Cut-off values of distal forearm bone density for the diagnosis of central osteoporosis in black postmenopausal South African women

Kruger IM, PhD,[a] **Kruger MC**, PhD,[b] **Doak CM**, PhD,[c] **Kruger A**, PhD[a]
[a]Africa Unit for Transdisciplinary Health Research (AUTHeR), North-West University, Potchefstroom Campus
[b]Institute of Food, Nutrition and Human Health, Massey University, Palmerston North, New Zealand
[c]Department of Nutrition and Health, Institute of Health Sciences, Vrije University, Amsterdam, The Netherlands
Correspondence to: Iolanthé Kruger, e-mail: 12079642@nwu.ac.za
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Abstract

Background: The objective of this study was to establish a triage cut-off point or threshold for peripheral bone mineral density (BMD), applicable to black postmenopausal women, and that could be used as a screening method to differentiate between women with normal BMD, and those with possible central osteoporosis. This was a cross-sectional study design conducted in the North West province. Central and peripheral BMD was measured in 184 black, urban postmenopausal women.

Method: Receiver operating curves (ROC) analysis was used to establish cut-off points. Sensitivity, specificity, positive and negative predictive value, odds ratios and likelihood ratios were determined.

Results: The results showed a prevalence rate of 41.3% for central osteoporosis. The area under the curve (AUC) for osteoporosis at the hip was 0.818, and for the spine, it was 0.771. Using the optimum cut-off point (0.371 g/cm^2), our results showed a misclassification rate of ≈ 49% for spine osteoporosis, and a negative predictive value of 0.825. Women who had a forearm BMD below this threshold were ~10 times more likely to have osteoporosis of the spine.

Conclusion: We recommend using 0.371 g/cm^2 as a cut-off point to differentiate between women who have normal BMD, and those with possible osteoporosis of the spine.

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Introduction

Osteoporosis is considered to be a silent killer and as a result of its neglected status, especially in developing countries, the associated risks (i.e. bone fractures) are fast becoming a serious public health concern.[1,2] Osteoporosis affects nearly 200 million people worldwide, and with an estimated prevalence of 30% in postmenopausal women, bone mineral density (BMD) has become the single most important measurement in the evaluation and diagnosis of osteoporosis and its concomitant risks.[3] The most significant sites for osteoporotic fractures are the spine and femoral neck, and according to Ivorra Cortés et al, the measurement of BMD at central sites (spine and hip) is the best prognostic factor of osteoporotic fractures.[1,2,4] It is widely recognised that the strength of BMD measurement to predict future fractures is approximately threefold higher than the strength of serum cholesterol to predict cardiovascular diseases.[5]

There are various techniques to measure BMD, but the one that is currently used most is dual-energy X-ray absorptiometry (DXA). DXA is a high-precision BMD measurement and is considered to be the "gold standard". However, it is expensive to purchase, is large and bulky, and the test measurements are costly. This makes it unsuitable for research studies. Therefore, it is advisable to consider alternative methods of identifying patients at high risk of developing osteoporosis.

According to the World Health Organization (WHO), osteoporosis can be defined as "a systemic skeletal disease, characterised by a low bone mass and a micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures".[6] It has been shown that the risk of fractures can be assessed from BMD measurements obtained from peripheral sites.[7-9] One such example, the distal forearm, might act as a surrogate for the spine and hip.

The current T-score criteria of the WHO to define osteoporosis (-2.5 SD) cannot be applied universally to BMD measurements of peripheral sites (such as the forearm). This is partially due to differences between the young reference populations, as well as different bone composition and age-related bone loss differences.[10] Criteria for the selection cut-off values for osteoporosis are based on data on Caucasian women. However, according to the latest Middle East and Africa regional audit (*Epidemiology, Cost and Burden of Osteoporosis in 2011*), released by the International Osteoporosis Foundation (IOF), black South African women appear to have similar vertebral BMD, and equal vertebral fractures, to those of Caucasian women, yet their hip BMD values still

remain significantly higher.[11] Furthermore, in addition to an increased life expectancy (osteoporosis risk factor), lifestyle behaviours generally associated with favourable overall and bone health, are also lacking in black women, viz. low dietary calcium intake, and vitamin D and human immunodeficiency virus (HIV)/ acquired immune deficiency syndrome (AIDS) status.[12]

It is becoming more evident that osteoporosis is an equal opportunity disease. Therefore, the aim of this study was to establish a triage cut-off point or threshold for peripheral BMD, applicable to black postmenopausal women, that could be used as a screening method to differentiate between women with normal BMD, and those with possible central osteoporosis.

