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Article *in* Women & Health · February 2018

DOI: 10.1080/03630242.2018.1434592

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To cite this article: Fatemeh Mohammadi, Jamileh Amirzadeh Iranagh, Seyedeh Ameneh Motalebi & Tengku Aizan Hamid (2018): Reproductive factors influencing bone mineral density in postmenopausal women, Women & Health, DOI: 10.1080/03630242.2018.1434592

To link to this article: https://doi.org/10.1080/03630242.2018.1434592

Accepted author version posted online: 05 Feb 2018.

Reproductive factors influencing bone mineral density in postmenopausal women

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Running head: Reproductive factors influencing bone mineral density

Abstract

Objective: This study examined the relationship between reproductive characteristics and bone mineral density in postmenopausal women who had been referred to the menopause clinics of the National Population and Family Development Board and of the Hospital Kuala Lumpur from July 2011 to January 2012.

Method: The participants of this study were 201 postmenopausal Malaysian women aged 45–71 years. Some socio-demographic, life style and reproductive factors were recorded. Calcaneal bone mineral density was measured by quantitative ultra-sonography. Correlations of reproductive factors with bone mineral density were assessed by Pearson's correlation test and multiple regression analysis.

Results: Age at menopause was not significantly correlated with bone mineral density, while the years after menopause, age at the first menstrual period, number of pregnancies and total lactation periods were inversely correlated with it. Among reproductive factors, only the

association between lactation duration and bone mineral density remained significant after adjusting for age, body mass index, activity, and calcium intake.

Conclusion: The results indicated that except for prolonged total time of lactation, other reproductive factors were not significantly associated with bone mineral density in post-menopausal women.

Keywords: Bone mineral density; osteoporosis; reproductive factors; quantitative ultrasound; postmenopausal

Introduction

Osteoporosis as a chronic metabolic disease is a major global public health problem. Significant morbidity and mortality due to associated fractures, deteriorating the quality of life and financial burden, are frequent consequences of osteoporosis. This age-related problem mostly occurs among the elderly population (Copês, Dal Osto, Langer, de Vieira, da Silveira Codevilla,… Premaor, 2017; Gielen, Bergmann, Bruyère, Cavalier, Delanaye, …. Rozenberg, S. 2017; Lunenfeld & Stratton, 2013; Ng, Lau & Ko, 2017). Women, especially in the early post-menopause period are more susceptible to bone loss (Varacallo, 2014; Ponnapakkam, tikaneni, Sakon, Stratford & Gensure, 2015).

The elderly population is growing fast, particularly postmenopausal women, and therefore occurrences of osteoporosis and hip fractures are increasing (Isnoni, Murallitharam, Tajuddin, Purany, & Manmohan, 2012) as one in two postmenopausal women and one in five older men are at risk for an osteoporosis-related fracture (Lunenfeld and Stratton, 2013). In Malaysia, in 1997, the rate of hip fracture among those at least 50 years of age was 90 per 100,000 of the total

population (Lee & Khir, 2007). Hasnah, Amin , Suzana (2012) also found that 6% of 125 postmenopausal Malay females, with a mean age of 59 years, were osteoporotic.

Several research studies have shown a controversial association between reduction in bone mass and many risk factors. A number of studies have shown both negative or positive correlations between reproductive characteristics and bone mineral density (Lenora, Lekamwasam & Karlsson, 2009; Sioka, Fotopoulos, Xourgia, Papadopoulos & Kalef-Ezra, 2010; Wiklund et al., 2012; Canal-Macias, Roncero-Martin, Moran, et al. 2013; Bolzetta, Veronese, De Rui, et al. 2014; Okyay, Okyay, Dogan et al., 2014; Heidari, Hedayati, Nourooddini & Hajian-Tilaki, 2015). Moreover, very limited data are available about risk factors for osteoporosis in developing countries (Keramat, Patwardhan, Larijani, et al. 2008). In Malaysia, previous studies addressing the relationship between bone mineral density (BMD) and reproductive characteristics have been very limited. Further, high morbidity and mortality due to osteoporosis are related to its late diagnosis and treatment, because osteoporosis is a silent disease, and no symptom exists until a bone fracture occurs. Early diagnosis and treatment are possible through measuring BMD, which is the best predictor for osteoporosis and fracture based on the WHO's recommendation (Arslantas, Metintas, Unsal, Isikli & Kalyuncu, 2008; Senn, Günther, Popp et al., 2014). In this study, we investigated the relations of reproductive factors to BMD in 201 postmenopausal Malaysian women, to ascertain whether reproductive characteristics are independent risk factors for low BMD with possible inter-correlations.

