Original Article

Does Bone Mineral Apparent Density Facilitate Accurate Identification of Osteoporosis in the Short Postmenopausal Women?

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Abstract

Objective: Height is one of the most important aspects affecting the areal bone mineral density (BMD). There are several height adjustments in children but none in widespread use for adults. This is specifically a problem in ethnic groups where mean height is substantially lower. We hypothesized that height adjustment of areal BMD would reduce the misclassification in short individuals. **Materials and Methods:** This is a retrospective study involving 373 postmenopausal women. Their records were reviewed and bone mineral apparent density (BMAD) were calculated. Areal BMD T-scores and BMAD T-scores were then compared. **Results:** The mean height of the cohort was 154.4 cm. There were 47 women who were defined as short (≤147 cm). In short women, BMAD neither showed improvement nor decrement in T-scores, and BMAD T-scores predicted more number of osteoporosis than BMD T-scores. When divided into height ranges, taller women (>160 cm) showed worsening of BMAD T-scores as compared to BMD T-scores (Chi-square test for trend $P < 0.001$). Hence, BMAD might actually "correct" for larger bone and not shorter bones. **Conclusion:** BMAD was not found to be a suitable alternative in short postmenopausal women to accurately determine whether the low bone density in them is because of dual-energy X-ray absorptiometry artifact or whether they truly have a low density.

Keywords: BMAD, Indians, short stature, volumetric bone density

Introduction

While there are numerous methods to measure bone density and several calculators to predict fracture risk, still the pursuit for the most suited, practical, cross ethnically applicable and widely available method remains. Due to ethnic differences in the bone mineral density (BMD) normative data (between the Caucasians and Indians) and the absence of long-term fracture data (with reference to BMD in Indians), the actual prevalence of osteoporosis in India is still debated. The cross-country Indian Council of Medical Research (ICMR) study had categorically shown that the young healthy Indian population had lower BMD compared to NHANES population. The differences were attributed to socioeconomic causes, ethnically different bone, vitamin D deficiency to name a few.[1]

Average height of healthy young Indian women was 152 cm as compared to 162 cm in United States.[2,3] It is very well known that dual energy X-ray absorptiometry (DXA) scans measure areal BMD in 2 dimensions rather than actual 3-dimensions. Hypothetically, when volumetric bone density is comparable in two individuals, taller individual will have higher areal BMD in comparison to shorter counterpart as measured in a conventional DXA scan. It is well known fact that areal BMD is related to height and even ICMR study showed a correlation ($r = 0.254$ between height and spine BMD).[1] Hence, correction for height is important in order to prevent overdiagnosis of osteoporosis in short women. Since height is dynamic in children, lots of literature regarding

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height adjustments are present in pediatric category.[4,5] Here, we attempt to use one such adjustment called bone mineral apparent density (BMAD) for calculating the volumetric BMD. Recently, centiles of BMAD in children and LMS values were published from Bone Mineral Density in Childhood Study.[6]

We hypothesized that with height adjustment in Indian postmenopausal women, there might be reclassification of substantial proportion of them from osteoporosis to osteopenia or normal BMD, thus changing the management in them.

Materials and Methods

This was a retrospective analysis of BMD of all postmenopausal women in a tertiary care center in South India. From the database, reports of all postmenopausal women who had undergone DXA scan in the past 1 year were retrieved. In total, 564 records were reviewed. Scans that showed obvious morphological vertebral fracture (reduced vertebral height with abnormal increase in density), difference of T-score ≥ 1 in adjacent vertebra or severe scoliosis were excluded resulting in inclusion of 373 scans for analysis.

Anthropometric details, bone mineral content, bone area, and bone density data were recorded. Height and weight were measured by standard measures. DXA was performed with GE Lunar™ Prodigy Advance (GE Medical Systems, Madison, Wisconsin, US) and analyzed using enCORE software version 17.4 by a single technician throughout the study period. The positioning and measurement of lumbar spine was done according to the manufacturer's manual. Briefly, patients were asked to change clothing and remove radiopaque objects. In supine position, the LASER point of the DXA arm was positioned 5 cm below navel and image obtained. If the scanned regions were satisfactory, it was analyzed with software. First, the regions of interests were verified followed by bone points, neutral points, and tissue points. The vertebrae were identified and final output was saved. The short-term precision study revealed a coefficient of variation of 1.2% for spine with the technician. The least significant change for 95% confidence level was 3.2% for lumbar spine.

Though there are several methods to calculate BMAD, we chose to use the method that has published standards.[7] BMAD (g/m^3) was calculated as[8]

$$(L1\ BMC + L2\ BMC + L3\ BMC + L4\ BMC)/(L1V + L2V + L3V + L4V)$$

Where BMC is bone mineral content in grams and V is calculated volume of vertebra [bone area in cm^2]$^{1.5}$.