Method

Research design

This cross-sectional study was part of the South African arm of the Prospective Urban and Rural Epidemiology study (PURE). The PURE study, coordinated from the Population Health Research Institute, Ontario, Canada, is a longitudinal study designed to track the development of chronic lifestyle diseases, in urban and rural subjects, in approximately 20 developing countries.[13]

Participants and experimental procedure

An availability sample of 184 black, urban postmenopausal women (> 47 years of age, and based on their follicle stimulating hormone status) from the North West province in South Africa was recruited for the study. Forearm bone density measurements (BMD_{DTX}) were performed at the distal and ultra-distal sites in the non-dominant arm, using a DTX-200 peripheral DXA system (Osteometer MediTech, Hawthorn, California, USA). Conventional central bone density (BMD_{DXA}) scans of the lumbar spine (L1-L4) and hip were performed using a Hologic Discovery-W (Hologic, Waltham, Massachusetts, USA). The results for each variable were calculated by the methodology described in the user manuals of each manufacturer. The following skeletal BMD results were recorded: distal (radius plus ulna) forearm, femoral neck, total hip, and lumbar spine (L1-L4). According to Patel et al, the distal site is defined as the 24 mm-long section of bone immediately proximal to the reference line where the separation between the radius and ulna is 8 mm.[14] It consists of 87% cortical bone, and 13% trabecular bone. The ultra-distal site is defined as the area distal to the 8 mm reference line, and it contains 45% cortical, and 55% trabecular bone.[14] The Osteometer DTX-200 yields data on both the distal and ultra-distal sites. However, only the distal site values are reported. An availability sample out of the original group of women (n = 86) participated in the next phase, during which peripheral BMD_{DXA} scans were performed to determine total forearm, distal forearm, and ultra-distal forearm bone densities. All BMD testing was performed by a licensed radiographer. A quality control (QC) scan was undertaken daily to ensure precision with the required coefficient of variation (CV). All scan analyses were performed by one operator.

The study was approved by the Ethics Committee of the North-West University (Potchefstroom Campus, NWU-00016-10-A1), and the study protocol conforms to the ethical guidelines of the Declaration of Helsinki, as revised in 2004. All subjects gave informed consent.

Data analysis

Data were analysed using the Statistical Software for Social Sciences programme (SASW Statistics 18 for Windows, SPSS, Chicago, Illinois, USA). Descriptive variables are presented as mean ± standard deviation (SD) or mean ± standard error of mean. Independent t-tests were used to compare the variables between groups, to determine significant differences. Pearson's correlation coefficient was used to examine the correlation between distal forearm BMD_{DTX} and BMD_{DXA} measurements, as well as between BMD_{DTX} and central sites. The osteoporotic status of the women was defined by a BMD_{DXA} T-score of ≤ -2.5 SD at any of the central sites. We calculated T-score values using the Caucasian reference range, due to a lack of an African reference range database. The percentage of subjects with a T-score of ≤ -2.5 SD at either hip or spine, was used to calculate the prevalence of overall central osteoporosis in the population-based sample, as determined by BMD_{DXA} scans.

