



Association between Body Composition Characteristics and Bone Mineral Density across Menopausal Transition Stages

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Objectives: This cross-sectional study assessed the association between body composition characteristics and bone mineral density (BMD) across different menopausal transition stages.

Methods: In total, 320 rural women aged 45–60 years were recruited. Body composition and BMD at different skeletal sites were evaluated by dual energy X-ray absorptiometry.

Results: The BMD and bone mineral content of the entire hip, lumbar region, and left arm significantly decreased across most of the menopausal transition stages, which was confirmed by Tukey post hoc analysis. Multiple linear regression analysis revealed that BMD at the hip, lumbar region, and left arm were strongly and positively associated with weight. However, BMD was negatively associated with % total body fat (TBF) across all the four menopausal stages except for lumbar BMD at the late postmenopausal stage (Model 1). Lean mass was positively and significantly associated with BMD at all the skeletal sites evaluated except for some fluctuations in lumbar BMD (Model 2). Furthermore, waist circumference was significantly associated with BMD in the late postmenopausal stage (Model 3).

Conclusions: Weight and lean mass are significant predictors of BMD during the menopausal transition and beyond. Furthermore, %TBF may be a negative indicator of BMD.

Key Words: Body composition, Body fat, Bone mineral density, Estrogens, Postmenopause

INTRODUCTION

Osteoporosis is a progressive systemic skeletal disease characterized by reduced bone mass and microarchitectural worsening of bone tissue thereby enhances the likelihood of fracture of fragile bone [1]. Bone mineral density (BMD) is an optimum indicator of osteoporosis exhibited an accelerated decrement during menopausal transition phase. Menopause is a natural and inevitable phase of biological aging among midlife women, which signifies the gradual progression from reproductive to non-reproductive period. It was recorded by Golden [2] that in postmenopausal women, a decline in the level of key regulator of bone metabolism i.e., estradiol hormone is responsible for the surge in bone resorption, because it stimulates circulating macrophages to release

osteoclastic cytokines. A study performed by Riis et al. [3] further established menopause transition as a vulnerable window for bone health of the women that may lead to the occurrence of osteoporosis, thereby enhances the possibility of fracture. So, the combined burden of all these challenges during menopausal transition and beyond make female sex more susceptible to serious short term as well as long term health issues.

It is recorded that with advancing age redistribution of fat from gluteo femoral area to abdominal region occurs and weight tends to increase among women. Previous studies in this realm have deciphered that 72.6% postmenopausal women were overweight [4]. Past literature has also highlighted the protective role of increased body mass index (BMI) [5,6] as well as total body fat (TBF) [7] on bone density owing to the

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adaptive counter of bone to mechanical loading. Body composition consists of fat mass, lean mass and bone is responsible of 90%–95% of weight and has significant effect on BMD [8]. Findings of earlier researches recorded conflicting results to establish the association of body composition parameters and BMD at different skeletal sites. Some studies revealed a positive association of fat mass on BMD [9,10], while others have depicted an inverse association [11,12] or no correlation [13]. However lean mass in most of the studies revealed a positive association with BMD of femur, spine, and whole body [14,15]. Limited studies have conducted on this domain using dual energy X-ray absorptiometry (DEXA) scan across menopausal transition stages. Therefore, to resolve the ambiguity, our research investigated the association of body composition characteristics on BMD of women of different menopausal status.

MATERIALS AND METHODS

Study population

In the present cross-sectional study, a sample of 320 women with the age ranging from 45 to 60 years were enrolled. The data was collected from the rural area of Haryana, India from March 2022 to January 2023. Before the initiation of data collection, a pilot study was carried out to check the feasibility as well as operational efficiency of the study. Only healthy women were enrolled in the sample, those who were pregnant/lactating, having any chronic illness or any physical deformity, surgical menopause, or hormonal replacement therapy were excluded from the study.

A schedule was employed to gather general information like age and diet (vegetarian/non-vegetarian) of the participants by house survey method. Physical activity of the participants was ascertained by using Madras Diabetes Research Foundation-physical activity questionnaire for Indian population [16]. In this total energy expenditure was assessed by factorial calculation of time spent in various activities in multiple domain and energy cost of these activities by following World Health Organization (WHO)/Food and Agriculture Organization of the United Nations/United Nations University expert consultation. The physical activity level was estimated as total energy expenditure/basal metabolic rate for 24 hours and based on their values, participants were assigned in sedentary (1.40–1.69), moderately active (1.70–1.99) and vigorously active

(2.00–2.40) groups.

