Cyril Fernando Memorial Oration

Bone mineral density and hip geometry in women referred for bone density testing

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Introduction

Until recently osteoporosis and fragile fractures were considered as a part of the aging process. However osteoporosis has now been recognized as a major metabolic bone disease in the modern world and it has received the attention of clinicians, researches and health care managers. In the past, the awareness of osteoporosis was low even among medical personal. In one survey in United Kingdom 20% of general practitioners in UK admitted that they have "never seen a case" of osteoporosis during their clinical work[1]. When the awareness of osteoporosis among general practitioners in Galle area was assessed by a pre-designed questionnaire in 2001, 50% considered osteoporosis as a disease and 67% of them considered osteoporosis preventable[2]. However this may well be an overestimation since the awareness of osteoporosis in general has improved in Southern area due to the availability of screening facilities for the last 3 years.

It is estimated that 1.7 million hip fractures occurred worldwide in 1990[3]. These fractures showed no uniform distribution worldwide and the highest prevalence was reported from the Scandinavian countries. One third of these fractures occurred in Asian countries. The exact cause of this geographical variation in the fracture incidence is still not clear and genetic, nutritional and environment factors are likely to play a role in the etiology. In 1994, the WHO expert committee on osteoporosis predicted the future incidence of osteoporosis related fractures for different countries[4]. Taking the changing patterns of the population composition into the consideration, more hip fractures have been predicted for all countries. However an exponential rise in hip fracture incidence is expected in Asian countries, where the health facilities are still overburden with communicable diseases and facilities to manage these fractures are limited.

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Although osteoporosis has drawn the attention of the medical community and health policy makers in many Western countries, only limited amount of information is available from Asian countries. In 1999, the age adjusted one-year cumulative incidence of hip fractures in Shenyang in China was found to be 67 per 100,000 for women and 81 per 100,000 population for men[5]. Hip fracture incidence rates in four Asian countries estimated by the Asian Osteoporosis Study[6] are shown in Table 1 together with data from European countries for comparison. Based on this data, in addition to the lower incidence of hip fractures in Asia in comparison to Europe or USA, there seems to be a wide variation of hip fracture incidence between Asian countries. Analysis of the Central Database in Singapore showed a five-fold increase in the incidence of hip fracture in their women from 1991 to 1998[7] and reasons for this trend is not clear. The entire picture of hip fractures in Asia is largely unknown currently and more studies are needed before making conclusions.

Table 1. Hip fracture incidence in Asian and European countries

Country	*Men (per 100,00)*	*Women (per 100,00)*
China	67	71
Hong-Kong	180	459
Singapore	164	442
Malaysia	88	218
Thailand	114	289
Oslo, Norway (1989)	384	903
USA (1989)	179	506
Switzerland (1991)	170	494
Southampton, UK (1986)	72	262

No studies have been done in Sri Lanka regarding the incidence or prevalence of osteoporosis or its resulting fractures. When 2860 patients admitted with new fractures to the Accident Department of the National Hospital of Colombo were included in a retrospective analysis, hip fractures accounted for

nearly 11% of those admissions. Further 17% had wrist fractures. Number of patients with hip fractures increased with the advancing age. The sex distribution of hip fractures beyond the age of 50 was equal[8]. Hip fracture is predominantly a disease of women in European countries but the sex distribution in some Asian countries has shown a different pattern[5,6]. Hip fractures among Asians seem to be equally distributed between men and women and the exact cause of this difference is not clear.

Diagnosis of osteoporosis

Fragile fracture is the clinical end result of osteoporosis and for many years this was the only way of recognizing the existence of osteoporosis in a patient. The diagnosis of osteoporosis is now based on WHO criteria, which takes the bone mineral density (BMD) values into the consideration. BMD of the patient estimated by Duel Energy X-ray absorptiometry (DEXA) is compared with the mean BMD of the young normal sex matched population and the deviation is expressed as a measure of the standard deviation (T Score). The WHO expert committee in 1994 recommended cut off thresholds for the diagnosis of osteoporosis, osteopenia and normal subjects using the T score and these guidelines are followed by clinicians all over the world (Figure 1)[9].

Figure 1. Formula for T Score and WHO classification

$$\text{T score} = \frac{\text{BMD of the patient} - \text{BMD of the young normal population}}{\text{Standard deviation}}$$

Osteoporosis:	T score of less than – 2.50
Osteopenia:	T score between – 2.50 and – 1.00
Normal:	T score above – 1.00

However these criteria were developed using a data of European postmenopausal women and applicability of these criteria to different ethnic populations, pre-menopausal women or men is questionable. Among European white women, a reduction of BMD by 1 standard deviation (T score of -1.00) doubles the risk of future fractures. Whether this association between reduction of BMD and fracture risk can be applied to a different ethnic population is also questionable.

In selecting the cut of value of -2.5 to diagnose osteoporosis, the intention of the WHO was to make osteoporosis a rarity in healthy women before the menopause. Assuming the Gaussian distribution of BMD, nearly 0.7% of young adult population would be characterized as having osteoporosis. Also with the current cut off point, nearly 30% of postmenopausal women will be classified as having osteoporosis either at hip, spine or forearm and this approximates the average lifetime risk of fractures at these three sites[10]. T score, which provides the basis of the diagnostic stratification, is dependent on the mean BMD and SD of the reference database used[10]. Lower T scores can be obtained by using a higher mean reference value with small SD leading to misclassification.