To give a representation of the range of BMD_{DTX}, and to assess the agreement between the BMD as measured by the DXA and Osteometer, two plots were drawn up as described by Bland and Altman.[15,16] Receiver operating curves (ROC) analysis was used as an evaluating graphical method to display the discriminatory accuracy of a diagnostic test, to distinguish between two populations ("diseased" and "non-diseased"). ROC curves are a trade-off between sensitivity (true-positive rate) vs. 1-specificity (false-positive rate) across a range of values of the marker. The sensitivity and specificity of BMD_{DTX} in detecting central osteoporosis were calculated by creating dichotomous variables for each central site. Using the study criteria, participants deemed to have normal or healthy central bone density, classified by the study criteria as osteoporotic, represented the false-positive rate. Participants with normal or healthy bone density, classified by the study criteria as normal or healthy, represented the true-positive rate. In the context of this study, the presence or absence of hip or spine osteoporosis was considered the diagnostic criterion for constructing the ROC curves. ROC analyses were used to determine the area under the curve (AUC), which is an indicator of the overall accuracy of the diagnostic value of the test. A rough guide used to classify the accuracy of a diagnostic test is the traditional academic point system: fail: 0.50-0.60;

poor: 0.60-0.70; fair: 0.70-0.80; good: 0.80-0.90; and excellent: 0.90-1.00.

The optimal cut-off point for the best trade-off is the value with the highest accuracy that maximises the sum of the sensitivity and specificity (Youden's index). Youden's index (YI) can be defined as J = sensitivity – (1-specificity), and ranges between 0 and 1. Complete separation of the distribution of the marker values for the diseased and healthy population results in J = 1, whereas a complete overlap gives J = 0. The YI is easy to apply, and does not require further information, such as prevalence rates and decision error costs. A second method was also used to calculate the shortest distance to the (0.1) point on the ROC curve: $[(1\text{-sensitivity})^2 + (1\text{-specificity})^2]$.

The National Osteoporosis Society (NOS) recommends that peripheral densitometers use a 90% sensitivity cut-off point. A second cut-off point was established at 90% sensitivity. Using statistics from both methods described above, an ideal threshold was established for peripheral densitometer measurements.

Primary analyses were performed without covariate adjustments to reflect the standard use of test results in a research environment. All analyses were two-tailed, and a significance level of p-value < 0.05 was used for the analyses.

Results

Descriptive data

The demographic data and number of subjects for each classified group are summarised in Table I.

The mean age ± SD of the whole study group was 62.47 ± 9.39 years, with a mean height of 1.54 ± 0.06 m, a mean weight of 68.46 ± 17.70 kg, and a mean BMI of 28.73 ± 7.24 kg/m^2. The mean forearm BMD_{DTX} was 0.423 ± 0.10 g/cm^2 vs. mean BMD_{DXA} of 0.624 ± 0.09 g/cm^2 (32.2% lower recorded value opposed to BMD_{DXA} values). According to the central BMD_{DXA} results, the overall prevalence of osteoporosis was 41.3% (19.6% with osteoporosis of the spine, 8.2% with osteoporosis of the hip, and 13.6% with osteoporosis at both sites), while 58.7% had normal levels of bone mass (Table I).

The Pearson correlation coefficient between forearm BMD_{DTX} and forearm BMD_{DXA} was r = 0.71, p-value < 0.01 (data not shown). Strong positive correlation coefficients were revealed for the relationship of BMD_{DTX} at the forearm with BMD at the hip (range from r = 0.53, p-value < 0.01 to r = 0.61, p-value < 0.01) and spine (r = 0.54, p-value < 0.01).

Bland-Altman plots

Results from the Bland-Altman plots are presented in Figure 1. The limits of agreement, determined by mean difference ± 1.96 SD, for BMD data, were 0.04 and 0.31 g/cm^2, and the mean difference ± SD was 0.177 ± 0.07.[13,14] Approximately 97% (96.55%) of all the differences lay between the limits of agreement.

Receiver operating curves analysis

The utility of peripheral bone densitometry to discriminate between subjects with normal or osteoporotic bone density, at the spine or hip site, was examined using ROC analysis (Figure 2).

