Manuscript

: DETERMINATION OF LOCAL MALAY FEMALE BONE MINERAL DENSITY AND ITS'CORRELATION WITH GEOMETRIC PROPERTIES IN THE EVALUATION OF SKELETAL STATUS

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ABSTRACT

Aims: To establish bone mineral density (BMD) reference data for local Malay female population and to determine the correlation of BMD and geometric properties

Methodology: A total of 137 Malay female volunteers who have given a written informed consent and undergone DEXA of the spine, dual femur and total body. Plain radiographs of non-dominant hand of all the subjects were also taken for the measurement geometric properties (GP). All the readings were analysed appropriately and results were recorded

Results: A reference curve of BMD (DEXA) versus age group was obtained from the mean and standard deviation of the peak age value. The local BMD corresponding to -2.0 standard deviation from the peak adult value for vertebral and total body BMD were 12.2% and 3.2% respectively lower whereas for the dual femur it was 1.2% higher compared to the Caucasian reference data (U.S/Europe). There were fair to good correlation between weight and BMD ($r = 0.344 - 0.642$). Generally fair to good correlation was seen between vertebral, dual femur and total body BMD with cortical area (CA), cortical thickness (CT) and metacarpal index (MCI), particularly of the second metacarpal. Multi linear correlation models accounting for CA2 and CT2 in addition to weight have improved the predictive power of a model for weight alone.

Conclusion: Bone mineral density data is available currently for overseas population; but not for Malays. Establishment of database for each race in Malaysia is important for proper skeletal status evaluation, in view of significant differences in the local Malay BMD value compared to other population reference data. Geometric properties can be used as a cheapest tool to predict BMD and may improve the accuracy of diagnosis of osteoporosis and prediction of fracture risk.

KeyWords: *Bone Mineral Density, DEXA, Geometric Properties, Cortical thickness.*

INTRODUCTION

Osteoporosis is a chronic progressive systemic deteriorating skeletal disease characterised by low bone mass and fragility with a consequent increase in bone susceptibility to fracture. The incidence among the white and oriental population are higher compared to other races, affecting female more than male. In Malaysia, Chinese has the highest incidence of hip fracture compared to Malays and Indians.[1,2] It is a serious health problem worldwide, resulting in progressive health deterioration, morbidity and increase annual health care cost. In view of these factors, prevention and treatment of osteoporosis is based on early identification of those at greater risk prior to the occurrence of fracture. There is no universally accepted algorithm for the assessment of women who are at risk or already have osteoporosis.

Among currently available few techniques for determination of bone density Dual Energy X-ray absorptiometry (DEXA) is the most accurate and widely used. Plain radiography is no longer generally used for evaluating bone mass in quantitative terms because as much as 30% to 40% of bone mass must be lost before changes can be seen on plain radiograph. Currently Dual Energy X-ray absorptiometry (DEXA) with other highly accurate and precise quantitative techniques such as single X-ray absorptiometry (SXA), single and dual photon absorptiometry (SPA, DPA) and quantitative computed tomography (QCT) have provided an accurate measurement of bone mineral density (BMD) that is useful to predict fracture[3]. However there are limitations. High attenuation material, extraneous calcification and sclerotic bone may increase the final result of BMD because DEXA software is unable to differentiate them to bone. QCT can exclude the unwanted high attenuation material however it gives higher radiation dose to patient. Both geometry and density contribute substantially to the strength of the skeleton.[4] Thus by incorporating geometric properties to BMD measurement these problems may be eliminate or reduced.

WHO in 1994 and the Japanese Society for Bone and Mineral Research 1996 criteria (that was revised in 1998 and also in 2000) have established diagnostic criteria used for diagnosis of normal, osteopenia and osteoporosis.[3] Except for white women and part of Japanese as well Chinese women, the reference database of hip fracture risk for other races and male population is unknown. Furthermore the bone mineral content, architecture and geometry of one population are different from another due to environmental and genetic influences. Most manufacturers of bone mineral densitometer in Asia are using the Oriental Women reference database that is

not specific. A standardized reference database for each skeletal site and a 'gold standard' technique to be adopted by all manufacturers are still not available. Thus the purpose of this research study is to establish a normal reference data of BMD for Malay population, and to determine the correlation of BMD data with geometric properties become very important.

