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Grand multiparity associations with low bone mineral density and degraded trabecular bone pattern

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ABSTRACT

Introduction: Pregnancy is associated with changes in bone remodeling and calcium metabolism, which may increase the risk of fragility fracture after menopause. We hypothesized that in postmenopausal women, with history of grand multiparity, the magnitude of trabecular bone deterioration is associated with number of deliveries.

Methods: 1217 women aged 69.2 ± 6.4 years, from the Bushehr Elderly Health (BEH) program were recruited. The areal bone mineral density (aBMD) of the lumbar spine and femoral neck and trabecular bone score (TBS) of 916 postmenopausal women, with grand multiparity defined as more than 4 deliveries, were compared with those of 301 postmenopausal women with 4 or fewer deliveries. The association of multiparity with aBMDs and TBS were evaluated after adjustment for possible confounders including age, years since menopause, body mass index, and other relevant parameters.

Results: The aBMD of femoral neck (0.583 ± 0.110 vs. 0.603 ± 0.113 g/cm^2), lumbar spine (0.805 ± 0.144 vs. 0.829 ± 0.140 g/cm^2) and TBS (1.234 ± 0.086 vs. 1.260 ± 0.089) were significantly lower in women with history of grand multiparity than others. In the multiple regression analysis, after adjusting for confounders, the negative association did persist for lumbar spine aBMD (beta = −0.02, p value = 0.01), and the TBS (beta = −0.01, p value = 0.03), not for femoral neck aBMD.

Conclusion: We infer that grand multiparity have deleterious effects on the aBMD and the trabecular pattern of the lumbar spine.

1. Introduction

Pregnancy and breastfeeding are associated with major changes in maternal calcium homeostasis, bone metabolism, and bone remodeling rate due to the calcium demand and its delivery to the fetus and the newborn. Excessive bone resorption during pregnancy may not be a characteristic of the mature women who has achieved full maximal bone mass; however, evidence shows that pregnancy at an earlier age, when the skeleton of both fetus and mother are maturing simultaneously, may result in lower bone mineral density (Sowers et al., 1992). The hormonal and maternal calcium changes may, partly, explain the reduction in bone mineral density (BMD) during pregnancy; however, compensatory mechanisms like; elevated intestinal calcium absorption, relatively higher estradiol levels during third trimester, and also weight gain may reduce the rate of bone loss (Soma-Pillay et al., 2016; Kovacs, 2016).

Reduced estrogen levels during lactation, and extended resorption phase of bone remodeling cycle through increased osteoclast lifespan cause an increase erosion depth in trabeculae leading to trabecular network deterioration and resulting in increased bone fragility (Sowers et al., 1995; Vajda et al., 2001; VanHouten and Wysolmerski, 2003; Sowers et al., 1993). This structural deterioration could be reversible to some degree; nevertheless, increased cortical porosity, reduced

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trabecular number, and greater trabecular separation reported in premenopausal women after cessation of breastfeeding (Bjornerem et al., 2017) and in some animal models studies (Liu et al., 2012).

Lactation is highly related to parity; however, its duration and frequency differ between cultures and communities. Almost all Iranian women, particularly in southern region, breastfeed their newborns, so data on frequency of parity can be used as surrogate to lactation frequency. Different meta-analysis has reported different results on association between lactation and bone status. While one has reported that long periods of breastfeeding is associated with fractures (Bolzetta et al., 2014a), the others found either no association between lactation and BMD (Chowdhury et al., 2015a), or even reduced osteoporotic fracture risk (Duan et al., 2017a).

There is a controversy on the effect of pregnancy and lactation on bone (Bolzetta et al., 2014a; Chowdhury et al., 2015a; Duan et al., 2017a; Salari and Abdollahi, 2014a; Song et al., 2017; Terzi et al., 2017a; Derakhshan et al., 2017) and the final net effect of reproductive state on bone is not obviously known. However, pregnancy and lactation could affect the bone later in life, especially in postmenopausal women who are already at the increased risk of fragility fracture due to long-term estrogen deprival.

Bone strength is dependent on bone quality as well as bone mass. Bone geometry, micro-architecture, micro-damage, mineralization, and turnover among all, can determine bone quality (Rubin, 2005). Impaired bone structure, independent of areal bone mineral density (aBMD), is associated with greater risk of fragility fracture (Seeman and Delmas, 2006; Halupczok-Zyla et al., 2019). Improvement of prediction of fracture risk based on Trabecular Bone Score (TBS), in addition to aBMD, has been reported considerably (Halupczok-Zyla et al., 2019; Ripamonti et al., 2018; Shevroja et al., 2017; Silva et al., 2014).