There are three manufacturers of densitometers and the young reference normative data provided by these manufacturers are different. Even in the same population, different inclusion and exclusion criteria (use of calcium, vitamins. and HRT) applied in different studies to define representative sample to obtain normative data would have led to differences in mean and SD values. Currently there is no uniform agreement regarding the age group that should be used to get reference data. In practice, reference ranges have been chosen variously from adults aged 20-29, 20-39 and even at the age of 50 years and these too have an impact on the prevalence of osteoporosis[10].

Recently reference data for hip were generated from the third National Health and Nutrition Examination Study (NHANES III), which included BMD data of 14646 USA men and women and this reference figures are being used by all three manufactures as a standard platform. However NHANES III does not provide data for spine or forearm and the reliability of stratifying patients using these USA based reference data outside USA still remains doubtful[11]. The International Society of Clinical Densitometrists (ISCD) encourages each country to develop their own databases. Although many European and Scandinavian countries have now developed their own reference data, the WHO working committee is uncertain whether reference data should be drawn from local populations[10].

Asian database

Norland densitometers are provided with European normative data as the standard and Asian database as an option. Noriand Asian database has been developed using a heterogeneous sample of Chinese and Singaporian women and the comparison of Asian and European reference data is shown in Table 2.

Although there is considerable heterogenicity among women in different Asian countries, the Asian normative data can be expected to be much closer than European data to our population. However no studies have been done to examine the degree of influence made to the diagnosis of osteoporosis by using these two different data sets in a same population of women. If a high degree of disparity is found, the need for developing normal reference data for Sri Lankan women will be justifiable.

Selection of cases

Osteoporosis is a silent disease and it fulfills many criteria required to justify mass screening. However the studies examining the cost effectiveness of mass screening and treatment have discouraged such an exercise[12].

Case finding in osteoporosis has been largely limited to screening high-risk groups, using risk factors identified in epidemiological studies. Densitometry is still considered the Golden standard in the diagnosis of osteoporosis and indications for densitometry differ in different countries. Indications given by WHO[12] are broad and applicable to many countries. Preferably each country should test the sensitivity and specificity of these risk factors by epidemiological studies. Considering risk factors, which have low sensitivity in the selection of cases will not be cost effective.

Hip geometry

BMD measurement provides the most quantifiable risk assessment for future fractures. In the femoral neck, reduction of bone mass by 1 standard deviation is associated with a significant 2.7 fold increase in hip fracture risk. Table 3 shows the relative risk (with 95% CI) of fracture in women for 1 SD decrease in BMD below the age-adjusted mean[10].

Table 2. Mean (and SD) of European and Asian reference data

Site	*European*	*Asian*	*Difference*
Lumber spine (g/cm^2)	1.164 (0.167)	1.073 (0.123)	+8.48%
Femoral neck (g/cm^2)	0.858 (0.120)*	0.842 (0.106)	+1.9%
Trochanter (g/cm^2)	0.708 (0.099)*	0.674 (0.112)	+5.04%

* Non-Hispanic white, age 20-29 years (NHANES III)

Table 3. Relative risk of fracture in women for 1 SD reduction of BMD

Site of measurement	*Foream fracture*	*Hip fracture*	*Vertebral fracture*	*All fractures*
Distal radius	1.7 (1.4-2.0)	1.8 (1.4-2.2)	1.7 (1.4-2.1)	1.4 (1.3-1.6)
Femoral neck	1.4 (1.4-1.6)	2.6 (2.0-3.5)	1.8 (1.1-2.7)	1.6 (1.4-1.8)
Lumbar spine	1.5 (1.3-1.8)	1.6 (1.2-2.2)	2.3 (1.9-2.8)	1.5 (1.4-1.7)

These calculations have been based on epidemiological studies done in Europe and applicability of these associations to other countries is questionable. It is well known that despite low BMD, hip fractures are uncommon among Asian and African women. In addition there is a wide variation in the incidence of hip fracture across European countries and this variation is not entirely explainable by variation of BMD seen in these different populations[13]. Apart from low BMD, hip fracture has many extra skeletal determinants and this explains the wide range of BMD seen in fracture patients. However during the recent years, researches have focussed their attention on mechanical strength and structural properties of hip, which go beyond BMD to try and explain this discrepancy between BMD and occurrence of a fracture.

Hip geometry assess how the bone is assembled and bone mass is distributed within the bone in order to resist loading. Independent of bone density, indices of hip geometry have been shown to predict hip fractures[14]. In this case control study done in Italy, patients with hip fractures were found to have longer hip axis length (HAL), wider femoral neck width (FNW) and wider neck shaft angle (NSA) when compared with age-matched women without fractures. All these comparisons were independent of femoral BMD and reached statistical significance.

The human skeleton is a mechanically optimized biological system whose composition and organization reflect the functional demand made upon it. It requires to bear the mechanical load place up on it during locomotion, protection and high impact activities. To understand the biomechanies of a bone the concepts such as "stress" and "strain" need to be understood. When a force is applied, the bone not only gets deformed from its original position, but also generates an internal resistance to counteract the applied force. This internal force known as "stress" is equal in magnitude to the applied force and distributed over the cross sectional area of the bone[15]. "Strain" is the term used to describe the changes of dimension of the bone under the influence of mechanical loading. At low level of stress there is a linear relationship between the applied force and resultant deformation. This linear part of the curve is known as the elastic region. Any mechanical load applied within this region will deform the bone only temporary and bone will resume the original dimensions once the load is removed. At the point where the curve becomes nonlinear the elastic region ends and loading beyond this causes permanent deformities in the bone. When the maximal stress of bone pass beyond the strength of bone tissue, mechanical failure and fracture occurs[15].