The ethical clearance to perform the present study was taken from institutional ethics committee Panjab University, Chandigarh (PUIEC 210630-II-052). All the selected women were aware regarding the purpose and nature of conducting the study. A consent form was signed by all the selected women for the present study. The women were categorized into four different menopausal stages i.e., premenopause (mean age 46.0 ± 1.4 years, having regular monthly periods), perimenopause (mean age 47.9 ± 3.0 years, irregular monthly periods), early postmenopause (mean age 51.4 ± 3.9 years, no monthly periods for last 5 years) and late postmenopause (mean age 58.2 ± 2.7 years, no monthly periods for last > 5 years) (WHO, 1996). Following four anthropometric variables were measured by following the standard techniques explained by Weiner and Lourie [17]. The height (cm) and weight (kg) of each woman were recorded using anthropometric rod and weighing scale to nearest 0.1 cm and 0.1 kg respectively. The waist circumference (cm) and hip circumference (cm) were measured nearest to 0.1 cm with freeman's measuring tape. BMI of all the participants was calculated as per WHO (2004) cut-off values for Asian population [18].

Body composition characteristics and BMD of all the subjects were evaluated using dual energy X-ray absorptiometry (Model Discovery A, Serial number 87292, Hologic) with standard procedures by the same trained technician. Fat mass was defined as whole body fat mass, whereas lean mass as body mass minus fat mass. For evaluating BMD the following sites i.e. left arm, lumbar (L1–L4), and total hip (neck, troch, inter area) of left hip was selected.

Statistical analysis

All the women enrolled in the present study were categorized into four sub-group of different menopausal status. Statistical Package for Social Sciences (SPSS) version 16 (SPSS Inc.) was accomplished to conduct the analysis. The continuous and categorical variables are deciphered as mean \pm standard deviation and percentages (%) respectively. Difference between four different menopausal stages were gauged using one-way analysis of variance (ANOVA) represented by F values. Post-hoc analysis displayed inter-group differences with Bonferroni adjusted *P* values (*P* value/number of groups) for paired group comparisons among different stages of the menopausal transition among rural women. Karl

Pearson's correlation coefficient (r) analysis was carried out between various body composition variables and BMD at three selected skeletal areas. Multiple regression models using enter method were performed to ascertain the association of body composition characteristics with BMD. To independently evaluate association with skeletal sites in Model 1, weight and %TBF was included, in Model 2 only fat mass and lean mass was incorporated, and in Model 3 waist circumference and hip circumference were included. All models were designed accordingly and adjusted for confounding factors like age, height, diet pattern, physical activity level. The beta values (β) in the models were representing units of the predictor variable and adjusted R^2 was depicting model accuracy (Goodness-of-fit). A value of 1 represents perfect prediction model, while value less than or equal to 0 indicate no prediction value.

RESULTS

The descriptive statistics of anthropometric, body composition and BMD at different skeletal sites of rural women across four menopausal transition stages was presented in Table 1. It is clear from the Table 1 that all the four menopausal transition stages depicted statistically significant differences for height (F value 3.64), weight (F value 2.65), and hip circumference (F value 4.21), as is clear from the results of one-way ANOVA. The mean value of body fat (%) revealed an increase ($P > 0.05$) from premenopause to late postmenopause stage, while an inverse trend was recorded for bone mineral content ($P < 0.01$). The mean value for fat mass and lean mass increased from premenopause to perimenopause stage followed by a decline till late postmenopause phase. The BMD at three selected skeletal sites i.e., total hip, lumbar, and arm BMD depicted a statistically significant decline among women from premenopause to late postmenopause stage except for

Table 1. Anthropometric, body composition, and BMD at different skeletal sites of women at different phases of menopause transition