Since breastfeeding is an estrogen-deficient state associated with bone loss and microstructural deterioration with unknown microstructure reversibility (Bjornerem et al., 2017), we hypothesized that women with grand multiparity have deteriorated lumbar spine trabeculae pattern due to more frequent and consecutive pregnancies and lactations leading to long term interruption on steady state bone remodeling phase, and therefore more prone to fragility fractures in the post-menopausal period.

In this study we aimed to evaluate the association between history of grand multiparity (defined as more than 4 deliveries) and aBMD and TBS of elderly women. To the best of our knowledge, this is the first study to examine the association between the multiparity and the TBS as well as aBMD in a large-scale population of elderly women while considering several potential confounders.

2. Methods

2.1. Study participants

The present study was conducted in 1217 women participating in the second stage of the Bushehr Elderly Health (BEH) program with available data on delivery, TBS, and BMD. This population-based prospective cohort study is being conducted on 3000 elderly women and men, aged above 60 years, in Bushehr, a southern province of Iran since 2013 (Ostovar et al., 2015). The second stage of the study aimed to determine the prevalence and risk factors of geriatric musculoskeletal disorders such as osteoporosis (Shafiee et al., 2017). The details of the rationale and design of the original study is described elsewhere (Ostovar et al., 2015; Shafiee et al., 2017). A validated questionnaire was used to collect all required information including socio-demographic, smoking, physical activity, reproductive health, number of deliveries, etc. Overnight fasting venous blood sample was obtained for all participants for biochemical measurement and storage for future use and other clinical examinations were taken according to the standard protocols. The study was approved by the Research Ethics Committee of Bushehr and Tehran University of Medical Sciences. All the participants had given an informed consent.

2.2. Bone mineral densitometry and trabecular assessment

DXA scans were acquired with Hologic instruments (Discovery WI, Hologic, Bedford, Virginia, USA) by trained operators and using the same scanner for all participant. The aBMD of femoral neck (FN) and lumbar spine (LS) (L1–L4) were measured following the International Society for Clinical Densitometry (ISCD) guidelines (Shepherd et al., 2015). TBS iNsight software (version 2.2; Medimaps Group, Plan-les-Ouates, Switzerland) was applied to quantify trabecular pattern of LS (L1–L4).

Data for this study is retrieved from 1242 women, aged more than 60 years, who participated in the second stage of the BEH program which were carried out in 2015 to 2017.

Main data including number of deliveries, aBMD of FN and LS, and TBS were extracted from BMD records of 1217 women. The covariates selected for this study were weight, height, daily calcium intake, vitamin D and calcium supplement intake, physical activity status, history of diabetes and hypertension, smoking status and lipid profile. Women with disease or treatments know to affect the BMD were excluded.

2.3. Definition of variables

Grand multiparity was defined as having more than 4 deliveries (the term "grand multiparity" defined as more than 4 or 5 deliveries was used commonly in the literature). Besides, we checked more than 3 deliveries as well to find the minimum number of parities associated with change in bone state. We described diabetes as fasting plasma glucose $\geq$126 mg/dl or HbA1C $\geq$ 6.5 or using anti-diabetic medications. Hypertension was defined as having either the systolic blood pressure $\geq$ 140 mmHg, or diastolic blood pressure $\geq$ 90 mmHg, or taking anti-hypertensive medications. Daily food intake of calcium was categorized in three groups as high (>1000 mg/day), moderate (500–1000 mg/day), and low (<500 mg/day). According to the four lifestyle categories (Mahan and Raymond, 2016), we divided the study population into two groups; low physical activity (sedentary: 1–1.39, and low active: 1.4–1.59), and high physical activity (active: 1.6–1.89 and very active: 1.9–2.5).

2.4. Statistical analysis

Summary statistics were expressed as mean $\pm$ standard deviation (SD) for data with normal distribution based on the Shapiro-Wilk normality test. Non-normal distributed variables were presented as median and interquartile range (IQR). Categorical data were tested by chi-square test and presented by percentages. Independent two-sample tests (independent *t*-test or Pearson chi square test) were used to determine the significance of trait differences between groups.