Measures of mechanical strength of bone (figure 2)

Hip axis length: the length from the pelvic brim to the outer margin of shaft of the femur through the mid femoral neck, position. Longer the femoral neck contributed to a larger the bending moment during a fall and therefore larger probability for fracture.

Neck shaft angle: the angle between the line going through the middle of the femoral shaft and line measuring the hip axis length. Wider the angle more weaker the structure of the hip leading to mechanical failure.

Femoral neck width: measures the distance between periosteal surfaces of femoral neck at its narrowest point.

Figure 2. Indices of hip geometry

Norland densitometers are provided with an in-build software to measure these three parameters. In 1990, Tom Beck in the John Hopkins University in USA developed a software using the Hologic BMD scan images to measure indices of hip geometry. Yoshikawa in 1994 developed a similar software based on the Lunar DPX scans to measure indices of bone strength. Both these approaches treat the entire proximal femur as a continuous curved beam from the proximal shaft to the femoral neck and extract mechanical properties based on the Euler beam theory used in structural engineering.

Indices common to both softwares in the region of femoral neck

- Neck shaft angle: as described earlier
- Neck width: as described earlier
- Neck length: the distance from the center of femoral head to the intersection of shaft and neck axes.
- Cross sectional area (CSA): the cortical bone equivalent area of the cross section of the neck. The strength of bone increases with increasing CSA.
- Cross sectional moment of inertia (CSMI): a property of cross sectional area that represents the magnitude of the greatest bending rigidity of the section
- Section modulus (SM): it is CSMI corrected for the neck width and still measures the bending rigidity of the section

Although these softwares have been used independently in epidemiological studies, no studies have been done to compare the agreement of

comparable indices generated by the two systems and hence the ability to use them interchangeably. In 2001 we scanned the right femur of 50 randomly selected postmenopausal women from Cambridgeshire, using both Hologic 4500QDR fan beam scanner and Lunar DPX pencil beam scanner. The BMD images were further developed using the two softwares by two independent observers and blind to results of each other to measure the indices in the femoral neck area. Results of common indices of both systems such a neck shaft angle, neck length, neck width, CSA, CSMI and Section modulus in narrow neck were compared to see the correlation. Good correlations were found for CSA and CSMI (r^2=0.86 and 0.72), while correlations of neck width and section modulus were only moderate (r^2=0.47 and 0.35)[16]. The differences in defining narrow neck in two methods, the inter-operator variability in identifying the region of interest (ROI) and magnification of BMD image in fan beam type Hologic images would have contributed to poor correlation seen in some parameters. Only CSMI and CSA were broadly concordant.

Aims of the current analysis

This analysis was done in retrospective way using consecutive BMD data files of women, who had undergone densitometry for clinical indications to find out

1. the success of case referral system
2. the prevalence of osteoporosis and osteopenia at different skeletal sites
3. the influence made by European and Asian reference data for the diagnosis of osteoporosis
4. the influence of age and parity on hip BMD and geometry

Method

Setting

Center for Metabolic Bone Diseases in the Department of Medicine, Karapitiya, Galle.

Study population

Case notes of all women aged 20 years or older who were referred for densitometry and underwent DEXA scan of lumbar spine or hip or both from August 1999 to April 2002 were included in the analysis (n=331). 189 women had additional data on forearm bone scans. Women who had only forearm BMD data (n= 10) were excluded from the analysis.

All patients were interviewed and medically examined prior to scanning. Data were collected using a pre-designed data collection format.

Data included in the questionnaire were

1. Demographic data: *height, weight and body mass index*
2. History of bone active diseases/drugs
3. Age at menarche and menopause
4. Parity: *number of deliveries and miscarriages of more than 20 weeks*
5. Period of lactation: *period breast-fed more than three times a day for all children*
6. Dairy milk intake: (excluding childhood)
7. Frequency of green leaves consumption
8. Use of HRT (more than 12 months): *ever/never*
9. Use of Ca ± vitamin D (more than 12 months): *ever/never*
10. Family history of fragile fractures: *either in mother or sister*
11. Past history of fractures: *any fracture after menopause.*

The accuracy of data was reexamined during the first follow up visit in women who required follow up (290). Height was measured without foot ware. Weight was measured while wearing light cloths and after emptying the bladder.

BMD data

BMD was assessed using the Norland Eclipse XR pencil type central bone densitometer (Norland Corp, USA). In vitro accuracy and precision of the instrument was tested each scanning day by scanning two phantoms provided by the manufacturers. The in-vitro accuracy and precision were below 1.5% during the whole period of study. Antero-posterior lumbar spine from L2 through to L4 and non-dominant hip were included in the routine scanning unless patients had

1. spinal deformities preventing positioning them on the scan table
2. radiological evidence of vertebral fractures, deformities or osteoarthritic changes
3. intra-abdominal calcification
4. fracture or previous surgery in the hip

Non-dominant forearm was not included in the routine scanning but this had been done initially in 189 women for academic purposes.

Hip geometry

The width of the femoral neck (FNW) at its narrowest point, which was determined visually was

measured using the 'ruler' function of the software. The width was measured between two periosteal surfaces. The Neck-Shaft Angle (NSA) was measured by the software automatically.