METHODOLOGY

This study was a comparative, cross sectional prospective study performed between July 2002 and June 2005 at Hospital Universiti Sains Malaysia and approved by the ethical committee. 137 Normal Malay female volunteers from Kelantan, above 20 years old were included in the study. The exclusion-criteria are stated in Table 1. All volunteers fulfilled the inclusion criteria were categorised to six age groups (every decade), from 20 to 79 years of age.

Bone mineral density measurement

The methods of this study is summarised in Figure 1. Bone mineral density measurement of volunteers was performed using LUNAR PRODIGY, GE Medical Systems. Attenuating objects such as jewellery or ornaments are removed from the volunteers. After the volunteer's identification, height and weight have been entered into the directory screen, the measurement site is selected. Software would automatically calculate scan length and scan mode based upon entered volunteer height and weight. AP Spine, dual femur and total body are the skeletal sites measured.

Hand Radiograph

Plain PA radiograph of non-dominant hand was performed using Optimus RAD, Philips Medical Systems. The volunteer's pelvis was shielded by a gonad shield. The hand was within the Kodak X-Omatic cassette (Lanex regular screen) that was placed on the top of the table. Double emulsion film for extremities, size 18cm X 24cm was used. Tube voltage was 50kV with mAs of 1.5 to 3.0 and Focal spot of 0.6mm. Film-focus distance was 100cm. The hand radiograph was to be used for measurement of geometric properties.

Establishment of T score

$$\text{Mean } (x^*) = \frac{\Sigma x}{n}$$

$$\text{Standard deviation } (SD^2) = \frac{\Sigma [x_l - x^*]^2}{}$$

n - 1

$$SD = \sqrt{\frac{\Sigma [x] - x*]^2}{n - 1}}$$

The graph of vertebral, dual femur and total body BMD was plotted against age with the standard deviation (SD) obtained from the peak age SD.

Geometric properties formula

From the hand radiograph: second, third and fourth metacarpal's inner and outer diameter were measured at middle of the shaft on the longitudinal axis as shown in Figure 2.

The geometric properties parameters:

OD – mediolateral outer diameter (mm)

ID – mediolateral inner diameter (mm)

CT – cortical thickness (mm)

CA – cortical area mm^2

J – polar moment of inertia (mm^4)

Z – section polar moment (mm^3)

MCI – Metacarpal index

Formulas derived from the above parameters.[5, 6]

1) $CT = (OD-ID)/2OD$

2) $CA = \pi R^2 - \pi r^2$

$= \pi (R^2 - r^2)$

3) $J = 2\pi (OD^4 - ID^4)/ 64$

$= \pi(OD^4 - ID^4)/ 32$

4) $Z = 2J/OD$

5) $MCI = (OD-ID)/ OD$

$R = OD/2mm$, $r = ID/2mm$

Statistical analysis

The data collected in this study were entered and analyzed using SPSS version 10.0 for Windows statistical software. The means and standard deviation (SD) for vertebral, dual femur and total body were calculated and expressed as mean $\pm$ SD. A graph of BMD (DEXA) versus age group was obtained from the mean of each age group with the ± 1 and ± 2 standard deviation obtained from the peak age bone mineral density group. The local reference data and graphs were compared with reference database of Caucasian (US/Europe) and Chinese female.

The relationship between BMD and geometric properties (GP) of total 137 volunteers were analyzed with Pearson correlation analysis. The strength and direction of the relationship between vertebral BMD (VTBMD), dual femur BMD (DFBMD) and total body BMD (TBBMD) respectively with each geometric properties which were CT, CA, J and Z of second, third and fourth metacarpal were analyzed. Interpretation of correlation coefficient were, no or poor correlation when $r < 0.25$, fair if $0.26 - 0.50$, good when $r = 0.51 - 0.75$ and excellent when $r = 0.76 - 1.0$.