In order to calculate BMAD Z-score, since there were no adult standards, we took the recently published standards from ALPHABET study, where age-specific BMAD values were published using GE Lunar prodigy in South Asian ethnicity.[9]

Standard deviation scores were calculated from least mean square (LMS) values with the formula

$$Z = [(y/M)^L - 1]/(L \times S)$$

Where y is measured value, M is the estimated mean, L is the skewness, and S is the distribution. Though it is called as Z-score while calculating from LMS data of BMAD, since the mean is that of young south Asian adult girls (which approximates with peak adult bone mass), the score obtained in postmenopausal women would technically be a T-score.

We chose the height of ≤147 cm to define short stature (SS) because it corresponded to −2 SD of height of girls at age of 18 years.[10] Compared to national surveys (where the average height of the community is published), the measurement of height in children for devising growth charts would be more rigorous and, hence, we used height at 18 years −2 SD for arriving at SS definition.

Statistics

Data were checked for normality using Shapiro-Wilk test. Nonparametric data were presented as median (interquartile range). Comparison between groups were done using Mann–Whitney U test. The trend of proportions was tested using Chi-square test for trends. Figures were prepared with the help of GraphPad Prism, Version 8 (GraphPad software Inc, San Diego, CA, USA). Level of significance to reject null hypothesis was 5%. Data were analyzed with IBM® SPSS® version 23 (IBM Corp, released 2015; Armonk, NY, USA).

Results

The median age of the cohort was 62 years and the other baseline characteristics are detailed in Table 1. Mean height of the women was 154.4 cm—this was excluding those with morphometric fractures—almost nearing the national average height of women. There were significant correlations between height of the women and L1-L4 BMC (r = 0.48, P < 0.001), L1-L4 height (r = 0.55, P < 0.001), L1-L4 bone area (r = 0.6, P < 0.001), L1-L4 volume (r = 0.61, P < 0.001), L1-L4 T-score (r = 0.35, P < 0.001), and BMAD T-score (r = 0.15, P = 0.005). Weight correlated positively with both BMD (r = 0.41, P < 0.001) and BMAD (r = 0.3, P < 0.001). BMI also correlated with both BMD (r = 0.31, P < 0.001) and BMAD (r = 0.26, P < 0.001).

The differences between individual BMD and BMAD T-scores for the whole cohort were depicted in the line graph in Figure 1. When the whole cohort was divided into those who showed improvement of BMAD T-scores (as compared to BMD T-scores) and not, significant differences were observed between the two. As displayed in graph, 40% (79/200) had osteoporosis as defined by BMD criteria among those whose BMAD T-scores worsened and on the contrary, only 9% (15/173) had osteoporosis among those whose BMAD improved. There was significant correlation between BMD T-score and BMAD T-score (r = 0.93, P < 0.001 by spearman correlation). In total, 94 women were diagnosed with osteoporosis by BMD while

Table 1: Characteristics of postmenopausal women

Parameters	Total $n=373$	Short women $n=47$	Women of normal stature $n=326$	P
Age in years	62 (57,68)	64 (58,68)	62 (56.8, 67.4)	0.28
Height in cm	154.4±6.3	144.5 (143,146)	155.5 (152,159)	<0.001
Weight in kgs	63 (56,72)	52 (48,63)	65 (58,74)	<0.001
BMI in Kg/m^2	26.5 (24,29.7)	25.3 (22.8,30.1)	26.7 (24.2,29.7)	0.1
L1-L4 bone mineral content in grams	45.64 (38.04,53.07)	35.43 (29.25,40.57)	46.63 (40,54.44)	<0.001
L1-L4 height in cm	12.23 (11.87,12.66)	11.48 (11.16,12.11)	12.31 (11.95,12.75)	<0.001
L1-L4 volume in m^3	153.1 (138.5,168.4)	126.5 (113.9,139.9)	157 (142.7,170.4)	<0.001
Bone mineral density in g/m^2	0.991 (0.861,1.111)	0.888 (0.789,0.983)	1.021 (0.902,1.127)	<0.001
Bone mineral apparent density in g/m^3	0.296 (0.265,0.326)	0.271 (0.252,0.308)	0.299 (0.269,0.327)	0.002
BMD T-score		−2.4 (−3.3, −1.6)	−1.3 (−2.3, −0.4)	<0.001
BMD T-score ≤−2.5		20	74	<0.001
BMAD T-score		−2.6 (−3.5, −1)	−1.4 (−2.7, −0.2)	0.002
BMAD T-score ≤−2.5		25	96	<0.001