Statistics and analysis

Descriptive data are given as mean (± SD) or as percentages. Distributions of parity and period of lactation were found to be skewed and median and IQR are given. T scores were calculated using the formula described previously using Asian reference data for lumbar spine, femoral neck and trochanter. T scores were also calculated using European reference data. NHANES reference data were used for femoral neck and trochanteric region while European data provided by the manufacturer was used for the lumbar spine. Patients were classified to "normal", osteopenic and osteoporotic using the WHO recommendations (described previously) and the agreement between two classifications was tested using two-way kappa statistics (see Figure 3).

Figure 3. The degree of agreement based on kappa

<0:	no agreement
0-0.2:	poor
0.2-0.4:	fair
0.4-0.6:	moderate
0.6-0.8:	substantial
>0.8:	almost perfect

Using the Asian reference data set, the prevalence of osteoporosis was determined for different skeletal sites. According to ISCD and WHO recommendation, patients with T score below -2.50 either at lumbar spine or femoral neck were considered to have "definite osteoporosis" and the sensitivity and specificity of other sites were examined. Correlations between BMD, FNW and NSA were examined while controlling for the effect of age, weight and height. Regression analysis was used to examine the effect of age, weight, height and femoral neck BMD on neck width and NS angle. Statistical significance was defined as two-tailed p less than 0.05 for all analyses.

Results

Descriptive data

Tables 4 and 5 show the descriptive data of 331 women included in the analysis.

Table 4. Descriptive data of 331 women included in the analysis

Parameter	*Mean (SD)*
Age (years)	54.3 (12.1)
Weight (km)	51.9 (10.84)
Height (m)	1.49 (0.62)
BMI (kg/m²)	23.2 (4.41)
Menopause (years)	46.3 (5.77)
Menarche (years)	13.9 (1.57)
Milk Ca (gm/day)	320 (171)
BMD spine (gm/cm²)	0.760 (0.164)
BMD femoral neck (gm/cm²)	0.711 (0.137)
BMD trochanter (gm/cm²)	0.548 (0.112)
BMD Ward's triangle (gm/cm²)	0.499 (0.131)
Parameter	*%*
Women menopaused	83.1%
Women with BA diseases	13.2%
Women taken HRT	6.6%
Women taken Ca ± vitamin D	4.5%
Women taken other BA drugs	17.5%
Family history of fragile fractures	7.9%

BA = Bone active

Table 5. Median and IQR of parity and period of lactation

Parameter	*Median*	*IQR*
Parity (number)	3	2-5
Lactation (years)	4	2-7

Mean BMD values of different age groups are shown in Table 6. Maximum BMD was seen in 40-49 age group and a gradual but significant decline was noted beyond 50 years at all skeletal sites.

Table 7 shows the mean T scores calculated using two reference data sets and their differences at three skeletal sites. Asian reference data produced significantly lower T scores at lumbar spine and femoral neck and significantly higher T scores at trochanter when compared with those produced using European data. Table 8 shows the percentages of osteoporotic, osteopenic and normal women at different skeletal sites when analysis was done using Asian and European reference data and their agreement. Almost perfect agreement was seen at lumbar spine and agreement at other two sites was moderate. Although the proportion of patients with osteoporosis at the lumbar spine was similar, certain degree of discordance was seen at two hip sites.

Table 6. Mean (and SD) BMD according to age groups

Site	*<40 ys (n=36)*	*40-49 (n=51)*	*50-59 (n=126)*	*60ys (n=96)*	*P value*
S BMD	0.831 0.168	0.860 0.179	0.766 0.141	0.669 0.132	<0.001
FN BMD	0.749 0.144	0.796 0.135	0.741 0.122	0.632 0.144	<0.001
Tro BMD	0.564 0.120	0.596 0.112	0.575 0.101	0.492 0.102	<0.001
Ward's	0.542 0.145	0.565 0.134	0.525 0.115	0.427 0.109	<0.001

S BMD = lumbar spine BMD, FN BMD = femoral neck BMD, Tro BMD = trochanteric BMD, Ward's = Ward's triangle BMD

Table 7. Mean (SD) of T scores using two reference data sets

Site	*Asian*	*European*	*Mean difference*	*95% CI*	*P value*
Lumbar spine (n=311)	-2.54 (1.33)	-2.49 (1.01)	-0.050	-0.086 to -0.014	0.006
Femoral neck (n=315)	-1.22 (1.29)	-0.94 (1.14)	-0.285	-0.302 to -0.268	<0.001
Trochanter (n-315)	-1.11 (1.00)	-1.48 (1.12)	-0.369	-0.351 to -0.381	<0.001

Table 8. Prevalence of osteoporosis and osteopenia based on Asian and European data sets and their agreement

Site	*% using Asian Data*	*% using European Data*	*Kappa*
Lumbar Spine			
Osteoporosis	49.5% (164)	49.2% (163)	0.922**
Osteopenia	38.7% (128)	43.2% (143)	
Normal	11.8% (39)	7.6% (25)	
Femoral neck			
Osteoporosis	15.1% (50)	8.2% (27)	0.743**
Osteopenia	45% (149)	43.5% (144)	
Normal	39.9% (132)	48.3% (160)	
Trochanter			
Osteoporosis	6.6% (22)	19% (63)	0.653**
Osteopenia	52.3% (173)	48.3% (160)	
Normal	41.1%(136)	32.6% (108)	

**P<0.01

Correlation of BMD between different sites

Crude BMD values at lumbar spine, femoral neck and trochanter showed positive and highly significant correlations with each other (Table 9). These correlations persisted even after controlling for the effect of age and body proportions (data not shown).