Methods

Participants

Purposive sampling was used. Inclusion criteria for the study were menopausal women who had no menstrual cycles, even spotting, for at least one year. Exclusions were women who: were on menopausal hormone therapy during the prior six months or longer; were taking medication for bone, or calcium or vitamin D supplementation for more than one month during the previous year; were taking medicines affecting bone density, such as glucocorticoids; or had diseases affecting bone health, such as hyperparathyroidism.

To identify the postmenopausal women, files were reviewed for women referred to menopause clinics of Hospital Kuala Lumpur and the National Population and Family Development Board (NPFDB) from July 2011 to January 2012. Contact information for menopausal women was extracted from the files, and they were then called for the initial screening. Women who appeared to meet the inclusion criteria were invited to come to the menopause clinics of Hospital Kuala Lumpur, depending on the region where they resided, at a certain time if they were willing to participate in the study.

At the time of the phone call, explanation about the study purpose and procedures was provided to the potential participants. From the approximately 1300 women seen during the study period, about 400 women (30.6%) were eligible to participate in the study. The day before the scheduled date for data collection, potential participants were called to remind them of their appointments. Out of about 400 eligible women, a total of 201 (50%) were enrolled.

This study was approved by the Medical Research Ethics Committee of the Universiti Putra Malaysia (UPM) [UPM/FPSK/PADS/T7-MJKEtikaPer/FO1 (IG_Oct (08)019)].

Data collection

All participants were interviewed for reproductive characteristics, life style and socio-demographic information using a structured questionnaire developed by the researcher. To determine the level of physical activity, respondents were asked to specify their daily activity based on a 10 cm Visual Analogue Scale (VAS). The range for physical activity score is 0 to 10. A validated food frequency questionnaire (Tee, et al., 1997) was used to determine calcium intakes, and height and weight of the individuals were measured to compute body mass index (BMI) as body weight by height squared (kg/m^2). Evaluation of bone status was based on calcaneal Quantitative Ultrasound (SONOST-2000, OsteoSys Co. Ltd). Parameters used in this study to report the bone mineral density (BMD) as results of densitometry were BUA (Broadband Ultrasound Attenuation). BUA was required as a continuous dependent variable and T-score, which is a value without units when a categorical dependent variable was required in certain statistical tests. Based on the literature, a T-score value < -1.8 was considered as the threshold to distinguish osteoporosis from normal BMD (Lim, et al. 2005; Arlantas, 2008).

Statistical analysis

All statistical analyses were conducted using the Statistical Package for Social Science (SPSS) version 18. Pearson's correlation was used to examine association between BMD as dependent variable and independent variables, including reproductive factors, age, BMI, calcium intake and physical activity.

A Chi- square test of independence was conducted to assess whether categorical variables were related to osteoporosis. Differences in the mean BMD for continuous variables were analyzed using independent-sample t-test. The associations between BMD as dependent variable and

independent variables were investigated using Pearson's correlation test and multiple regression analysis.

For linear regression, potential confounding factors, including socioeconomic status, BMI, physical activity, calcium intake, years since menopause, ages at menarche and menopause, parity and duration lactation were included as potential covariates in multivariate models. Multiple forward stepwise regression analysis was conducted to find variables independently associated with the calcaneal BMD measurement as the dependent variable, including age, BMI, family history of osteoporosis, calcium intake, physical activity, and total lactation duration. In the forward selection, we started with no variables in the model, then tested the model fit with the addition of each variable by a criterion of $p<0.05$. Variables were added until the greatest improvement of the model fit was achieved, repeating this process until no additional variables improved the model to a statistically significant extent. All tests were two-tailed, and the 5% level of statistical significance was chosen.

Ethical approval

All stages of the study were according to the Provisions of the Declaration of Helsinki of 1975. Written informed consent form was signed by all participants, and ethical approval for the study protocol was obtained from Medical Research Ethic Committee (MREC) of Ministry of Health Malaysia and from Ethic Committee of Medical Research, Faculty of Medicines and Health Sciences, Universiti Putra Malaysia (UPM).