The overall performance of the ROC analysis was quantified by computing the AUC. An area of 1.0 represents a perfect test fit, while 0.5 indicates a

Table I: Demographic and bone mineral density characteristics of subjects with normal or osteoporotic bone status

			Osteoporosis*			
Variable	Whole group (n = 184)	Normal (n = 108) (58.7%)	Group 1 Spine (n = 36) (19.6%)	Group 2 Hip (n = 15) (8.2%)	Group 3 Hip and spine (n = 25) (13.6%)	n
Age (years)	62.47 ± 9.39	60.69 ± 7.90	62.81 ± 8.52	64.20 ± 12.04	68.68 ± 12.11†	184
Height (m)	1.54 ± 0.06	1.55 ± 0.06	1.55 ± 0.05	1.55 ± 0.05	1.50 ± 0.06†	184
Weight (kg)	68.46 ± 17.70	73.85 ± 18.57	65.91 ± 11.36	60.31 ± 16.35†	53.92 ± 10.36†	184
BMI (kg/m^2)	28.73 ± 7.24	30.75 ± 7.74	27.50 ± 4.72	25.08 ± 6.50†	24.08 ± 4.92†	184
DXA total forearm BMD (g/cm^2)	0.505 ± 0.08	0.529 ± 0.06	0.480 ± 0.07	0.461 ± 0.09†	0.391 ± 0.07†	86
DXA distal forearm BMD (g/cm^2)	0.624 ± 0.09	0.649 ± 0.07	0.581 ± 0.08†	0.595 ± 0.11	0.503 ± 0.11†	86
DXA ultra distal forearm BMD (g/cm^2)	0.367 ± 0.06	0.387 ± 0.05	0.354 ± 0.05	0.318 ± 0.07†	0.276 ± 0.05†	86
DXA lumbar spine BMD (g/cm^2)	0.845 ± 0.15	0.931 ± 0.11	0.703 ± 0.05†	0.874 ± 0.10	0.664 ± 0.07†	184
DXA total hip left BMD (g/cm^2)	0.831 ± 0.14	0.900 ± 0.11	0.806 ± 0.10†	0.677 ± 0.14†	0.661 ± 0.07†	184
DXA total hip right BMD (g/cm^2)	0.831 ± 0.14	0.899 ± 0.11	0.803 ± 0.10†	0.662 ± 0.14†	0.670 ± 0.07†	184
DXA femoral neck left BMD (g/cm^2)	0.724 ± 0.13	0.787 ± 0.10	0.707 ± 0.09†	0.598 ± 0.18†	0.554 ± 0.05†	184
DXA femoral neck right BMD (g/cm^2)	0.741 ± 0.14	0.804 ± 0.10	0.715 ± 0.10†	0.584 ± 0.15†	0.594 ± 0.12†	184
DTX-200 forearm BMD (g/cm^2)	0.423 ± 0.10	0.464 ± 0.100	0.391 ± 0.08†	0.380 ± 0.08†	0.319 ± 0.04†	184

*Osteoporosis diagnosed according to gold standard (dual-energy X-ray absorptiometry), †: Indicates significant difference from normal bone mineral density, p-value < 0.05, BMI: body mass index, DXA: dual-energy X-ray absorptiometry, BMD: bone mineral density

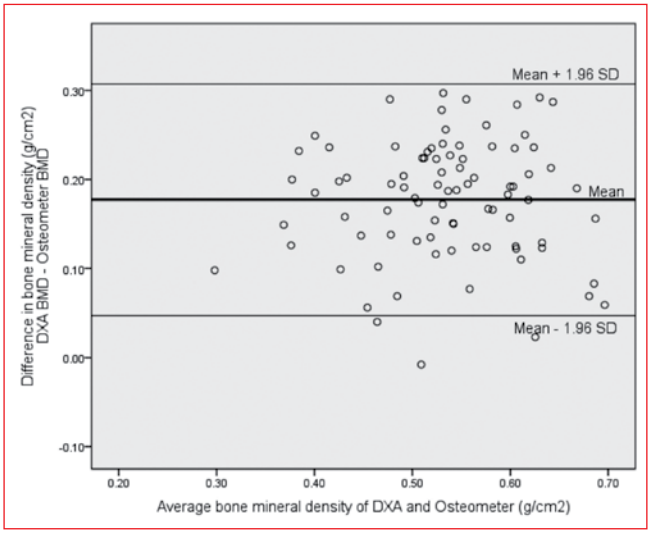

Figure 1: Bland-Altman plots for the difference vs. the mean bone mineral density data of 86 subjects