Table 10 illustrates the percentage of patients labeled osteoporotic, osteopenic and "normal" at different skeletal sites when Asian reference data set was used on this cohort of women. A high degree of T score discordance was seen across skeletal sites. Prevalence of osteoporosis varied from 6.6% at trochanter to nearly 50% at lumbar spine and proximal radius. Even within the two hip regions the prevalence varied from 6.6% to 15%. The variation in the prevalence of osteopenia across skeletal sites was less pronounced and varied from 30% to 55%. 8% women were diagnosed "normal" at proximal radius, but 40% of them found to have normal BMD at the hip. This discordance persisted in all age groups included in the analysis (Table 11).

Table 9. Correlation coefficient (r) of BMD between different sites

	Lumber spine	*Femoral Neck*	*Trochanter*	*Ward's triangle*
Lumber spine	-	0.739**	0.732**	0.695**
Femoral neck	-	-	0.861**	0.905**
Trochanter	-	-		0.855**

**P<0.01

Table 10. Prevalence of osteoporosis and osteopenia (Using the Asian reference data) at different skeletal sites

	Osteoporosis	*Osteopenia*	*Normal*
Lumber spine (n=331)	49.5% (164)	38.7% (128)	11.8% (39)
Femoral neck (n=331)	15.1% (50)	45.% (149)	39.9% (132)
Trochanter (n=331)	6.6% (22)	52.3% (173)	41.1% (135)
Distal radius and ulna (n=189)	31.2% (59)	31.7% (60)	37% (70)
Proximal radius (n=189)	55% (140)	36.5% (69)	8.5% (16)

Table 11. Prevalence of osteoporosis at dfferent sites in three age groups

Age	*Lumbar spine*	*Femoral neck*	*Trochanter*
Less than 50 years (n=88)	28.4%	6.8%	2.3%
Between 50 - 69 years (n= 213)	57.7%	16%	7.5%
Over 70 years (n= 27)	55.6%	37%	11.1%
All (n=328)	49.5%	15.1%	6.6%

Patients were considered to have "definite osteoporosis" when T score was equal or below -2.5 either at spine or femoral neck (n=174). Analysis was done to determine the sensitivity and specificity of other skeletal sites in detecting osteoporosis in this cohort (Table 12). By definition spine and femoral neck had 100% specificity. Trochanter and distal forearm bones had specificity above 90% and proximal radius showed the lowest but acceptable specificity. Lumbar spine had the highest sensitivity (94%) followed by proximal radius with 84% and distal forearm bones with 55%. Both regions in the hip were found to have a low sensitivity.

Misclassification was defined as '% of patients not identified as having osteoporosis despite having definite osteoporosis when a single skeletal site is taken into the consideration' (Table 13). Misclassification at lumbar spine was minimum (5.7%) while at hip misclassification was very high (70%). Misclassification at proximal radius was only 16%.

Hip geometry

Table 14 shows the mean (and SD) values for femoral neck width, neck-shaft angle, BMD at femoral neck and trochanter in four chosen age groups. The mean height and weights were significantly different in these age groups and above four parameters were adjusted for these two confounding factors. Adjusted BMD values at both sites, femoral neck width and neck-shaft angle were significantly different in four age groups. Regression analysis was done to examine the effect of advancing age on hip BMD and geometry (Table 15). Advancing age reduced BMD at both hip sites, widen the femoral neck width and narrowed the neck-shaft angle. Independent of the height and weight, 10 year age increase would reduce the femoral neck and trochanteric BMD by 0.050 gm/cm^2 and 0.030 gm/cm^2 respectively, expand the neck width by 2 mm and reduce the neck-shaft angle by 0.58 degrees.

Table 16 shows the effect of parity on hip BMD and geometry. The mean BMD values of femoral neck and trochanter were relatively higher in nulliparous compared to parous women but this difference was not statistically significant. Although the femoral neck width was not different between the two groups, the average neck-shaft angle of parous women was 2 degrees wider than that of nulliparous women and this difference was statistically significant.

Table 12. Specificity and sensitivity of different skeletal sites, when a patient is recognized to have "definite osteoporosis" (n=174)

	Sensitivity	*Specificity*
Lumbar spine (n=174)	94.3% (164)	100%
Femoral neck (n=174)	28.7% (50)	100%
Trochanter (n=174)	11.5% (20)	98.7% (172)
Distal radius + uina (n=99)	54.5% (54)	94.4% (94)
Proximal radius (n=99)	83.8% (83)	76.7%. (78)

Table 13. Percentage (n) of patients with definite osteoporosis but classified as osteopenia or "normal" at a different skeletal site

	Osteoporosis	*Osteopenia*	*Normal*
Lumbar spine	94.3% (164)	5.7% (10)	0
Femoral neck	28.7% (50)	54% (94)	17.2% (30)
Trochanter	11.5% (20)	71.8% (125)	16.7% (29)
Distal radius + ulna	54.5% (54)	31.35 (31)	14.1% (14)
Proximal radius	83.8% (83)	14.1% (14)	2% (2)