Results

The participants who met criteria for inclusion in the study were 201 postmenopausal women. Their ages ranged from 45 to 71 years, with a mean age of 53.6 ± 3.6 years. Using Ultrasonography and the cut of value of t<-1.8 to distinguish osteoporosis from normal BMD, 144 women (71.6%) were categorized as normal, and 57 women (28.4%) met the criterion for osteoporosis.

A significant negative correlation was seen between BMD and age (r= -0.20, p= 0.004), age at the first menstrual period (r= -0.22, p=0.002), years since menopause (r= -0.17, p= 0.014), number of pregnancies (r= -0.16, p= 0.020) and total duration of breastfeeding (r= -0.15, p= 0.034). A positive correlation with BMD was observed for physical activity (r= 0.40, p<0.001), calcium intake (r= 0.58, p<0.001) and BMI (r= 0.43, p<0.001), and no significant correlation was found between age at menopause and BMD (r= 0.02, p= 0.824) (Table 1).

The mean age in osteoporotic women was significantly higher than women with normal BMD. Similarly, statistically significant difference was observed in the mean of age at first menstrual period (p<0.01), number of pregnancies (p<0.05), total duration of breast feeding (p<0.05), physical activity (p<0.001), body mass index (p<0.001) and calcium intake (p<0.001), but the difference in mean age at menopause between the two groups, was not significant. Women with normal BMD experienced their first menstrual period earlier and the final menstrual period later than women categorized as having osteoporosis. Although the mean number of years since the final menstrual period in women with osteoporosis was higher than that in the normal group, this difference was not statistically significant (p=0.06). Women in the osteoporotic group had more

pregnancies and longer durations of breastfeeding. The mean score for physical activity was significantly lower in osteoporotic women. Further, mean body mass index and mean calcium intake were higher in normal women. A significant association was seen between having a family history of osteoporosis and having lower BMD (p<0.001), while such relationship was not seen between ethnicity and osteoporosis (p= 0.282). Women categorized as having osteoporosis were more likely to have a positive family history of osteoporosis than women categorized as normal (56.1% vs 13.2%) (Table 2).

Multiple stepwise regression analysis was conducted with age, BMI, family history of osteoporosis, calcium intake, physical activity score, total lactation duration as independent variables to determine their independent associations with calcaneal BMD. After performing stepwise regression analysis, calcium intake, family history of osteoporosis, VMI, physical activity score and age of respondents had strikingly significant relationships with BMD (P<0.001, <0.001, 0.004, 0.002, respectively, r^2=0.502). Among reproductive factors investigated, only breast feeding was found to be associated with low BMD in these postmenopausal women (p=0.015) (Table 3).

A one-way ANOVA between-groups analysis of variance was conducted to assess the relation of the duration of breastfeeding to bone mineral density. The mean level of BUA determined BMD for a total lactation period of <24 months, 24-48 months, 48-72 months and >72 months are presented in Figure 1. The plot revealed a general trend of decreasing BMD related to increased duration of breastfeeding. Also, women with the longest period of lactation (>72 months) had the lowest mean BMD than other groups, and women with duration of <24 months breastfeeding had the highest mean BMD value.

Discussion

The purpose of the present study was to ascertain whether reproductive characteristics were correlated with BMD. The findings corroborate the results of a great deal of the previous work on the association between BMD and age, family history of osteoporosis, calcium intake, physical activity level and BMI. Despite the lack of correlation between BMD and most reproductive factors investigated in the current study, after adjustment for age, having family history of osteoporosis, the amounts of calcium intake, physical activity level and BMI, the only reproductive variable associated with osteoporosis was total duration of lactation.

The inverse association of number of pregnancies with BMD was explained by a study conducted among Moroccan postmenopausal women, indicating that lumbar spine and hip BMD were significantly lower in multiparous women, and this negative relationship remained unchanged after adjustment for age and BMI (Allaliab, Maaroufi, Aichaoui, et al. 2007). Another study in Morocco and two studies in Turkey and Iran supported this strong negative association (El Maghraoui, Guerboub, Mounach et al. 2007; Demir B, Haberal A, Geyik P, et al. 2008; Gharenaz, Ozgoli, Aghdashi & Salmany, 2014). In contrast, Lenora et al. (2009) suggested that high parity had no positive or negative relationship with maternal BMD. Even the protective role of multiparity for osteoporosis has been reported by some researchers (Schnatz, Marakovits & O'Sullivan, 2010; Song, Kima, Parka, Kimb, Kangc & Kim, 2017). In this regard, Hillier, Rizzo, Pedula, et al (2003) reported that the risk of hip fracture increased up to 44% in women who had not any pregnancies compared with parous women. Also, Streeten, Ryan, McBride, Pollin, Shuldiner & Mitchell (2005) agreed on the benefit of multiparity with regard to BMD; however, they believed that such a positive statistically significant correlation would be lost after

menopause, so they concluded that high parity had no beneficial or risk for bone health in later life.

