattingen en omdat piek BMD schattingen kunnen verschillen in meer klinisch relevante plaatsen zoals de lumbale wervelkolom of de proximale dijbeen. Bovendien, hebben vorige studies aangetoond dat er grote etnische en geografische verschillen in de piek BMD acquisitie zijn. Hoewel uit een grote in de VS gebaseerde studie bleek dat de piek BMD daar bereikt wordt tussen 20-30 jaar, hebben studies die in andere landen gedaan werden aangetoond dat er daar een aanzienlijke vertraging in BMD accural plaatsvindt. In onze enquête, werd gezien dat bijna 95% van de piek BMD overname heeft plaatsgevonden in de leeftijdsgroep van 20-30 jaar en er alleen een verdere verhoging van 5% is opgetreden tijdens de komende 10 jaar.

Operationele eigenschappen van de BMD meting zijn belangrijk om te worden beschouwd in het kader van de klinische toepassingen van hetgeen hierboven besproken werd. Volgens onze waarnemingen in hoofdstukken 3.1 en 3.2, wordt de nauwkeurigheid van wervelkolom BMD schattingen niet beïnvloed door de mate van de heup flexie. Het effect dat gezien werd kwam meer voort uit de interpretatie van het repliceren van de BMD schattingen waar door een belangrijke wijziging in de wervelkolom BMD puur als gevolg van variatie in de positionering kan optreden. Dezelfde mate van nauwkeurigheid kan worden verkregen door het behoud van een mindere mate van heup flexie, en het vergemakkelijken van de meting in patiënten met problemen bij het gebogen houden van de benen (bijvoorbeeld ouderen of gehandicapten mensen). Niettemin, de technicus die de MB4 scan uitvoert moet er voor zorgen dat bij latere scans dezelfde mate van heup flexie gebruikt word. Vandaar, dat wij voorstellen dat de mate van heup flexie die gehandhaafd word tijdens het scannen duidelijk moet worden gedocumenteerd in de notities over de patiënt.

In hoofdstuk 3.3 bevestigd we dat het been van de gemeten kant intern moet worden gedraaid om de juiste plaatsing van het proximale dijbeen te verkrijgen tijdens het scannen van de heup. We vonden dat variatie van been rotatie met 10^0 (intern of extern) een grote invloed kan hebben op de metingen van het BMD. Het effect was duidelijk te zien in de precisie van BMD schattingen. Als dezelfde mate van rotatie van het been niet wordt gehandhaafd tijdens

herhaalde MB4 metingen, moet worden overwogen dat een wijziging van BMD meting aanzienlijke kan verschillen terwijl het louter een gevolg is van het verschillen in de positionering van het been. Vergelijkbaar met de aanbeveling voor de heup flexie in lumbale wervelkolom scans, moeten technici MB4 bij het meten van de heup zich bewust zijn van deze technische beperking en zullen zij moeten proberen om een zelfde mate van been rotatie te bereiken in alle herhaalde scans. Ook raden we u aan de mindere trochanter als een gids voor de mate van been rotatie in eerdere scans te gebruiken. Gelijkaardig aan BMD, laten de indexcijfers van heup geometrie leeftijd -gerelateerde trends zien.

In hoofdstuk 4.1 vonden we dat de indexcijfers van de sterkte van de botten zoals kruis doorsnede (CSA), transversale traagheidsmoment (CSMI) en sectie modulus (SM) een geleidelijke daling aantonen met het voort schreiden van de leeftijd in vrouwen uit het Verenigd Koninkrijk. Terwijl CSA het equivalent in de corticale doorsnede van het bot meet, zijn zowel CSMI als SM indicatief voor de buigende sterkte van het bot. Wij hebben ook een tendens waargenomen (niet statistisch significant) voor uitbreiding van de femorale nek breedte bij postmenopauzale vrouwen tijdens hogere ouderdom. Deze patronen van geometrische verandering helpen bij het begrijpen van de onderliggende mechanisme die leiden tot het structurele falen van de femorale nek en de verhoogde risico van breuk op gevorderde leeftijd. Op basis van deze bevindingen bevestigen wij dat de groeiende femorale nek een structurele aanpassing is om de daling in bot sterkte en het gevolg van een vermindering van de CSA en het dunner worden van de corticale envelop tegen te gaan.

In hoofdstuk 4.2 geven we verslag van de gevonden “ ongunstige" indexcijfers van heup geometrie in mannen en vrouwen tijdens de volwassenheid die werden geassocieerd met kleiner lichaams grote op 1 jarige leeftijd, deze suggereren en ondersteunen een potentiële vroege programmering voor de kwetsbaarheid voor heupfracturen later in het leven. Deze bevindingen ondersteunen de bestaande hoeveelheid van bewijs dat vele organen en lichaamsfuncties zijn geprogrammeerd in de vroege periode van leven en klinische resultaten zoals fractuur of myocardiaal infarct al vroeg in het leven zijn vastgelegd.