The relationship between BMD and Geometric properties according to age group were also analyzed with Pearson correlation analysis if n (number of volunteers) were more than 20 and Spearman correlation if $n < 20$. Significantly correlated results were selected using MANOVA and entered into a stepwise regression to determine the major factors that were the age, weight, height body mass index (BMI) as well as geometric properties in prediction of vertebral, dual femur and total body BMD. For all the analysis of significance, α value of 0.05 is used.

RESULTS

The numbers of volunteers who were involved in this study and have met the inclusion criteria are 137. They range from 20.2 to 75.3 years old and limited to six age groups. The number of volunteers for each age group was as follows: 20-29 (n= 40), 30-39 (n= 24), 40-49 (n=39), 50-59 (n=22), 60-69 (n=8) and 70-79 (n=4).

Normative reference curve:

From the BMD obtained from each age group (Table 4), a scatter plot (Graph 1,2,3) for BMD of each skeletal sites versus age was generated to demonstrate local population T score with the SD obtained from peak age bone mineral density. The peak age bone density for vertebral body bone mineral density (VTBMD) is 40-49, for dual femur BMD (DFBMD) and total body BMD (TBBMD) are 50-59.

Anthropometric correlation (Table 5):

There is good correlation between weight and DFBMD as well as TBBMD whereas the correlation between weight and VTBMD is fair. The total body BMD (TBBMD) has the greatest correlation with weight. There is no correlation between age and height with VTBMD, DFBMD and TBBMD.

Geometric properties correlation:

Poor or no correlation between internal diameters of second metacarpal (ID2), third metacarpal (ID3), fourth metacarpal (ID4), second outer metacarpal (OD2), third outer (OD3), fourth metacarpal (OD4) with VTBMD, DFBMD AND TBBMD. Overall, positive correlation is seen between cortical thickness (CT) and metacarpal index (MCI) of the second, third and fourth metacarpals with BMD of the three skeletal sites measured by DEXA (Table 6 and 7). Otherwise DFBMD and TBBMD are fairly correlated with the CT2, CT3, CT4, MCI2, MCI3 and MCI4. VTBMD has fair correlation with CT2 and CT3 but not with CT4. The VTBMD and MCI2, MCI3, MCI4 are also poorly associated. All fair to good correlation, $p<0.05$.

The correlation between geometric properties particularly cortical area (CA) of the three metacarpals with VTBMD($r = 0.391$-0.536), DFBMD($r = 0.314$-0.466) and TBBMD ($r = 0454$-0.593) according to age group shows the greatest association in the younger age group (20-29). Similarly when the total of 137 volunteers' VTBMD, DFBMD and TBBMD correlated with CA, polar moment of inertia (J) and section polar moment (Z) respectively, correlation with CA is greatest with $r = 0.314, 0.284, 0.360$, $p<0.05$ (Table 8). All geometric properties of second, third and fourth metacarpals of second decade group, $p < 0.05$ when correlated with VTBMD, DFBMD and TBBMD except for J and Z of second and fourth metacarpal when correlated with DFBMD. The older age group 60-69 and 70-79 also showed good to excellent correlation but statistically not significant due to small sample size.

Limitation:

The major limitation of the study is the small sample size. Most of the older age group volunteers were excluded due to numerous reasons. Most of the excluded patients have chronic diseases particularly hypertension and diabetes. Some of them were on hormonal replacement therapy more than six months. Data with improper positioning and selection of region of interest were excluded as well. All these limitations contribute to the small sample size. The target sample size was 240 (40 in each age group) but a total of 137 volunteers only were included. In view of the small sample size, some of the results may not be statistically significant particularly when

the data were analyzed according to age group. However, this can be a starting point for future larger scale study.

DISCUSSION

Demographic data

This research study mainly concentrates on Malay female because 90% of Kelantan population is Malay. There were six age groups. The total target sample size was 137 and the numbers of volunteers in 20-29 are n =40, 30-39 (n=24), 40-49(n =39), 50-59 (n =22), 60-69 (n = 8) and 70-79 (n = 4). The last two groups had the smallest sample because most of them were on prolonged medication that might affect the bone.