Characteristic	Premenopause (n = 98)	Perimenopause (n = 96)	Early postmenopause (n = 57)	Late postmenopause (n = 69)	ANOVA
Height (cm)	157.2 \pm 5.3	157.4 \pm 5.2	156.0 \pm 6.1	154.6 \pm 7.0	3.64*
Weight (kg)	64.9 \pm 12.3	66.7 \pm 13.6	63.8 \pm 12.7	61.2 \pm 11.7	2.65*
BMI (kg/m ²)	26.3 \pm 4.9	26.9 \pm 5.4	26.2 \pm 4.8	25.5 \pm 4.4	1.06
WC (cm)	87.0 \pm 12.7	89.2 \pm 11.7	86.8 \pm 10.5	87.0 \pm 13.3	0.75
HC (cm)	91.0 \pm 8.8	92.6 \pm 10.6	89.1 \pm 9.0	86.8 \pm 13.3	4.21**
Body fat (%)	39.4 \pm 4.9	40.3 \pm 4.6	40.7 \pm 5.5	40.8 \pm 5.0	1.37
Fat mass (kg)	25.9 \pm 7.3	26.8 \pm 7.4	25.8 \pm 7.2	25.0 \pm 7.1	0.83
Lean mass (kg)	36.6 \pm 5.3	37.0 \pm 7.2	34.9 \pm 5.7	33.8 \pm 6.0	4.58**
BMC (g/cm ³)	2.1 \pm 0.2	2.0 \pm 0.2	1.8 \pm 0.3	1.7 \pm 0.3	27.59**
Total hip BMD (g/cm ³)	1.0 \pm 0.1	1.0 \pm 0.1	0.9 \pm 0.1	0.8 \pm 0.1	32.97**
Lumbar BMD (g/cm ³)	1.0 \pm 0.1	0.9 \pm 0.1	0.9 \pm 0.1	0.8 \pm 0.1	24.36**
Arm BMD (g/cm ³)	0.7 \pm 0.1	0.7 \pm 0.1	0.7 \pm 0.1	0.6 \pm 0.1	33.31**
Dietary pattern (χ^2)					
Vegetarian	57	62*	31	48*	-
Non-vegetarian	41	34	26	21	
PAL (χ^2)					
Sedentary	2	2	5	10	
Moderate	76**	69**	38**	45**	-
Vigorous	20	25	14	14	

Data are presented as mean \pm standard deviation.

BMD: bone mineral density, ANOVA: analysis of variance, BMI: body mass index, WC: waist circumference, HC: hip circumference, BMC: bone mineral content, PAL: physical activity level.

Level of significance * $P \leq 0.05$, ** $P \leq 0.01$, χ^2 : Chi-square test.

a slight fluctuation for arm BMD at perimenopausal stage.

Further Tukey post-hoc analysis presented the inter-group differences among women across different menopausal stages (Table 2). It is evident from the Table 2 that bone mineral content and BMD at different skeletal sites (hip, lumbar, and left arm) exhibited statistically significant differences in their mean values from premenopause to early postmenopause stage, premenopause to late postmenopause stage, perimenopause to early postmenopause stage and perimenopause to late postmenopause stage. It is interesting to highlight that transition from premenopause to perimenopause phase exhibited statistically non-significant results.

Association of body composition characteristics with bone mineral density

Karl Pearson correlation coefficient (r) was applied to ascertain the association of body composition parameters with BMD at three skeletal areas of four phases of menopause transition is demonstrated in Table 3. Total hip BMD depicted significant association with weight, BMI, %TBF, waist circumference, fat mass and lean mass in most of menopausal transition stages. Lumbar and left arm BMD demonstrated strong association with weight and lean mass at all the four menopausal stages. During late postmenopausal stage, all the se-

lected body composition characteristics demonstrated a significant association with BMD at lumbar and left arm except for non-significant association of %TBF with arm BMD (Table 3).

Multiple linear regression of BMD at different skeletal sites with body composition characteristics in different stages of menopausal transition was evaluated by designing different models after controlling for other factors i.e., age, height, diet pattern, physical activity level (Table 4). In model 1 after adjusting %TBF by weight, it was noted that the weight was significantly and positively correlated with BMD at total hip, lumbar and left arm in all menopausal stages, whereas, %TBF had a negative association with BMD at hip, lumbar spine and left arm in all menopausal stages except for lumbar BMD at late postmenopause stage, while significant association was noted only at all menopausal stages of left arm and early postmenopausal stage of lumbar.