The age at menopause and the years since menopause could be correlated with BMD due to estrogen deficiency after menopause, which most studies have accounted as the main reasons for osteoporosis (Andersen, 2007; Gallagher & Christopher, 2007; Francucci, Romagnia, Camilletti et al., 2008). However, our findings showed no correlation between age at menopause and BMD, and a very weak non-significant correlation between years since menopause and BMD. A possible explanation for this might be that the average age of the sample investigated in our study was rather young (mean age=53.6 years), and consequently the mean years since menopause also was low in the present study (mean=4.1 years). However, our results are consistent with those of El Maghraoui et al. (2007) who reported no association between age at menopause and BMD. Further, a relationship has been hypothesized between age at first menstrual period and BMD. This hypothesis was not confirmed either by our data or by some other studies (Sioka, 2010; El Maghraoui et al. 2007).

In reviewing the literature about the relationship between BMD and breastfeeding, very different results have been reported. These discrepancies can be attributed to differences in the samples studied with regard to some factors, such as age of the mother during lactation, amount of breast-milk produced, episodes and duration of breastfeeding and mother's habitual calcium intake (Aksakal, Aytan, Cavkaylar, et al. 2008).

The data from our study confirmed that duration of breastfeeding was the important risk factor related to osteoporosis even after adjusting for other variables. This result accords with prior research studes, which concluded that the bone mass decreases with longer lactation periods (Okyay, et al. 2013; Bolzetta et al., 2014). Also, Hwang et al. (2016) found that the negative

correlation between the lactation duration and BMD was dependent on other co-variates, such as age, BMI, age at menarche, time since menopause and oral contraceptive use. Similarly, Tsvetov et al. (2014) confirmed the negative relations of parity and breastfeeding on bone mineral density.

Our finding regarding the negative relation of duration of lactation with BMD is in disagreement with those of Kojima et al (2002), which showed a non-significant correlation of BMD and duration of lactation after adjusting for age, years since menopause, height, weight, and parity in postmenopausal women. Also, our results differ from some published studies (Lenora et al, 2009, Sioka et al, 2010, Aksakal, et al. 2008). Further, the present study results are inconsistent with those which found unexpectedly higher BMD and lower prevalence of osteoporosis in women with a history of breast feeding (Brunk, 2009; Okyay, et al. 2013; Bolzetta, et al 2014). Moreover, Karlsson et al. (2005) from a review inferred that elderly women with high parity and longer total duration of breastfeeding had higher BMD and lower risk of fracture compared to nulliparous women. They explained this discrepancy through differences in life style factors. Lactating mothers lose calcium in breast-milk, and in this way calcium metabolism and consequently bone metabolism are related directly to breastfeeding, which can place significant stress on bone health. Hence, this rather contradictory result usually is attributed to a rebound anabolic phenomenon (Brunk, 2009). Other possible explanations for different results might be the differences between the participants for the amount of breast-milk produced, episodes of lactation and total duration of breastfeeding.

However, inconsistencies in the results from different studies usually have been arisen from the differences in study design, variation in the number of enrolled women, the bone sites used in measurement, statistical tests used for analysis, the follow-up period in some studies and the age

of participants as very important factors related to BMD. Thus, age adjustment is essential to reveal the correlation between BMD and breastfeeding. On the other hand, many factors amongst reproductive factors may influence bone metabolism during various phases of life; thus, some discrepancies and lack of relationships may be due to masking of these factors by factors associated with BMD later in life.