Determination of local Malay female BMD reference data

The mean peak age VTBMD and TBBMD of local Malay females were 4.6% and 1.3% lower than the Caucasian whereas the DFBMD was 1.1% higher than the Caucasian. The BMD data of Caucasian female was taken from Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 4th edition, 1999. However, the Malay females' VTBMD and DFBMD were 10.7% and 13.6% respectively higher than the peak bone mass values of Hong Kong Chinese women.[7] The value of peak bone mass of the spine and femoral neck for Hong Kong Chinese women were 1.03 $\pm$ 0.12 and 0.86 $\pm$ 0.11 g/cm^2 respectively. These findings indicate that if the Malay female BMD for dual femur were based on Caucasian or Hong Kong Chinese female reference data base, they will be under diagnosed for osteoporosis and appear to have lower fracture risk of the hip. If the Caucasian vertebra and total body reference data bases are used to diagnose osteoporosis in Malay female, this will overestimate the incidence of osteoporosis in Malay female. Similarly if local Chinese female BMD are based on Hong Kong Chinese female reference data, the diagnosis may not be accurate even though they come from the same descendent. As reported by previous study in which the BMD of Japanese overall are lower than Japanese living in the United States though they are of similar genetic stock.[8] These could be attributed to adaptation of new life style which eventually affects the individual body built. The rate of bone loss is also different among populations of same ethnicity. Er-Yuan et al (2003), found that there is remarkable difference in the reference figures between the newly established Chinese Women BMD Reference Databases (CWD) and the Oriental Women reference curves from the Hologic QDR 4500A bone densitometer.[9] The CWD curve rises with age whereas the Hologic

reference curve inclined to declined continuously. In addition the rate of descent after the peak value of CWD figure of AP spine, lateral spine and radius as well as ulna site is remarkably greater than that of Hologic Reference figure. These findings suggest that factors such as differences in genetic, environmental and life styles should be taken into account. Due to this complex relationship between BMD and the factors involved, it is important to establish a local database for correct diagnosis of osteoporosis.

Numerous report have also suggested of higher BMD in Caucasian than Asian population.[2, 8] Similar findings noted in a longitudinal study of bone mineral acquisition in healthy Asian, Hispanic, Black and Caucasian youth. Asian females had lower mean femoral neck BMD, whole body BMD and whole body BMC/height ratio than Whites and Hispanics.[10] Many factors could contribute to these higher BMD in Caucasian than Asian. The Caucasian females may have higher health and fitness conscious and maintain this awareness throughout their life. Taechakraichana et al, 2003 found that most Bangkokian women regarded menopause as a natural change of life although some think treatment is needed.[11] In addition, more than 50% of the total respondents did not have enough clear information on menopause and hormonal replacement therapy (HRT). However increased knowledge and awareness may overcomes ethnic differences.[12] Nevertheless many Asian women living in the United Kingdom have fears and concerns similar to those of the Caucasian population but they still prefer to enquire more information from female doctors who can communicate in their own language.[13] This means that unawareness of HRT among Asian ladies may not be the sole factor that causes less Asian female seeking treatment for osteoporosis or postmenopausal symptoms but the preferences of these women on how to get the treatment and their cultural background should be taken into account.