Table 14. Hip BMD, femoral neck width and neck-shaft angle in four age groups

	Below 40 ys (n=24)	*41-50 ys (n=46)*	*51-60 ys (n=97)*	*Above 61 ys (n=68)*	*P value*
Height (m)	1.49 (0.06)	1.51 (0.06)	1.50 (0.06)	1.47 (0.04)	<0.001
Weight (kg)	48.3 (8.0)	54.5 (12.2)	52.7 (8.8)	48.9 (9.1)	0.007
BMD FN					
Crude	0.804 (.128)	0.782 (.135)	0.741 (.123)	0.622 (.095)	<0.001
Adjusted*	0.825 (.128)	0.768 (.135)	0.739 (.123)	0.638 (.095)	<0.001
Troc BMD					
Crude	0.604 (.106)	0.584 (.116)	0.572 (.101)	0.488 (.090)	<0.001
Adjusted*	0.630 (.106)	0.572 (.116)	0.570 (.101)	0.505 (.090)	<0.001
Neck width (cm)					
Crude	2.88 (0.22)	2.90 (0.21)	2.88 (0.21)	2.94 (0.19)	0.28
Adjusted*	2.87 (0.22)	2.87 (0.21)	2.87 (0.21)	2.97 (0.19)	0.012
NS angle (degree)					
Crude	129.7 (3.77)	128.6 (4.57)	126.5 (5.15)	126.7 (5.00)	0.006
Adjusted*	129.2 (3.77)	128.2 (4.57)	126.4 (5.15)	126.9 (5.00)	0.059

* adjusted for height and weight
BMF FN = femoral neck BMD, Troc BMD = trochanteric BMD, neck width = femoral neck width and NS angle = neck-shaft angle

Table 15. The effect of advancing age on hip BMD and geometry

	Coefficients	*se*	*P value*
Femoral neck BMD			
Crude	-0.006	0.001	<0.001
Adjusted*	-0.005	0.001	<0.001
Trochanteric BMD			
Crude	-0.004	0.001	<0.001
Adjusted*	-0.003	0.001	<0.001
Femoral neck width			
Crude	0.002	0.001	0.21
Adjusted*	0.003	0.001	0.015
Neck shaft angle			
Crude			
Adjusted*	-0.058	0.031	0.063

* adjusted for height and weight

Table 16. BMD and hip geometry between parous and nulliparous women (corrected for age, height and weight)

Parameter	*Parous*	*Nulliparous*	*P value*
Femoral neck BMD	0.688 (0.024)	0.700 (0.009)	0.69
Trochanteric BMD	0.534 (0.020)	0.542 (0.007)	0.15
Femoral neck width	2.95 (0.041)	2.90 (0.015)	0.31
Neck shaft angle	128.78 (1.14)	126.40 (0.401)	0.05

Discussion

Population based studies using central densitometers are limited due to practical and economic limitations. Major populations based studies on osteoporosis were either multi-centered or employed mobile units, both of which are expensive. Useful information, especially of clinical interest has been obtained by studying referred patients for densitometry, although this would not be representative of general population[17]. This limitation should be kept in mind when generalizing data of this study.

83% of women in our study were postmenopausal and average age at menopause or menarche in our cohort are comparable with those of general population. 12% of them had asthma at some stage of their life. 18% were taking bone active medications, mainly corticosteroids. 6.5% were either current or past users of HRT and 4.5% were taking prescribed calcium with or without added vitamin D. Although the percentage of asthmatics was comparable, proportions of patients taking bone active drugs including HRT, calcium and vitamin D were higher in the study sample than what are expected in the general population. Diary calcium consumption was well below the recommended intake for this age group[16].

In a similar analysis, the mean age, height, weight and BMI of a group of women referred for densitometry in Michigan USA were 65.2 (8.8) years, 1.59 (0.71) meters, 63.8 (12) kg and 25.3 (4.4) kg/m^2 respectively[17]. Although the Sri Lankan women are expected to be lighter and shorter than the USA counterparts, the difference of age by nearly 10 years between two groups, who had been selected for densitometry on clinical criteria needs an explanation. Does postmenopausal bone loss and hence osteoporosis start at an earlier age among Asians or is this due to different selection criteria? Limited amount of data from India has shown that the peak age of Indians with hip fractures to be at least 10 years below the European patients (Table 17)[19]. In a previous study, the age distribution of our patients with hip fractures showed a median and IQR of 68, 50.5 -76 years[8]. Whether Asians develop osteoporosis and suffer fragile fractures at an earlier age in comparison to Europeans is a valid question that needs to be answered in the future.

Table 17. Age distribution of patients with hip fractures in different countries

Author	*Average age (years)*	*Males %*
Evans	74	37%
Stewart	71	26%
Cleveland	75	11%
Wong		
Chinese	63	27%
Malay	59	62%
Indians	58	76%
Gupta	55	63%

How did clinicians fare in selecting cases?

Patients numbering 173 (53%) were found to have osteoporosis at a central site such as lumbar spine and or femoral neck and they required further laboratory evaluation and therapeutic interventions. Further 116 (35%) had osteopenia either at lumbar spine or femoral neck and they qualified for follow up scans to assess the progress. Hence 88% of patients referred for

densitometry had "abnormal scan result at a central site". Comparable figures have been reported in a similar study in USA. In this study 53% women referred for densitometry had osteoporosis while further 38% had low bone mass at a central site[17] . Although densitometry was added as a new facility and clinicians had no formal guidelines for referral, the selection of cases was remarkably comparable to a Western country, where the facility has been available for many years and strict guidelines are available.