It was observed that after adjusting fat mass by lean mass (Model 2), fat mass exhibited positive correlation with hip and lumbar BMD in all menopausal stages except premenopause ($\beta = -0.07$) and early postmenopause stage ($\beta = -0.23$) with lumbar BMD. However, fat mass represented negative association with arm BMD in all the four menopausal stages. Alternatively, lean mass exhibited a positive and significant association with total hip and left arm BMD in four different

Table 2. Inter group comparison of body composition, BMC and BMD at different skeletal sites of women at different phases of menopause transition using Tukey post-hoc test

	Pre vs. peri	Pre vs. early post	Pre vs. late post	Peri vs. early post	Peri vs. late post	Early post vs. late post
Height (cm)	0.992	0.617	0.033	0.466	0.016*	0.581
Weight (kg)	0.740	0.951	0.250	0.498	0.030	0.669
BMI (kg/m ²)	0.796	0.999	0.783	0.797	0.289	0.894
WC (cm)	0.606	1.000	0.922	0.667	0.961	0.924
HC (cm)	0.509	0.849	0.122	0.191	0.003*	0.632
Body fat (%)	0.603	0.387	0.290	0.955	0.921	1.000
Fat mass (kg)	0.799	1.000	0.883	0.844	0.402	0.929
Lean mass (kg)	0.966	0.343	0.022	0.168	0.006*	0.766
BMC (g/cm ³)	0.917	0.001*	0.001*	0.001*	0.001*	0.022
Total hip BMD (g/cm ²)	0.985	0.001*	0.001*	0.002*	0.001*	0.001*
Lumar BMD (g/cm ²)	0.309	0.001*	0.001*	0.024	0.001*	0.016*
Left arm BMD (g/cm ²)	0.878	0.001*	0.001*	0.001*	0.001*	0.055

Level of significance * $P < 0.01$ (after Bonferroni correction).

BMC: bone mineral content, BMD: bone mineral density, Pre: premenopause, Peri: perimenopause, Early post: early postmenopause, Late post: late postmenopause, BMI: body mass index, WC: waist circumference, HC: hip circumference.

*Values present significant results.

Table 3. Karl Pearson correlation coefficient (r) of body composition characteristics with BMD at different skeletal sites of four phases of menopause transition

Body composition characteristic	Premenopause stage (r)	Perimenopause stage (r)	Early post menopause stage (r)	Late postmenopause stage (r)
Total hip BMD				
Weight	0.44**	0.54**	0.42**	0.55**
BMI	0.47**	0.54**	0.44**	0.50**
%TBF	0.29**	0.17	0.15	0.21
WC	0.40**	0.40**	0.20	0.47**
Fat mass	0.36**	0.49**	0.31*	0.48**
Lean mass	0.39**	0.53**	0.37**	0.59**
Lumbar BMD				
Weight	0.27**	0.36**	0.41**	0.55**
BMI	0.17	0.28**	0.30*	0.45**
%TBF	0.07	0.01	-0.17	0.28*
WC	0.12	0.23*	0.10	0.52**
Fat mass	0.17	0.26*	0.12	0.49**
Lean mass	0.27**	0.35**	0.47**	0.49**
Arm BMD				
Weight	0.34**	0.49**	0.32*	0.49**
BMI	0.31**	0.42**	0.24	0.36**
%TBF	0.06	-0.08	-0.13	0.09
WC	0.29**	0.42**	0.09	0.46**
Fat mass	0.24*	0.31**	0.15	0.38**
Lean mass	0.44**	0.55**	0.45**	0.57**

BMD: bone mineral density, BMI: body mass index, TBF: total body fat, WC: waist circumference.
Level of significance * $P \leq 0.05$, ** $P \leq 0.01$.

stages of menopause, while BMD at lumbar depicted significant association in perimenopause and early postmenopausal phase only. Moreover, β values for lean mass were found to be stronger than fat mass, thereby exhibiting greater effect of lean mass on BMD sites.

In Model 3 after adjusting waist circumference by hip circumference, waist circumference demonstrated a positive association with total hip BMD ($\beta = 0.39$, $P < 0.05$), lumbar BMD ($\beta = 0.49$, $P < 0.05$) and left arm ($\beta = 0.39$, $P < 0.05$) among late postmenopause women only. The results depicting stronger effect of waist circumference in late postmenopausal stage among women. While hip circumference depicted a positive association with total hip BMD among perimenopause ($\beta = 0.52$, $P < 0.01$) and early postmenopause women ($\beta = 0.40$, $P < 0.05$), lumbar BMD at premenopause stage ($\beta = 0.46$, $P < 0.05$) and early postmenopause phase ($\beta = 0.39$, $P < 0.05$) of left arm (Model 3).