In our study, the vertebral BMD of fifth decade group as well as the total body BMD of sixth and seventh decades were higher than Caucasian. This could be related to higher weight in this age group as shown in Table 3 (mean weight for fifth decade=64.4kg, sixth decade=64.4kg and seventh decade=53.8kg). More weight gain is associated with less bone loss. In postmenopausal women, the advantages of higher body weight on bone mass are due to aromatise activity in adipose tissue which eventually results in more estrogen formed from circulatory androgens.[14]

In the analysis of correlation of BMD and anthropometric data, we found there is fair to good correlation between BMD and weight ($r = 0.344 - 0.642$). Previous studies

also reported that there is linear correlation between BMD and weight. Bauer et al (1993), in their study on appendicular bone mass in older women found that weight loss after age 50 was associated with lower bone mass.[15] Each 10 kg of weight loss was associated with 3.9% reduction in bone mass. Hence strong association of lower weight with low bone mass may eventually lead to an increased risk for hip fracture. Therefore clinicians should be alert to the increased risk for fracture in slender women.[16] Our results also show that the highest correlation was between weight and BMD of the three skeletal sites, with the vertebral BMD (r = 0.344), dual femur (r =0.599) and total body (r = 0.642).

Apart from weight, other factors such as dietary, exercise habits, reproductive and lactation history could also attributed to higher VTBMD and TBBMD in older age group of local Malay women. Numerous studies showed that optimal exercise and dietary intake particularly calcium were beneficial to bone mass.[17, 18,19] On contrary to vertebral and total body BMD, the dual femur BMD of Malay women in all age group are higher than the Caucasian except for second and seventh decade group. Lau et al (2001), in their study on the incidence of hip fracture in Asian countries, found that Chinese men and women in Singapore and Malaysia have higher hip fracture rates.[24] The fracture rates for Indian subjects were comparable to the Chinese while Malays had lower rates. Malay women have less risk of hip fracture than other race possibly due to higher BMD as shown in our study when compared to the Caucasian reference data. Other explanation could be related to the rate of bone loss as reported by Xiaoge et al (2000). [25] They found that BMD and the rate of bone loss in Chinese women were lower than reference curves (Caucasian women) at all age groups and all sites, except for the femoral neck and Ward's triangle. From their observation, Chinese women take longer time to reach peak BMD and have a lower BMD decrease rate at the neck and Ward's triangle after peak BMD is attained. This may be the factor, which protects them against hip fractures. In spite of that, local Malay female reference curves showed that there is a transient rise from 20-29 to 30-39 age group then plateau until 50-59. Thereafter the rate of descent for local reference curve is steeper compare to Caucasian indicating the rate of bone loss is higher in local Malay female.

No correlation was found between age and height with BMD of Malay women. Bauer et al (1993) reported that taller women had higher bone mass and each 10-cm increase in height was associated with a 5.7% increase in bone mass.[15] this possibly attributed to the bone area size whereby the larger the skeletal size, the greater the

bone area. However in this study, height was not significantly correlated with BMD, possibly because not much difference in height among the volunteers noted. The mean height was 152.7 with a standard deviation of 6.3.

Correlation between Geometric properties and BMD

Our results show no or poor correlation between BMD with ID and OD. The internal diameter (ID) of second, third and fourth metacarpal have poor inverse correlation with VTBMD, DFBMD, TBBMD. Theoretically the ID increased with age after puberty, but our result showed that the bone is still in the process of mineralization until the age of 50-59, evidenced by overall BMD plateau from third to fifth decade. This is possibly due to the difference in the rate of bone resorption at different skeletal sites. Therefore ID and OD may not be good parameters to combine with BMD for the evaluation of skeletal status at different site. The periosteum tends to grow or expand with age. Although it occurs at a slower rate than bone loss in the endosteal surface this process results in a slight increase in overall total bone width. When bone width increase and cortical thickness decrease, the Metacarpal Index (MCI) will decrease with age. Cortical index represent the degree of osteoporosis. In our local Malay female population data there was no linear correlation of CT and MCI with age. Nevertheless CT and MCI declined with age. Somewhat similar findings have been reported by Russo et al, (2003). [29]. They compared the changes in trabecular and cortical bone in men and women using pQCT and found no significant age-related difference in cortical bone area in men and women before the age of 60 years old but became progressively lower in women after the age of 60 years. They hypothesized that this could be attributed to postmenopausal reduction in sex hormones. Other possible explanation to the difference in this parameter in men and women would be sex-related differences in lifestyle, such as physical activity and nutrition. Apart from reduction of sex hormone in postmenopausal women, a decline in cortical thickness may also be related to imbalance level of sex hormone. Hui et al (2002) found that higher levels of Follicular stimulating hormone (FSH) and Luteinizing hormone (LH) and lower levels of E1 sulfate and E2 were associated with faster bone loss in premenopausal women.[14] E1 sulphate is formed from both E1 and E2. They suggested that some pre-menopausal women despite not having any symptoms might have sub-optimal level of sex hormones.