The mean BMD at all sites showed an accelerated loss after 50 years. This is an universal phenomenon, vvhich has no ethnic or geographical barriers. Classification of patients to osteoporosis, osteopenia or normal based on T score thresholds and using two different reference data sets showed good agreement at all sites. The percentages of patients classified as having osteoporosis at the lumbar spine were similar for both reference data sets and the agreement was almost perfect. A substantial agreement was seen at hip region, although European data set overestimated osteoporosis at trochanter and underestimated it at the femoral neck. There was an overlap of patients with osteoporosis, osteopenia and normal BMD at different sites and this is reflected in the mean T scores seen. The mean T scores obtained using two data sets showed inconsistent but significant differences at all three sites

Making a country specific reference data set is a daunting task. Previous work has shown that 100-150 representative subjects should be selected to each decade from 20 years onwards to get a reliable mean and SD values for the population. Scanning this number in community based study need to be multi-centered with cross calibration between different types of scanners. The manpower and cost required for this kind of study is prohibitive to many Asian countries. Until such data are available we see no major obstacle in using NHANSE III data for the analysis of our women.

T score discordance between sites?

T score discordance has been observed in previous studies. Discordance indicates that a patient with T score in the osteoprotic range at one skeletal site to have less pronounced changes at a different skeletal site. The reason for this phenomenon appears to be multifactorial. The composition of bone with regards to the proportions of cortical and calcellous bone, the differential rate of bone loss at different skeletal sites, presence of degenerative changes and accuracy of BMD measurements at different sites all contribute to this phenomenon. Estrogen deficiency and prolonged corticosteroids treatment cause rapid bone loss at sites which are rich in cancellous bones. Changes in steroid induced osteoporosis or postmenopausal osteoporosis are greater in the spine (60-70% cancellous bone) than in the femoral neck (50% cancellous bone). Sub-clinical vitamin D deficiency mediated through secondary hyperparasthyroidism causes deterioration of cortical bone at peripheral sites and changes are maximally seen in the mid radius level.

The major causes for T score discordance are classified into five etiologic types:

1. **Physiologic**: the skeleton's adaptations to mechanical stress
2. **Pathophysiologic**: a disease state affecting the skeleton
3. **Anatomic**: differences in sites in content of cortical and trabecular bone and rate of bone loss
4. **Artifactual**: the presence of manmade or natural artifacts within the region of interest
5. **Technical**: faulty hardware or software.

We observed a substantial T score discordance among our patients. Site-specific prevalence of osteoporosis was highest at the lumbar spine while prevalence at proximal radius was only marginally low. Hip had the lowest prevalence while distal forearm bones were in between. The discordance of T score between spine and hip sites were apparent in all age groups although the discrepancy was less pronounced as age increased. Hip is less vulnerable to the effects of artifacts and the prevalence of osteoporosis increased at hip sites with the advancing age. The proportion of patients with osteoporosis at the spine did not increase or slightly decreased over 70 years. Osteophytes formation and other degenerative changes in the spine seen in old age would have caused falsely elevated BMD at the spine in old age.

In USA, a similar analysis showed that the prevalence of osteoporosis was highest in mid-radius (37.9%), followed by lumbar spine and femoral neck (34% at each site) and discordance of the entire patient sample was not great. When analysis was redone taking the age into the consideration, the discrepancy between spine and hip area increased in women above 80 years but remained same in other age categories[17].

In a separate analysis by Hong-Wen Deng et al, nearly 30% of patients, the difference between hip and spine T scores was >1.00 while in 15.2% of patients the difference of >2.00 was observed[20]. In a community-based study, the minor discordance

(defined as having T scores in two different WHO categories) between hip and spine was encountered in about two in every five patients scanned. Major discordance (defined as having osteoporosis at one site and normal BMD at another site) was found in one in every 20 patients tested[21].

The T score discordance appears to be an universal phenomenon with some degree of geographical variation and clinicians have no control over this since they do not understand the reasons behind it. The contribution of genetic, nutritional and environmental factors for this phenomenon is largely unknown. The vitamin D status of these patients and its contribution to differential bone loss have not been tested. When a group of postmenopausal women with osteoporosis but free of chronic liver and renal diseases were assessed for their calcium levels, 30% of women had low corrected serum calcium and further 23% (total of 53.3%) had 24 hour urinary calcium excretion below 100mgs[22]. If low 24 hour urinary calcium excretion in the absence of liver or renal diseases can be considered a surrogate marker of vitamin D deficiency, significant proportion of our free living postmenopausal women can be expected to have this condition. When Mithal, et al checked the vitamin D levels in 75 young healthy adults in Lucknow, India 56% of them had severe vitamin D deficiency, determined by 25 hydroxy vitamin D levels[23]. However vitamin D levels in other parts of India have produced inconsistent results and the entire picture is not completely clear[19].

It is interesting to know whether the marked difference in the prevalence of osteoporosis between spine and hip is reflected in the prevalence of hip and spine fractures in the community. Although the exact figures of the incidence of fragile fractures in Asia are unknown, WHO working group considered the current hip fracture incidence among Asian to be lower than that of European and Africans. However the incidence of vertebral fractures is expected to be relatively higher and lie between that of Europeans and Africans. No studies have been done on vertebral fractures in our country although several studies on hip fractures are currently underway. In a prospective study, total of 40 hip fracture patients were seen during the initial 4 months in Galle district (unpublished data) and this indicates very low incidence of hip fractures in our set up.