In hoofdstuk 5.1 verslaan wij een samenhang tussen BMD en vetvrije massa onder een groep van premenopausal vrouwen geselecteerd uit de Gemeenschap in Sri Lanka. Bovendien, in hoofdstuk 5.2, in dezelfde groep van vrouwen vonden wij een samenhang tussen BMD en lipiden. In onze studie onder deze bevolkingsgroep hadden vrouwen met lagere BMD, hogere

totaal en LDL lipide niveaus. Recent bewijs suggereert dat bot metabolisme niet een geïsoleerde reeks van gebeurtenissen is, maar dat het gekoppeld is aan andere stofwisselingsroutes zoals lipiden. Deze constatering heeft diverse potentiële klinische implicaties.

Het kan helpen bij het begrijpen van de hogere cardiovasculaire mortaliteit en morbiditeit gezien bij vrouwen met osteoporose of bij hen die lijden aan fracturen. Ook, op basis daarvan kunnen wij clinici aanbevelen een meer holistische aanpak te gebruiken bij de evaluatie van patiënten, en het inschatten van het totale risicoprofiel van hun patiënten, met gebruik van verschillende systemen. Om Fysieke oefeningen aan te bevelen als niet-farmacologische interventies en aan deze patiënten aan te bieden bij het behandelingsaanbod zou zeer voordelig kunnen zijn. Aanvullende gegevens die met name voortvloeien uit Interventionele proeven moeten worden gebruikt om het evalueren van de voordelen bij meer spiermassa in deze patiënten te verbeteren.

In de hoofdstukken 5.3 en 5.4 verslaan wij een positieve associatie tussen BMD van het proximale dijbeen en FEV1 die een meting van de pulmonale functie is. Deze samenhang werd gezien in de jonge, de middelbare leeftijd groep en onder oudere vrouwen, maar in mindere mate bij mannen. De samenhang gezien tussen FEV1 en BMD was onafhankelijk van de prevalentie van de ziekten, druggebruik, lichaamsverhoudingen en rookgedrag. Deze bevindingen postuleren de co-existentie van gecompromitteerd longfunctie (lage FEV1) en osteoporose (lage heup BMD) in dezelfde personen die de mogelijkheid van een verband tussen deze twee voorwaarden aangeeft. Hoewel het onderliggende mechanisme van deze samenhang niet duidelijk was, lijken lichaamsbeweging en vitamine D-status hiervoor de meest waarschijnlijke uitleg.

Ten slotte, in de algemene discussie in hoofdstuk 5 worden de algemene aspecten van deze operationele kenmerken en samenhang met de ziektes besproken in het kader van de klinische praktijk. Verder, worden de bevindingen die in deze stelling gerapporteerd worden met betrekking tot de meting van BMD in het perspectief van toekomstig onderzoek en klinische toepassingen geplaatst.

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List of Publications

This thesis is based on the following papers.

1) Osteoporosis and cardiovascular risk among premenopausal women in Sri Lanka. Lekamwasam S, Weerarathna T, Rodrigo M, Arachchi WK, Munidasa D. J Clin Densitom. 2009;**12**(2):245-250.

2) Association between bone mineral density, lean mass, and fat mass among healthy middle-aged premenopausal women: a cross-sectional study in southern Sri Lanka. Lekamwasam S, Weerarathna T, Rodrigo M, Arachchi WK, Munidasa D. J Bone Miner Metab. 2009;**27**(1):83-88.

3) Lekamwasam S, Wijerathne L, Rodrigo M, Hewage U. Age-related trends in phalangeal bone mineral density in Sri Lankan men and women aged 20 yrs or more. J Clinical Densitometry 2009;**12**(1):58-62.

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About the Author

Sarath Lekamwasam was born on 16th June, 1959 in the Galle district in Sri Lanka and received his primary education, first in village school and then Christ Church Boys' School in Baddegama and Dharmasoka College in Ambalangoda. He entered Peradeniya Medical School in 1978 and passed out in 1983 with second class honors. While working in Colombo General Hospital (now National Hospital of Sri Lanka), he quickly started his postgraduate education. In 1998 he qualified with MD (Medicine) and proceeded to UK for overseas training. In 1993 he became a member of the Royal College of Physicians, Glasgow and in 2000, a fellow of the Royal Collage of physicians, London. After returning to Sri Lanka in 1993 he joined the Department of Medicine, Karapitiya, Galle and got promoted to senior lecturer position and then in 2003 a merit promotion to professor in medicine, the position he still holds. Osteoporosis and elderly care are his main research areas and he is involved with teaching EBM, critical appraisal of medical literature and scientific writing. The commonwealth fellowship he received in 2000-2001 allowed him to undergo training on osteoporosis-related research in the Cambridge University in UK, under supervision of Professor Juliet Compston and Dr Jonathan Reeve. Currently, he is a member of the Scientific Advisory Committee of the IOF. He has received numerous awards including Presidential Awards for medical research in Sri Lanka. In 2012, he became the President of the Ceylon College of Physicians.

Sarath is married to Vajira, Consultant Physician in Karapitiya Hospital, Galle and blessed with two children; Bhanuka and Raveen.