performance that was no different from chance. The AUC with regard to the hip (Figure 2a) was 0.818 (0.747-0.888 95% CI), whereas the overall performance fit for the spine (Figure 2b) was an AUC of 0.771 (0.697-0.845 95% CI). Maximum efficiency was at 77.50% sensitivity and 81.25% specificity with regard to the hip, and 65.57% sensitivity and 84.55% specificity for the spine. Based on the guidelines detailed in the methodology section, the value of the hip AUC suggests that using BMD_{DTX} represents good accuracy, while the AUC value for the spine represents fair accuracy. The YI was 0.588 and 0.501 for the hip and spine respectively.

The ROC curve analyses returned a maximum or optimum cut-off point at a distal forearm BMD (BMD_{DTX}) of 0.370 g/cm^2 for possible hip osteoporosis, and an optimum cut-off point of 0.371 g/cm^2 for the spine. Using these cut-off values, participants were then classified as having normal central BMD, or having central osteoporosis, at either the hip or spine. Classification statistics are summarised in Table II and III.

ROC analyses depicted the positive likelihood ratio (LR) for the hip (3.986) and spine (4.139), while the negative LR was 0.279 and 0.427, for the hip and spine, respectively. The proportion of women with a positive BMD_{DTX} indication of hip osteoporosis that was correctly diagnosed [i.e. positive predictive value (PPV)] was 0.525 (52.5%), while PPV for the spine was 0.672 (67.2%). In contrast, the negative predictive value (NPV) (the proportion of women with normal BMD who were correctly diagnosed) for the hip and spine was 0.928 (92.8%) and 0.825 (82.5%) respectively. Approximately 35% of the women evaluated by peripheral measurements were classified in different diagnostic strata, when evaluated by central DXA using the optimum hip cut-off value. The misclassification rate for the spine was higher, with approximately 49% of the women being misdiagnosed. The odds ratio for the hip was 14.27, while that of the spine was 9.70.

ROC analysis was repeated to establish an alternative threshold: having 90% sensitivity. This value was identified as 0.414 g/cm^2 for the hip and 0.475 g/cm^2 for the

Table II: Performance of BMD_{DTX} as a diagnostic test for the presence of osteoporosis, at either the hip or lumbar spine, using optimum cut-off points

Variable	Hip	Spine
Absolute value (g/cm^2)	0.370	0.371
Specificity (%)	81.25 (0.749-0.876)	84.55 (78.17-90.94)
Sensitivity (%)	77.50 (64.56-90.44)	65.57 (53.65-77.50)
Youden's index	0.588	0.510
Positive predictive value	0.525	0.672
Negative predictive value	0.928	0.825
Prevalence (%)	21.74	33.15
Type I error rate or false positive rate (%)	19.44	15.45
Type II error rate or false negative rate (%)	22.50	36.07
Positive likelihood ratio	3.986	4.139
Negative likelihood ratio	0.279	0.427
Misclassification (%)	34.78%	48.91%
Relative risk	7.298	3.851
Odds ratio	14.270	9.703