Associations between multiparity and the aBMD/or TBS of the LS (L1–L4) and the aBMD of the FN were assessed using Pearson correlation coefficient and multiple linear regression analysis. In regression analysis we adjusted the models for potential confounders (age, years since menopause, body mass index (BMI), diabetes, smoking, hypertension, waist circumference, physical activity, and calcium intake). Variables were included in the final model given that their *p*-values were less than 0.2 in univariate analysis. Standardized coefficients were presented.

P-value less than 0.05 (two-tailed) was considered as significant difference. Statistical analysis was performed using StataCorp 2014 (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

3. Results

3.1. Demographics and biochemical outcomes

The participants were 1217 women with the mean age of 69.2 $\pm$ 6.4

years. The median number of deliveries was 6 with interquartile range of 5 to 8. We stratified the participants in two groups of grand multiparous and others, according to the number of deliveries (more than 4 deliveries ($n = 916$) and 4 deliveries or less ($n = 301$)). The basic characteristics of the participants, including body and aBMD status, comorbidities (diabetes mellitus and hypertension), smoking status, physical activity, daily calcium intake, and vitamin D and calcium supplements are presented in Table 1.

Grand multiparous women had higher waist circumference, lower LS aBMD, lower TBS, higher prevalence of diabetes, hypertension, and smoking, lower daily calcium intake, and lower vitamin D supplement intake compared with other women (Table 1).

3.2. BMD and TBS findings

The box plots of the LS and FN aBMDs and the TBS against delivery groups are illustrated in Fig. 1, revealing lower aBMD and TBS in grand multiparous women compared to others. Mean value of LS and FN aBMD and TBS by quantiles of number of deliveries is presented in Fig. 2 which shows a decreasing pattern in the LS-aBMD and the TBS by increments in the number of deliveries.

The association of grand multiparity with the LS and the FN-aBMD and TBS in a univariable and multivariable linear regression analyses are presented in Table 2.

The mean FN aBMD was 0.583 ± 0.110 g/cm^2 in grand multiparous women, which was significantly lower than other women (0.603 ± 0.113 g/cm^2). However, no significant difference between delivery categories were detected after adjustment (beta = −0.066, p value = 0.3).

The mean LS aBMD in women with history of grand multiparity was significantly lower than in other women (0.805 ± 0.144 g/cm^2 vs 0.829 ± 0.140 g/cm^2, p value = 0.013). The negative association between aBMD of LS and with history of grand multiparity persisted in multiple regression analysis, after adjusting for confounders (beta = −0.022, p value = 0.01).

Grand multiparous women had significantly lower TBS compared with other women (1.234 ± 0.086 and 1.260 ± 0.089, respectively). This association persisted after adjusting for confounders (beta = −0.012, p value = 0.036).

4. Discussion

This study included elderly women, aged above 64 years, with more than 75% having history of grand multiparity (defined as more than 4 deliveries). We observed that postmenopausal women with a history of grand multiparity had lower aBMD and more degraded lumbar spine TBS compared to less parous women. After adjusting for possible confounders, the LS aBMD and TBS, not the FN aBMD, were found to be statistically significantly lower in women with a history of grand multiparity compared to other women. The relatively lower FN aBMD emphasizes the higher risk of femoral neck fracture in the postmenopausal women with history of grand multiparity.

Maintaining the level of circulating ionised calcium within a narrow physiological range is crucial for the body to function normally. Pregnancy and breastfeeding are associated with considerable changes in the maternal calcium homeostasis due to the higher calcium demand and delivery to the fetus and the newborn (Kovacs, 2016; Prentice, 2000; Oliveri et al., 2004). These changes lead to alterations on bone metabolism via bone remodeling. Higher required calcium delivery to the fetus can explain, partly, a reduction in the aBMD during pregnancy; however, increased intestinal calcium absorption caused by higher 1,25 (OH)2 vitamin D (Woodrow et al., 2006), and estradiol levels during the third trimester of pregnancy (Soma-Pillay et al., 2016; O'Leary et al., 1991), and also the increased loading as a consequent of weight gaining (Moller et al., 2012), may compensate the bone loss rate. These would explain unchanged, or even increased aBMD, reported in some studies on women with multiparity (Song et al., 2017; Karlsson et al., 2001; Cure-Cure et al., 2002; Okyay et al., 2013; Terzi et al., 2017b). However, the aBMD elevation after weight gain needs to be interpreted with caution, because changes in body composition statues alters aBMD measurements (Yu et al., 2012; Amnuaywattakorn et al., 2016). In this regard, TBS may help identify women at risk of fracture, in particular,

Table 1
Characteristics of the study population and comparison of women with ≤4 and >4 deliveries.