This study had some limitations which may affect the inferences derived from the results and thus need to be acknowledged. The cross-sectional design was the first weakness of the study, which did not permit assessment of the temporal and thus potentially causal relations of the factors. Another limitation of the study was that dual energy X-ray absorptiometry (DXA), the gold standard for bone measurement, was not used. However, the DXA machines are not portable; so, using DXA would have entailed some inconveniences for participants and researchers. Furthermore, DXA is expensive and due to limited funding, this option was not selected. More importantly, most people prefer devices without ionizing radiation. QUS as a portable, cheap, and non-radiation diagnostic tool might provide a convenient alternative to DXA (Hans & Krieg, 2009; Knapp, 2009).

Recall bias was another potential problem in the study, because most data, including amount of calcium intake from food, physical activity level, ages at menarche and menopause and family history of osteoporosis were obtained through participants' recall. For example, as osteoporosis is a "silent disease" that only manifests itself after a fracture has occurred, family history of osteoporosis reported by the participants may have been underestimated.

Conclusion

Among reproductive characteristics investigated in the current study, total time of lactation was the only variable related to bone mineral density, after adjusting for some confounding factors. Because the number of children among most of the participating Malaysian postmenopausal women was high, reduction in the number of pregnancies and appropriate spacing of pregnancies can be recommended to retain bone mineral density later in life. Many controversies exist about the relationship between often-cited risk factors and BMD; hence, a comprehensive research study using longitudinal and multidimensional approaches is needed to evaluate the independent association of each factor with bone health. Prevention of loss of bone density may be possible via early intervention that is possible with better understanding of determinants of bone mineral density and controlling them in various phases of life, especially in postmenopausal women who are the most vulnerable group to develop osteoporosis.

Acknowledgements

We would like to thank the staff of menopause clinics in Hospital Kuala Lumpur and the National Population and Family Development Board for their valuable assistance during data collection and also we gratefully acknowledge menopausal women which without their kind cooperation this study would not have been feasible.

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Table 1: Characteristics of participants and their simple correlations with bone mineral density

	Overall sample	BUA[a]
Variables	Mean (SD)	R
Age, years	53.6 (3.6)	-0.20**
Age at menarche, years	13.4 (1.4)	-0.22**
Age at menopause, years	49.5 (2.3)	0.02
Years since menopause	4.1 (3.2)	-0.17*
Parity	5 (2)	-0.16*
Total lactation period, months	41.6 (22.3)	-0.15*
Physical activity score (total possible range: 0-10)	5.5 (1.4)	0.40***
Calcium intake, grams	451 (182)	0.58***
Body mass index, kg/m^2	24.8 (3.6)	0.43***

[a] Broadband Ultrasonography Attenuation

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

*** Correlation is significant at the 0.001 level (2-tailed).

Table 2: Comparison of factors among normal and osteoporotic postmenopausal women

Variables	Normal Mean (SD)	Osteoporosis Mean (SD)	*P*
Age (years)	53.09 (3.29)	54.50 (4.02)	0.008
Age of first period (years)	13.18 (1.24)	13.70 (1.55)	0.009
Age of last period (year)	49.54 (2.47)	49.47 (2.11)	0.839
Years since menopause (years)	3.74 (3.22)	4.63 (3.08)	0.06
Number of pregnancy	4.77 (2.05)	5.43 (1.89)	0.027
Lactation period (months)	39.07 (23.16)	46.30 (19.75)	0.028
Physical activity score (total possible range: 0-10)	5.89 (1.31)	4.73 (1.24)	<0.001
Body mass index (kg/m^2)	25.63 (3.62)	23.20 (3.02)	<0.001
Calcium intake	519.78 (171.48)	321.88 (121.04)	<0.001
Osteoporosis history(%positive)	13.2	56.1	<0.001
Ethnicity			0.282
Malay	68.4	69.4	
Chinese	12.5	8.8	
Indian	9.0	5.3	
Other	9.0	17.5	

Values are the mean ± SD except osteoporosis history and ethnicity which are percent. P value for continuous variables was obtained by Student's t-test and for categorical variables by Chi-square test.

Table 3: Stepwise regression analysis of factors independently associated with BMD

	B	SE	P
Calcium intake	0.005	0.396	<.001
Family history of 0steoporosis	1.974	-0.195	<0.001
Body Mass Index	0.241	0.188	0.001
Physical activity	0.616	0.162	0.004
Age of respondent	0.226	-0.160	0.002
Total lactation duration	0.036	-0.126	0.015

R=0.708 R^2=0.502 F=32.545 P<0.05

Figure 1. BMD by total breastfeeding period