DISCUSSION

BMD is the inorganic mineral content which helps to maintain the strength of the bones. Therefore, present research is an attempt to evaluate the association of body composition characteristics on BMD across different menopausal status of women. Results of the present study documented a significant decrement of bone mineral content and BMD at various skeletal site (total hip, lumbar, and left arm) during gradual progression from premenopause stage to late postmenopause stage. In convergence to our findings, a study performed by Khan et al. [19] reported significantly reduced BMD among women during transition from reproductive to post reproductive stage. A study of Women's Health Across the Nation carried out by Greendale et al. [20] established that there is an initial acceleration of bone loss in a 3-year span surrounding final menstrual peri-

Table 4. Multiple linear regression of BMD at different skeletal sites with body composition characteristics in different stages of menopausal transition

	Premenopause phase (β)	Perimenopause phase (β)	Early postmenopause phase (β)	Late postmenopause phase (β)
Model 1				
Total hip BMD				
Weight	0.49**	0.61**	0.54**	0.74**
%TBF	-0.03	-0.10	-0.10	-0.23
Adjusted R ²	0.20	0.35	0.17	0.48
Lumbar BMD				
Weight	0.28*	0.39**	0.60**	0.55**
%TBF	-0.12	-0.14	-0.43**	0.05
Adjusted R ²	0.10	0.20	0.30	0.28
Arm BMD				
Weight	0.54**	0.64**	0.47**	0.65**
%TBF	-0.26*	-0.37**	-0.33*	-0.29*
Adjusted R ²	0.16	0.35	0.19	0.34
Model 2				
Total hip BMD				
Fat mass	0.09	0.21	0.13	0.12
Lean mass	0.36*	0.41**	0.37*	0.49**
Adjusted R ²	0.17	0.36	0.13	0.50
Lumbar BMD				
Fat mass	-0.07	0.05	-0.23	0.27
Lean mass	0.27	0.26*	0.57**	0.24
Adjusted R ²	0.10	0.17	0.24	0.29
Arm BMD				
Fat mass	-0.22	-0.13	-0.16	-0.03
Lean mass	0.62**	0.63**	0.54**	0.54**
Adjusted R ²	0.20	0.32	0.22	0.38
Model 3				
Total hip BMD				
WC	0.23	0.00	-0.05	0.39**
HC	0.21	0.52**	0.40*	0.06
Adjusted R ²	0.17	0.29	0.07	0.36
Lumbar BMD				
WC	-0.29	0.02	-0.02	0.49**
HC	0.46**	0.20	0.30	-0.03
Adjusted R ²	0.14	0.12	0.08	0.28
Arm BMD				
WC	0.29	0.40*	-0.28	0.39**
HC	0.01	-0.01	0.39*	0.01
Adjusted R ²	0.08	0.18	0.10	0.30

Model 1, 2 and Model 3 adjusted for age, height, diet pattern, physical activity level.

BMD: bone mineral density, TBF: total body fat, WC: waist circumference, HC: hip circumference.

Level of significance * $P \leq 0.05$, ** $P \leq 0.01$.

od (FMP), but a decline in BMD was observed around 1 year before the FMP, and continues to decrease in early postmenopause, with a slight deceleration in loss rate around 2 years after attaining the menopause. A plethora of prior researches [21-23] illustrated accelerated bone loss during the menopause transition stage and beyond among women. Golden [2] attributed this loss to decreasing level of serum estradiol during menopause transition thereby causing an increased osteoclastic bone resorption.

Karl Pearson correlation coefficient (r) of our study observed a significant positive association of weight, BMI, fat mass and lean mass with BMD at different skeletal sites among women at most of the menopausal transition stages. Vast literature illustrated a positive association of weight [24,25], BMI [26], fat mass [27] and lean mass [28] with BMD. In convergence to the findings of present study a positive and significant association between fat mass and BMD has been documented among women of India [29], Thailand [30], and New Zealand [27]. Fat mass is considered as a beneficial contributor of BMD by enhancing the mechanical strain on the bone particularly among postmenopausal women. It is believed that production of estrogen by adipose tissues contribute significantly to BMD of adult women [31]. Although fat mass is a crucial source of estrogen, but in our study, lean mass found to have a positive and moderate association with BMD at all the selected skeletal sites as compared to fat mass. Previous studies [25,27,28] have also documented that the lean mass was positively correlated and strongest determinant of BMD of different skeletal sites.