95% confidence interval in parentheses

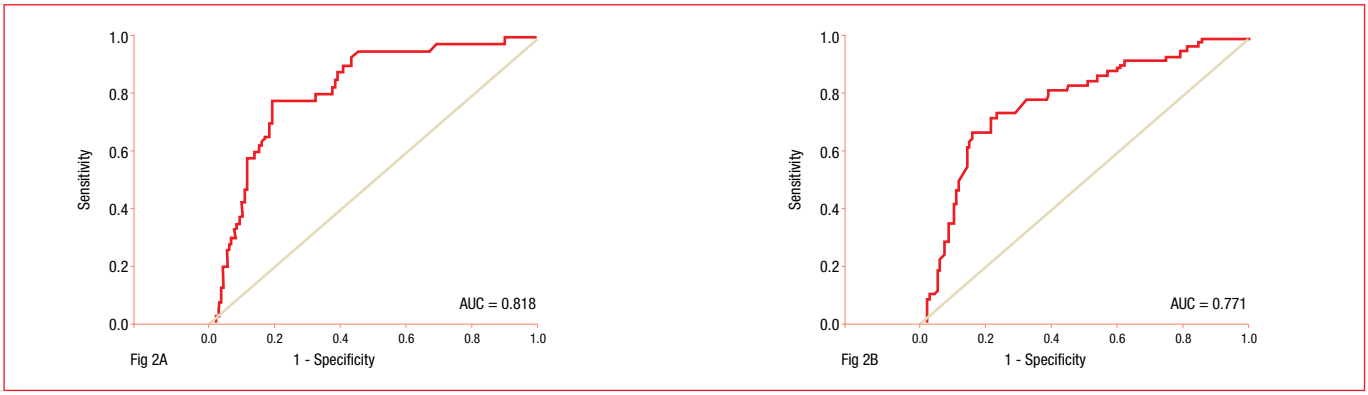

Figure 2: Receiver operating curve showing the diagnostic validity of the forearm bone density measurement in identifying osteoporosis at the hip (2a), or spine (2b), in postmenopausal women.

Table III: Performance of BMD_{DTX} as a diagnostic test for the presence of osteoporosis, at either the hip or lumbar spine, using 90% sensitivity cut-off points

Variable	Hip	Spine
Absolute value (g/cm²)	0.414	0.475
Specificity (%)	59.00 (51.00-67.06)	38.20 (29.62-46.80)
Sensitivity (%)	90.00 (80.70-99.30)	90.00 (82.70-97.64)
Positive predictive value	0.375	0.389
Negative predictive value	0.955	0.811
Prevalence (%)	21.74	33.15
Type I error rate or false positive rate (%)	41.67	65.04
Type II error rate or false negative rate (%)	10.00	16.39
Positive likelihood ratio	2.16	1.285
Negative likelihood ratio	0.171	0.469
Misclassification (%)	20.11%	54.35%
Relative risk	8.25	2.063
Odds ratio	12.6	2.741

95% confidence interval in parentheses

spine. The hip threshold yielded higher NPV (95.5%), yet it had a lower PPV (37.5%). NPV for the spine was 81.1%, and PPV was 38.9%. The positive LR was 0.375 for the hip, with a negative LR of 0.171. In contrast, both the positive and negative LR for the spine yielded weaker values (1.285 and 0.469 respectively). Women who had BMD values below the thresholds were 12.6 times more likely (odds ratio) to have osteoporosis in the hip, and 2.7 times more likely to have osteoporosis in the spine.

Discussion

South Africa is undergoing a process of rapid urbanisation. Because of this and the affiliated lifestyle changes, the black South African population might now, more than ever, be considered at high risk of developing osteoporosis.[11,17] In their study, Pongchaiyakul et al found lower BMD levels in urban men and women, compared to rural men and women.[18] Our data revealed a disconcertingly high prevalence of osteoporosis (hip and/or spine) in black, urban postmenopausal women (≈ 41.3%). The prevalence of osteoporosis of the hip was 8.2%, which is comparable to the prevalence reported by Clowes et al in their study.[10] Although the hip prevalence in our group equalled that reported by Clowes et al, the risk factor outcomes for hip fractures differ between ethnic groups, i.e. hip geometry. Some studies have found that a longer hip-axis length is associated with a higher risk of hip fractures. Hip-axis lengths seem to be shorter in African-Americans, compared to their Caucasian peers.[19] However, another study found that hip-axis length does not explain ethnic differences in hip fractures.[20] Drawing any definite conclusions about the prevalence of osteoporosis based on the hip BMD alone might lead to inaccurate prevalence rates. On the other hand, osteoporosis of the spine seems to be much more prevalent (≈ 20%), compared to that at the hip.