Variables		Total ($n = 1217$) Mean ± SD	≤4 deliveries ($n = 301$) Mean ± SD	>4 deliveries ($n = 916$) Mean ± SD	P value
Age (years)		69.2 ± 6.4	68.0 ± 6.1	69.5 ± 6.4	<0.001
Years since menopause (years)		21.9 ± 8.2	21.1 ± 8.4	22.1 ± 8.1	0.080
Anthropometrics and body composition	BMI (kg/m^2)	28.7 ± 5.3	28.4 ± 4.9	28.8 ± 5.5	0.220
	Waist circumference (cm)	100.2 ± 12.5	98.5 ± 11.8	100.8 ± 12.7	0.005
	Weight (cm)	66.6 ± 13.2	66.0 ± 12.1	66.9 ± 13.5	0.308
	Height (kg)	152.3 ± 6.2	152.4 ± 6.1	152.2 ± 6.2	0.628
Bone status	TBS (L1-L4)	1.241 ± 0.088	1.260 ± 0.089	1.234 ± 0.086	<0.001
	L1-L4 aBMD (g/cm^2)	0.811 ± 0.143	0.829 ± 0.140	0.805 ± 0.144	0.013
	T-score ≥−1	205 (17%)	60 (20.2%)	145 (15.9%)	
	<−2.5 T-score <−1	502 (41.5%)	125 (42.1%)	377 (41.4%)	
	T-score ≤−2.5	501 (41.5%)	112 (37.7%)	389 (42.7%)	
	Femoral neck aBMD (g/cm^2)	0.588 ± 0.111	0.603 ± 0.113	0.583 ± 0.110	0.009
	T-score ≥−1	98 (8.1%)	36 (12.2%)	62 (6.8%)	
	<−2.5 T-score <−1	531 (44.0%)	127 (42.9%)	404 (44.4%)	
	T-score ≤−2.5	578 (47.9%)	133 (44.9%)	445 (44.8%)	
Comorbidities	Diabetes	442 (36.41%)	86 (28.67)	356 (38.95)	0.001
	Hypertension	920 (75.60%)	215 (71.43%)	705 (76.97%)	0.052
Physical activity (Yes)		276 (22.68%)	79 (26.25%)	197 (21.51%)	0.088
Smoking	Never	573 (47.8%)	187 (62.13%)	386 (42.14%)	
	Past	421 (34.59%)	75 (24.92%)	346 (37.77%)	
	Present	223 (18.32%)	39 (12.96%)	184 (20.09%)	<0.001
Supplements	Vitamin D	156 (12.82%)	51 (16.94%)	105 (11.46%)	0.014
	Calcium	155 (12.74)	39 (12.96%)	116 (12.66%)	0.895
Calcium intake	High	42 (3.47)	15 (5.03)	27 (2.96)	
	Moderate	394 (32.59)	111 (37.25)	283 (31.06)	
	Low	773 (63.94)	172 (57.72)	601 (65.97)	0.020

BMI: Body Mass Index; TBS: Trabecular Bone Score; aBMD: areal Bone Mineral Density; Calcium intake: high >1000 mg/day, moderate 500–1000 mg/day, and low <500 mg/day; ǂ Median (IQR).