After establishing correlation between body composition characteristics and BMD sites, to determine the association of body composition parameters (fat and lean mass) on BMD at different skeletal sites across menopausal transition stages multiple linear regression analysis with different Models were designed. Further, models were adjusted for age, height, physical activity level, diet (vegetarian/non-vegetarian) which might accounted for variance. Our results depicted that weight had a strong correlation with BMD at all the three selected skeletal sites, but a negative correlation of %TBF with BMD at total hip, lumbar, and left arm across all the four menopausal stages except for late postmenopause stage of lumbar (Model 1). A study performed by Karlamangla et al. [23] ascertained the bone health of women during menopause transition and beyond, where they recorded beneficial role of higher weight in

stimulating bone formation thereby an increase in the level of BMD. This is also exhibiting a protective role against fracture by adding tissue padding at vulnerable sites of impact in a fall. Similarly, Kim et al. [25] studied reported negative association of %TBF with BMD of different skeletal sites amongst premenopausal and postmenopausal women of Korea.

Our study exhibited that fat mass shown a positive correlation with hip and lumbar BMD in all menopausal stages except premenopause and early postmenopause stage with lumbar BMD, while an inverse relationship was witnessed for fat mass at left arm. It is witnessed in previous literature [32,33] that obesity is positively associated with high bone mass which possibly happened due to increased levels of hormones such as leptin, insulin, and estrogen which are responsible to promote bone growth and inhibit the bone remodelling process.

It was observed in the present research that lean mass was better determinant of BMD than fat mass and lean mass presented a positive and significant association with BMD at most of the menopausal stages in all skeletal sites. Findings of de Matos et al. [34] established that lean mass is the crucial component to influence BMD of women under 50 years of age and ≥ 50 years. Similarly, lean mass showed strongest association with BMD of femoral neck in middle-aged elderly men and women of Western Norway. Another study [35] with applying adjusted models highlighted a surge in BMD with increasing lean mass. It was also observed by Garvey et al. [36] that BMD exhibited a positive association with lean mass ($r = 0.43$, $P = 0.002$) and opposite correlation with total fat percentage ($r = -0.31$, $P = 0.03$). Based on multiple linear regression models, they further indicated BMD was positively associated with lean mass ($\beta = 0.007$, $P < 0.001$), while inverse association with fat mass ($\beta = -0.003$, $P = 0.03$) and total fat percentage ($\beta = -0.004$, $P = 0.03$).

Our findings reported waist circumference as a significant component of BMD at the late postmenopausal stage of all the three selected skeletal sites (Model 3). It was established by the earlier studies [37,38] that the effect of fat mass on BMD depends on its location in the individual body. Visceral fat demonstrated a negative association with BMD. It was reported that waist circumference was significantly associated with bone mineral content independent of total fat mass [11].

The present research was cross-sectional in nature which was not helpful to evaluate the changes over the

time. However, due to cost as well as accessibility very few studies were performed using DEXA scan to establish association of body composition characteristics with BMD of different skeletal sites across menopausal transition stages. Therefore, present study will contribute immensely in bridging the huge data gap in the studies concerning the bone health of the women during and after transitioning menopause.

In conclusion, this study highlighted a significantly reduced bone mineral content, total hip BMD, lumbar BMD and arm BMD with menopause transition stages among women. Karl Pearson coefficient correlation revealed a significant association of lean mass and fat mass with BMD at all the selected skeletal sites during different menopausal stages but the association was more pronounced with lean mass instead of fat mass. Weight had a positive correlation with BMD, while %TBF depicted an opposite trend. This may be attributed to moderate physical activity (absence of regular exercise regime) among women of the present study that might results in the reduced development of lean mass, which is advantageous for BMD. Therefore, specific types of exercise which enhance the muscle development during menopausal transition are essential for promoting their bone health. More cross-sectional as well as longitudinal studies in this realm from different ethnic groups are needed to corroborate these findings.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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