Data are expressed as mean±SD or median (interquartile range). P value is for the comparison of last 2 columns. BMD: Bone mineral density, BMAD: Bone mineral apparent density, BMI: Body mass index

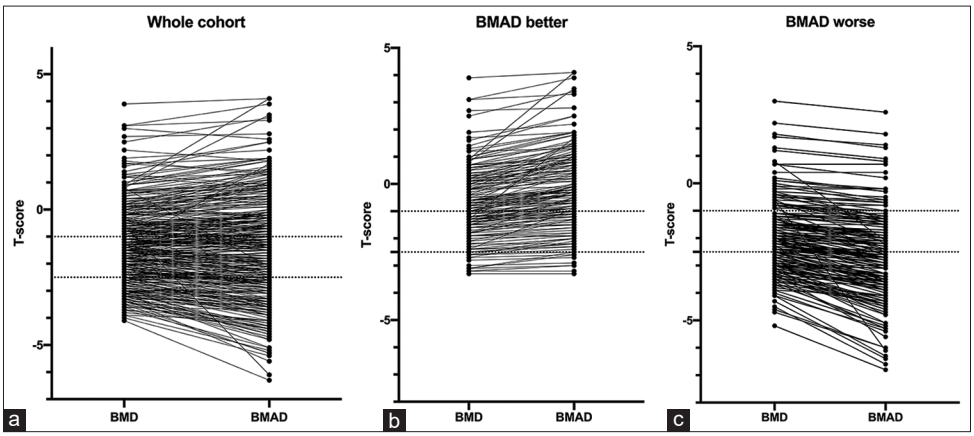

Figure 1: (a-c). Individual datasets of bone density of the whole cohort showing a difference in T-score with two methods. 1b and 1c show the datasets of people with BMAD T-scores better and worse than BMD T-scores, respectively. Abbreviations: BMD—bone mineral density in g/m^2, BMAD—bone mineral apparent density calculated as (bone mineral content/bone area1.5) in g/m^3. T-scores between BMD and BMAD of the cohort

121 had BMAD T-score ≤ −2.5. The Venn diagram shows the relation between the two subsets [Figure 2].

There were 47 women with height below 147 cm. The prevalence of osteoporosis in women ≤147 cm was 45% (20/47) as compared to 23% (74/326) in those >147 cm ($P < 0.001$). The differences in other characteristics are highlighted in Table 1. The differences in BMAD between the two groups were significant (0.27 g/m^3 vs. 0.29 g/m^3). Though the sample size was not calculated for the primary outcome, the power by normal approximation method for the difference of BMAD was 84%. In only 24 of 47 (~50%) women with SS, BMAD showed better T-score than BMD. Since our hypothesis was in short women, it could be seen that BMAD did not improve or help in betterment of diagnosis of osteoporosis as compared to BMD.

Discussion

Encountering a postmenopausal woman who is short, is quite common in endocrine practice. Determining whether such a woman (with areal BMD defined osteoporosis) has a truly low bone mass or whether it is a reflection of measurement artifact of DXA is of utmost importance. This scenario was clearly depicted in a case report wherein unnecessary treatment with antiosteoporosis agents could have been averted by measuring volumetric BMD.[11] In our study, the primary hypothesis that short women with artifactually low density would be reclassified by BMAD was proved wrong. Moreover, in relatively tall women, BMAD T-scores became worse than BMD T-scores, implying that oversize artifact was corrected by BMAD.

Several studies have established the superiority of volumetric bone density over areal bone density for predicting osteoporosis and fractures in postmenopausal women.[7,12] For volumetric BMD, quantitative computed tomography (CT) remains the gold standard but several measures of areal DXA have been proposed as alternatives—each with good prediction of breaking strength.[13] BMAD is another measure that is frequently used for calculating volumetric BMD in

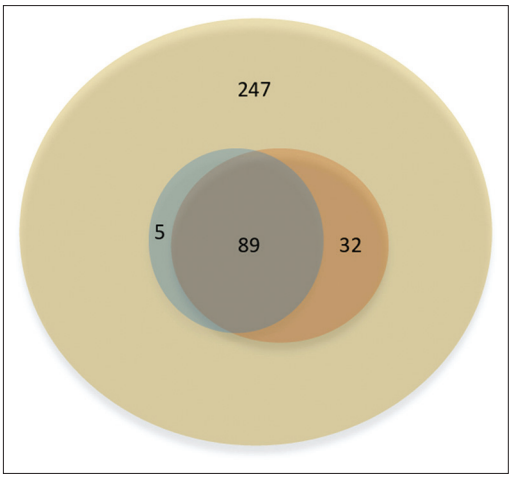

Figure 2: Venn diagram showing the overlap of number of women with osteoporosis as defined by T-score ≤ −2.5 through 2 ways of bone density measurement. Light chocolate: nonosteoporotic women by either measurements, light brown: women with osteoporosis defined by BMAD, and light blue: women with osteoporosis defined by areal BMD