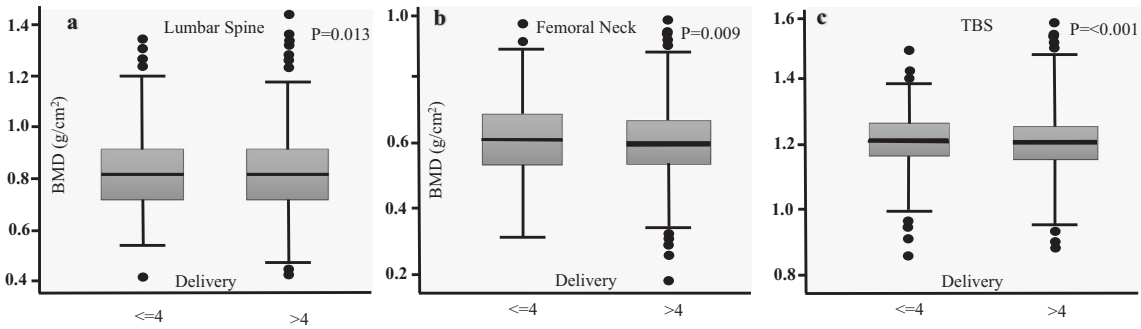

Fig. 1. The box plot of Lumbar spine and femoral neck aBMDs and TBS vs delivery groups.
(a) Relatively lower lumbar spine aBMD in women with more than 4 deliveries in comparison to women with 4 or fewer deliveries. (b) Relatively lower femoral neck aBMD in women with more than 4 deliveries. (c) Relatively more degraded TBS in women with more than 4 deliveries.

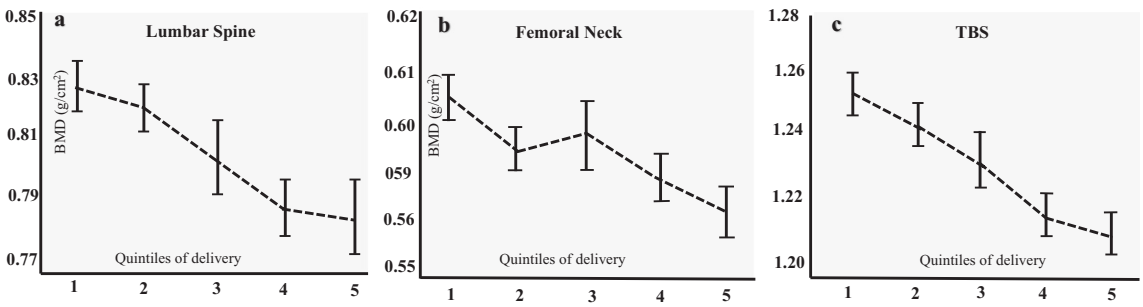

Fig. 2. Mean value of lumbar spine aBMD (a), femoral neck aBMD (b), and TBS (c) by the quantiles of delivery numbers.
Negative association between quantiles of delivery with lumbar spine aBMD (a), femoral neck aBMD (b), and trabecular bone score (c). Number of deliveries in quintiles 1: 0–4, 2: 5–6, 3: 7, 4: 8–9, 5: 10–16.

Table 2
The association of grand multiparity with aBMD and TBS in a univariable and multivariable linear regression analysis.

Variables		L1-L4 aBMD			Femoral neck aBMD			TBS		
		Coefficient (univariable)	Coefficient (multivariable)	P value	Coefficient (univariable)	Coefficient (multivariable)	P value	Coefficient (univariable)	Coefficient (multivariable)	P value
Grand Multiparity		−0.0236*	−0.0223	0.012	−0.0194*	−0.0655	0.343	−0.0251**	−0.0124	0.036
Age		−0.0071**	−0.0018	0.051	−0.0076**	−0.0051	<0.001	−0.0031**	−0.0027	<0.001
Years since menopause		−0.0059**	−0.0031	<0.001	−0.0052**	−0.0015	0.004	−0.0024**	−0.0013	0.004
BMI		0.0127**	0.0102	<0.001	0.0070**	0.0045	<0.001	−0.0022**	0.0004	0.650
Waist circumference		0.0044**	0.0002	0.733	0.0026**	0.0003	0.421	−0.0014**	−0.0020	<0.001
Diabetes Mellitus		0.0445**	0.0228	0.004	0.0192*	0.0071	0.247	−0.0101	−0.0097	0.066
Hypertension		0.0458**	0.0234	0.010	0.0090	–	–	−0.0100	0.0090	0.138
Smoking^	Past	−0.0286*	−0.0154	0.073	−0.0290**	−0.0145	0.032	−0.0320**	−0.0150	0.009
	Current	−0.0232*	0.0009	0.928	−0.0181*	−0.0118	0.140	−0.0171*	−0.0067	0.332
Physical activity		0.0133	−0.0041	0.639	0.0281**	0.0066	0.340	0.0149*	−0.0006	0.922
Calcium intake#	Moderate	−0.235	−0.0341	0.106	−0.0118	−0.0191	0.250	−0.0252	−0.0219	0.121
	Low	−0.0427	−0.0479	0.021	−0.0234	−0.0248	0.127	−0.0421*	−0.0360	0.010