Generally fair correlation was seen between total body and vertebral BMD with cortical area (CA) of second metacarpal with r = 0.360 and 0.314 respectively. This probably due to a non-significant reduction in BMD with age particularly in the first five

decades in TBBMD and VBBMD compared to DFBMD. A study conducted in Denmark by Warming et al (2002) also showed no significant changes in distal forearm BMD in women less than 50 years old.[32] However there was statistically significant fall in BMD at the hip and lumbar spine. The explanation to this, possibly related to the rate of trabecular and cortical bone loss whereby the former is greater than latter. If the rate of trabecular bone loss is slow, this appears to level off with the changes in the cortex. Therefore no gross changes to the human eye will be seen in the cortex of the bone but the micro architecture within the bone may change. In addition, intracortical resorption within cortical haversian canals can be detected radiographically and are best observed in the cortex of the second metacarpal bone. As predicted, the geometry properties (ID, CT, CA, J and Z) of the second metacarpal were correlated well with BMD than the third and fourth metacarpal.

From multi linear regression analyses, the BMD of the three skeletal sites are primarily related to weight. When geometric properties particularly from the second metacarpal were added into the model they improved the prediction power. Geometric properties (ID, OD, CA, J and Z) associated with BMD were also done according to age group. Parameters, which derived from the second decade group, showed fair to good correlation. Possible cause could be owing to cortical growth level off with bone mineral content at this age. This may indicate that geometric properties values obtained from this group can be used as the peak age values and its' standard deviation will form the 'T score' as in BMD. There were also good to excellent correlation between the older age group but the sample size were too small in these two age group (60-69 and 70-79) to draw a conclusion. Further studies with larger sample size are needed to support this postulation.

CONCLUSION

A reference curve has been established for local Malay women for proper and accurate diagnosis of osteoporosis.

CT, MCI and CA particularly from the second metacarpal are the geometric properties that fairly correlated with VTBMD, DFBMD and TBBMD. Furthermore when geometric properties (CA, CT and MCI) were added into models that consist of anthropometric data (weight and age), they increase the predictive power. This implies that incorporation of these geometric parameters with BMD is possible for the evaluation of skeletal status.

The following are equations to predict BMD, derived from multi linear regression analysis.

VTBMD = 0.708 + 0.121 (CT2)

VTBMD = 0.755 + 0.006175 (CA2)

DFBMD = 0.429 + 0.102 (CT2)

TBBMD = 0.699 + 0.0820 (CT2)

TBBMD = 0.539 + 0.00619 (CA2)

Recommendation

Based on these results, the author would like to suggest that apart from local Malay population reference curve, other races data should be established for better evaluation of BMD. In addition, multicenter study is more appropriate as the data reflects the whole Malaysian population. Prediction of fracture risk of a skeletal site is more accurate when it is done on the same site. Similarly geometric properties of a particular region may predict fracture risk of the same region better than other sites. A larger sample size and more detail information regarding subjects dietary habits, physical activity, profession, medical, obstetric and gynecological history, duration of lactation, menopausal history as well as family history of osteoporosis should be included. The relationships among these factors should be look into when assessing the skeletal status.

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ABBREVATIONS

BMD – Bone mineral density

DEXA – Dual Energy X-Ray Absorptiometry

DFBMD – Dual femur BMD measured by DEXA

MC – Metacarpal

PABM – Peak age bone mass

pQCT – Peripheral Quantitative Computed Tomography

QCT – Quantitative Computed Tomography

TBBMD – Total body BMD measured by DEXA

VTBMD – Vertebral BMD measured by DEXA

WHO – World health Organization