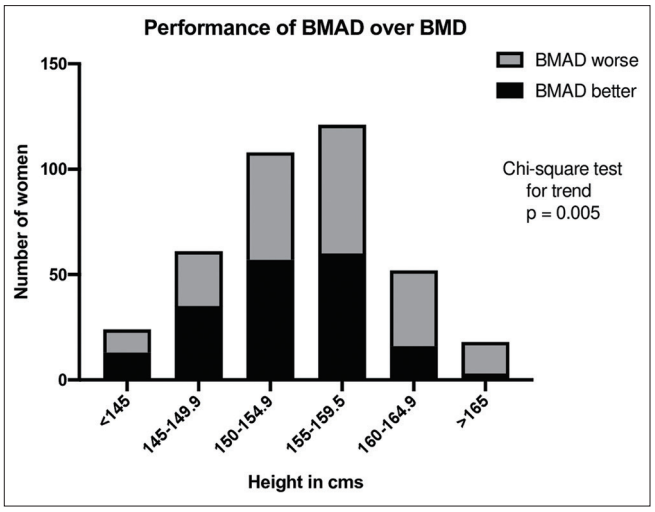

Figure 3: Comparison of BMAD over BMD in terms of betterment or worsening of the T-scores. As can be seen from the graph, the proportion of worsening of BMAD T-score increases with height

children, to adjust for height variations and has normative data till adulthood.[6,9] BMAD is thought to "correct" for height variations but there are contradictory literature regarding the claim.[5,14] Similar to our study, a study from Brazil evaluated the utility of BMAD and trabecular bone score in short postmenopausal women (<144 cm) and concluded that both were greater in SS when compared to their taller counterparts.[15] There were several differences between two studies. The mean age was different (69 years vs. 64 years in our study), and BMD was same in the case and control group in that study (whereas in our study, it was different) and BMAD was substantially different (0.16 g/cm^3 vs. 0.27 g/cm^3 in our study). Hence, the conclusion in that study that BMAD might help to mitigate the height disadvantage of areal BMD was different from ours.

The influence of height on BMAD T-scores was appreciated in our study [Figure 3]. When we compared the T-scores generated from BMD and BMAD, taller individuals in our cohort had a higher proportion of worsening T-score with BMAD than with BMD. Hence, it seems that BMAD "corrects" bone density for taller individuals probably by reducing the apparently increased density calculated by areal BMD. With invitro studies, BMAD had underestimated volumetric density and overestimated bone volume.[13] Since similar invitro experiments have not been performed across different vertebral heights, the performance of BMAD in short and tall individuals could not be ascertained.

Short women had a higher prevalence of osteoporosis as defined by DXA in our study. The fact remains that the DXA would underestimate BMD in short women because of the disadvantage of measuring 3-dimensional structure in 2 dimensions. However, on the other hand, height is also a reflection of health status of the person. Throughout the past century, due to improvement in nutrition and health, people had gained height.[16] Economic factors and income also decide the height of the individual.[17] Hence, whether short women (who also have low body weight) have in reality a low peak bone mass or whether it is a measurement artifact has to be determined. In such a scenario, since in our study, BMAD calculated volumetric density did not improve the status of osteoporotic short women, it may be presumed that they, in fact, had a truly low volumetric bone.

Several limitations were present in the current study. Volumetric bone density was just calculated and gold standard of quantitative CT was not performed. However, the reason for this study was to find a suitable alternative through DXA to "correct" for height. Paired lateral and PA DXA calculated bone density would have been the best alternative for volumetric BMD but was not performed. The hard endpoints of fracture data were not looked at for BMAD T-scores before being compared to BMD T-scores. The BMAD LMS values were available only for South Asians and not Indians but were used for deriving T-scores. Though we attempted to exclude the patients with vertebral fractures through morphological verification and discrepant T-score of adjacent vertebra, radiological assessment should have been done for accurate fracture detection.

In conclusion, BMAD did not "correct" for size artifact in short postmenopausal women. Whether this depicts the "true" nature of low bone density in these women or whether BMAD is not the appropriate measure to distinguish artifactual and actual bone density in short women has to be answered by future studies.

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Conflicts of interest
There are no conflicts of interest.

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