*p value <0.05 and **p value <0.001 in univariable analysis; Multiparity: defined as having more than four deliveries, aBMD: areal Bone Mineral Density; TBS: Trabecular Bone Score; BMI: Body Mass Index; ^ No smoking was used as reference; # High Calcium intake was used as reference; Calcium intake: high >1000 mg/day, moderate 500–1000 mg/day, and low <500 mg/day.

those having relatively higher BMD-osteopenia or normal BMD (Lee et al., 2017).

Excess bone resorption with pregnancy may not be a characteristic of the mature woman who has achieved full maximal bone mass. However, evidence shows that pregnancy at an earlier age, when the skeleton of both fetus and mother are maturing simultaneously, may result in lower aBMD and increased perimenopausal bone loss (Sowers et al., 1985). In contrast, a retrospective study with a small sample size ($n = 50$) reported that teenage pregnancy (age of 15–19 years) and breastfeeding had no negative effect on peak bone mass (Teerapornpuntakit et al., 2018). Furthermore another study conducted on 240 perimenopausal women, observed better FN aBMD in women with history of adolescent pregnancy (Yuce et al., 2015). There is evidence of a net decrease in aBMD during pregnancy with a further decrease postpartum related to the length of breastfeeding with a gradual recovery thereafter (fully regained 19 months after delivery), which occurs sooner in the trabecular bone (Moller et al., 2012). Postpartum overcorrection may occur in the LS, with only partial recovery in the FN (Holmberg-Marttila et al., 2000), which can be explained by higher ratio of trabecular bone in the LS with an increased bone remodeling rate compared to the cortical bone. During lactation, due to estrogen deficiency, unbalanced remodeling upon trabecular surfaces perforates thicker trabeculae, and removes the thinner trabeculae producing a reduction in the trabecular number and greater separation between them which leads to reduced

bone strength. These morphological effects did not reverse fully following cessation of lactation and the return of menses (Bjornerem et al., 2017). In addition to the calcium delivery to the newborn, the longer lactation periods and prolonged estrogen deficiency may have caused further and accumulated bone loss in grand multiparous women leading to increased risk of fragility fracture later in life (Tsvetov et al., 2014; Compston, 2001); however, data are conflicting (Duan et al., 2017b; Chowdhury et al., 2015b; Bolzetta et al., 2014b) and there is no consensus on bone loss during lactation, nor on long-term effects of parity and breastfeeding on the measured bone mineral density by DXA (Salari and Abdollahi, 2014b).

Duration of lactation differs between cultures and communities significantly. Pregnancy at young age were not uncommon in our study population. We did not have exact data on cumulative breastfeeding duration; however, culturally, especially in the past decades, almost all Iranian women in Bushehr Province had breastfed their newborns, so data on parities could be used as a surrogate of lactation.

Our study has several limitations. Data on duration of breastfeeding, vitamin D level, and incident fragility fractures were not available, also there were no bone markers available for analysis. Second, due to the cross-sectional design of the study, there were no access to premenopausal aBMDs of the participants. However, we evaluated the association between TBS and grand multiparity in a large population of elderly women taking into account many possible confounders, and our data shows deteriorated trabecular pattern and aBMD of the LS before reduction in FN aBMD. Besides, we compared grand multiparous women with less parous women rather than nulliparous women, whose decrease in aBMD could be explained by factors that caused infertility. Further follow up studies are needed to establish whether grand multiparity has destructive effects on appendicular skeleton contributing to fragility fracture and to evaluate the association of multiparity with fragility fractures and sarcopenia in elderly population.

5. Conclusion

This study suggests that grand multiparity (more than 4 deliveries) may have adverse effect on bone which would be more pronounced in the LS. Using TBS in addition to aBMD of the lumbar spine could improve our ability to identify postmenopausal women at the risk of deteriorated bone status. However, further studies are needed to establish whether the deterioration in the trabeculae of the LS contributes to fracture.

CRediT authorship contribution statement

Study design and conduct: all authors; Data collection: AO, GSH; Statistical analyses: NF, NP, SGH, AO; Drafting manuscript: NP, AGH. Data interpretation and approving final version of manuscript: all authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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