Despite DXA being considered the first choice in assessing bone density, cost and effectiveness do not allow for its generalised use in target populations. The use of peripheral densitometers has received much attention. However, it is important to establish ethnic-specific, cut-off values for bone density, due to the differences in heritability and genetic contribution to BMD in different ethnic groups.[21] According to our knowledge, this is the first South African study that has attempted to address the lack of cut-off values for peripheral bone density that are specific to sub-Saharan Africa.

According to Miller et al, bone mass at peripheral sites correlates well with central sites such as the hip and spine, with correlation coefficients of between 0.6 and 0.7.[22] Our study confirmed this highly significant relationship between BMD measurements of the distal forearm and hip and spine, and was in line with reports from previous studies.[10,23]

The overall accuracy of peripheral BMD in predicting hip osteoporosis (as reflected in the AUC values) seems to be superior to that of the spine. This was also found in other studies.[10,24] This discordance between the hip and spine AUC might be explained by the difference in the amount of cortical and trabecular or cancellous bone found in each site. The lumbar spine is estimated to contain approximately 66% cancellous bone, whereas the femoral neck and distal radius contain approximately 25% and 30%, of cancellous bone, respectively. Cancellous bone is more sensitive to changes in bone resorption due to its more porous surface, therefore providing more surface area that is exposed to metabolic activity (bone remodelling). This results in the cancellous skeleton being affected first.[25,26]

In their article, Clowes et al reported that, in their population-based cohort, the Osteometer DTX-200 identified 73% of the women, i.e. a 27% misclassification, in whom a treatment decision could be made without additional central DXA measurements, with 95% certainty.[10] Blake and Fogelman published similar results, showing 38% misdiagnosis using peripheral densitometry.[27] However, using the optimum BMD_{DTX} cut-off value (0.371 g/cm²) for the spine, we could place ≈ 51% of the women in the correct diagnostic strata. This excludes at least half of the population from being referred for additional DXA scans. On the contrary, when we used the spine 90% sensitivity cut-off value, our results indicated a much higher misclassification rate (≈ 54%). Therefore, it is recommended that the 0.371 g/cm² cut-point be used on the DXA_{DTX} as a criterion for excluding black, urban postmenopausal women as having possible spine osteoporosis.

The women in our study who exhibited low distal forearm BMD (< 0.371 g/cm²) were ≈ 10 times more

likely to have osteoporosis of the spine, compared to those with BMD measurements above the threshold.

Despite the novelty of this study, it had some shortcomings. We assessed black South African postmenopausal women, but refer throughout the paper to data on white postmenopausal populations. We surmise, but have no data to adequately support this, that the fracture risk in our population is similar to that of the white reference population at each BMD level.

The characteristics of bone loss differ between menopause osteoporosis and senile osteoporosis. One limitation of this study is that the study group was not divided into age increments to determine the accuracy of peripheral measurements for different age groups. In their article, Jones and Davie recommended that, should distal forearm BMD be used to assess large numbers of potentially osteoporotic women, it is best used in women between the ages of 60-79 years, since the best detection rate was found in this group of women.[23] Future studies should investigate, and elaborate upon, this important point.

Measuring central BMD is the best method to identify patients with osteoporosis. Nevertheless, measuring BMD in all postmenopausal women is not cost-effective, especially in developing countries such as South Africa. To reach a maximum number of women who are at risk, screening approaches that are easy to use and cost-effective, should be employed. Using peripheral BMD as a triage screening tool can help to safely exclude women with normal BMD in order to reduce unnecessary, expensive DXA densitometry measurements. To conclude, our study revealed that the incidence of low forearm BMD acts as a possible marker of central osteoporosis in black, urban postmenopausal women in South Africa. We suggest that the proposed distal forearm cut-off value (> 0.371 g/cm^2) be used to exclude women who do not have osteoporosis of the spine.

"There is every reason, therefore, to apply bone mass measurements as widely as possible to discover those subjects at risk of osteoporosis in a manner that is effective and affordable." – Miller et al.[22]

Conflict of interest

There was no conflict of interest.

Declaration

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