When the sensitivity and specificity of different skeletal sites were analyzed, lumbar spine appeared to be the most appropriate site to scan to detect osteoporosis. Both sites at hip showed a low sensitivity. The specificity of distal radius and ulna was acceptable although the sensitivity was only 54.5%. High sensitivity and specificity seen at proximal radius is encouraging since this will be of clinical relevance. Proximal radius can be included as an additional site for scanning to improve the sensitivity of the densitometry when a central site is not suitable or not available for scanning. Presence of artifacts and abnormal calcification can change the actual BMD values at both hip and spine. Proximal radius can be the alternative site for these patients. Peripheral densitometers, which can scan forearm bones are available now and these less expensive and portable devices will be appropriate for mass screening of our women.

Hip geometry

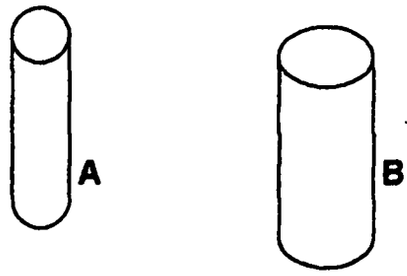
For the first time we have looked at hip geometry data in Sri Lankan women. Indices of hip geometry, independent of BMD have been shown to be determinants of hip fractures[14] . These indices show a wide geographical variation and this in part considered to be responsible for wide variation in hip fracture incidence seen between countries.

Asian woman is believed to have a wider femoral neck and a smaller neck-shaft angle, both of which are protective against a hip fracture. However we have only limited amount of data to support this belief. In a study by Nakamura and others, white American women were found to have longer neck length and a larger neck-shaft angle when compared with Japanese women[24]. Despite lower BMD, the favorable hip geometry in Japanese probably explains the lower hip fracture incidence seen among them. In this study, the mean neck-shaft angle of Japanese women was 128 degrees and this was significantly smaller when compared with 130 degree neck-shaft angle of Americans. We have observed a 126 degrees average neck-shaft angle among Sri Lankan women in the comparable age group. Since different machines were used in these two studies, direct head to head comparison of these figures can produce wrong conclusions. When two groups of Italian post-menopausal women with and without hip fractures were measured using a Norland machine and the same software, the neck-shaft angle estimated were 122.6 and 125.5 degrees in healthy and fractured women respectively[14]. These figures are much similar to our data. However femoral neck width of 2.94 cm we detected in our women is much smaller when compared with that reported from the Italian women. Italian women with and without hip fractures in this study had femoral neck widths of 3.18 and 3.34 crn respectively.

Tom Beck and others demonstrated age-related changes in neck width in a cohort of USA men and women[25]. The femoral neck BMD of these women showed the typical age-related decline, which is seen

universally in all ethnic groups and all countries. Gradual expansion of neck width expressed as subperiosteal expansion was also seen in the same cohort of women. It is well known that the force required to induce buckling or bending a tube increases with the tube diameter. Tube with larger diameter can resist bending and torsion forces and will be less vulnerable to fractures (Picture 1). Hence the subperiosteal expansion shown in this study was believed to compensate at least in part the negative impact on bone strength caused by BMD reduction.

Picture 1. Width of the tube and resistance to bending



Tube B offers a greater resistance for bending than tube A.

Age related bone loss has not been studied in our women previously. In our data, reduction of hip BMD with age was accompanied with expansion of femoral neck and reduction of neck-shaft angle. In the regression analysis, independent of height and weight, aging by one decade was associated with reduction of BMD at femoral neck and trochanter by 0.050gm/cm^2 and 0.030gm/cm^2 respectively and expansion of femoral neck width by 3mm and reduction of neck-shaft angle by 0.030 degrees. These trends in the neck diameter and neck-shaft angle must be compensating for the age related bone loss seen in our women.

In a USA based study, Tom Beck and others estimated age related changes in BMD and indices In hip geometry[28]. Femoral neck BMD declined by 3.41% and 5.03% per decade after 20 years in men and in women. However a significant expansion of femoral neck width by 1.04% per decade was observed in men while no significant change in neck expansion was seen in women. These trends probably explain the gender differences in hip fracture incidence in Western countries. In contrast, women in our cohort lost femoral BMD by 7.2% while neck expansion occurred by 1.04% per decade after 40 years of age. Although our women lose more bone with the advancing age the compensatory subperiosteal expansion may protect them from fractures.

The effect of parity and lactation on femoral BMD has been examined in few studies. In a case control study, parity and lactation both induced additional bone loss but the recovery of bone following weaning was complete[27]. We were unable to demonstrate a difference in BMD or hip structure parameters between nulliparous and parous women in our cohort. However retrospective power calculations showed that for the numbers included for the analysis and for the mean differences, power of the estimations to range between 9-16% only. We need to test these differences in a larger sample to have more power for the estimations.

Conclusions

Most patients referred had an abnormal scan and clinicians were accurate in referring cases. However national guidelines for densitometry should be developed in future. A marked heterogenicity in the prevalence of osteoporosis across skeletal sites was seen and the degree of disparity was greater than what has been reported from European countries. The prevalence of osteoporosis was high in the proximal radius and lumbar spine and a low prevalence was detected in the femoral neck. Proximal radius showed an acceptable sensitivity and specificity to be used as an alternative site for screening. Until, country specific reference data are developed, we see no major problem in using NHANES III data for the stratification of our women. Age related changes in hip BMD and geometry showed promising trends for further research. Parity had no profound effect on either hip BMD or geometry.

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