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**Brief communication (Original)**

# Body weight, BMI, and stature have a protective effect on bone mineral density in women with postmenopausal vertebral osteoporosis, whereas greater age at menarche and years after menopause have a negative effect

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***Background:*** Osteoporosis is a metabolic bone disease with a risk factor of being female, particularly after the onset of menopause.
***Objectives:*** To evaluate the influence of age, anthropometric, and reproductive variables on spinal bone mineral density (BMD) in women with postmenopausal vertebral osteoporosis.
***Methods:*** The study was retrospective and included data from 171 patients with postmenopausal vertebral osteoporosis. We performed both simple and multiple regressions considering BMD in spine as the dependent variable. Coefficients of correlation ($r$), coefficients of determination ($r^2$), and their level of significance were calculated.
***Results:*** The associations between spinal BMD and each of the following variables were extremely significant: age at menarche ($P = 0.0003$), weight ($P < 0.0001$), stature ($P = 0.0004$), and BMI ($P < 0.0001$). The associations between spinal BMD and age ($P = 0.004$), and between spinal BMD and number of years after menopause were very significant ($P = 0.0093$). BMD was not associated with age at menopause or number of reproductive years. For multiple regressions there was an increasing trend of $r^2$ with increasing number of independent variables included in the analysis: $r^2 = 21.84\%$ (2 variables), $r^2 = 24.93\%$ (3 variables), 26.45% (4 variables), and $r^2 = 27\%$ (5 variables).
***Conclusion:*** BMD is positively associated with weight, BMI, and stature, and is negatively associated with age, time of menarche, and years after menopause. BMD is not associated with age at menopause and reproductive period.

***Keywords:*** Age, bone mineral density, menarche, menopause, osteoporosis, stature, weight

Osteoporosis is characterized by a decrease of bone mass, but without detectable changes in the mineralized and nonmineralized matrix ratio. Microarchitectural deterioration of the bone tissue occurs in osteoporosis, followed by enhanced bone fragility and increased risk of fracture [1]. It is estimated that in USA and European Union around 30% of women who have reached menopause are suffering from osteoporosis [2]. In Asia, the overall prevalence of osteoporosis is higher than in the western countries [3]. In Taiwan, there is a 10.08% prevalence of osteoporosis in the lumbar vertebrae [4]. The age-specific prevalence of osteoporosis among Thai women is more than 50% after 70 years old [5]. Postmenopausal Malaysian women have a prevalence of osteoporosis of 42.1% [6]. Of crucial importance for the development of postmenopausal osteoporosis, is the decline of ovarian function, with decreased production of estrogens and increased FSH level. The loss of bone material caused by the estrogen deficiency constitutes the outcome of converging multiple pathways and a range of cytokines, which act on osteoclastogenesis and osteoblastogenesis [7]. Exposure to estrogens occurs throughout life, including the prenatal period, undergoing changes because of events such as the occurrence of menarche and the onset of menopause. The cumulative exposure to estrogens throughout life has a protective effect

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against osteoporosis [8]. Menarche occurring after the age of 14 is associated with an increased incidence of osteoporosis [9]. The age at menopause onset is a risk factor for long-term morbidity and mortality, late menopause being a risk factor for endometrial and breast cancer, and early menopause being a risk factor for osteoporosis and cardiovascular diseases; a risk that occurs because of estrogen deficiency [10]. In Chinese women with postmenopausal osteoporosis, the onset of menopause before 46 years old is associated with an increased risk of osteoporosis [11]. Although the estrogen hormonal decline is the main driver of bone metabolism imbalance in osteoporosis, it explains only a small proportion of the interindividual variations of bone mineral density (BMD) and bone loss [12]. Although all women reach menopause and have subsequent estrogen deficiency, only a third suffer of osteoporosis [7]. Osteoporosis falls under the category of multifactorial conditions, where genetic and nongenetic factors interact, each of them having a contribution to the increased risk of developing the disease [13]. Anthropometric and reproductive variables represent risk factors of greater importance for osteoporosis than the risk factors related to life style [14]. A low body mass index (BMI) is a risk factor for bone loss [15], and being overweight has a protective effect against osteoporosis [16]. The outcomes of another study showed that women with postmenopausal osteoporosis do not have a higher BMI than the values recommended by the National Institutes of Health [17]. The same authors determined that patients with osteoporosis did not have a lower stature than healthy subjects before the onset of disease.

The aim of this study was to assess the influence of age, time of menarche, age at menopause, number of reproductive years (reproductive period), number of years after menopause, body weight, stature, and BMI on spinal BMD in women with postmenopausal vertebral osteoporosis.

## Materials and methods

The study was a retrospective examination of data from the medical records of 171 Caucasian patients with postmenopausal vertebral osteoporosis admitted to the Endocrinology Section of the Clinical County Hospital at Timisoara, Romania, between 2003 and 2007. Osteodensitometry of the lumbar spine was previously determined using a QDR Delphi W Osteodensitometer (Hologic, Bedford, MA, USA). A diagnosis of osteoporosis was confirmed when the value of bone mineral density was equal or lower than 2.5 standard deviations than the mean value for a young adult [1]. Data from patients who underwent treatment known to influence bone metabolism (corticotherapy for more than 3 months) and cases of complex etiopathogeny were excluded. Menopause was defined as after a 12 consecutive month period of amenorrhea. Anthropometric data included stature, weight, and BMI. BMI was calculated based on the formula: weight (kg)/height squared ($m^2$).

To determine the relationship between spinal BMD as dependent variable, and the independent (explanatory) variables comprising patient's age, age at menarche, age at menopause, reproductive period (years between menarche occurrence and menopause onset), number of years after menopause, stature, weight, and BMI, several regressions, both simple and multiple, were performed. In cases of multiple regressions, the number of independent variables was gradually increased in various associations to determine how spinal BMD is influenced by more factors acting simultaneously.

Descriptive statistical parameters were calculated for the analyzed variables. Pearson correlation coefficients ($r$) and the coefficients of determination ($r^2$) were determined. The interpretation of the correlation coefficients was as follows: $r > 0.7$ = strong correlation, $r = 0.4–0.7$ moderate correlation, $r < 0.4$ = weak correlation [18]. For statistical tests, the following interpretation of two-tail $P$ values was used: $P < 0.05$ = significant, $P < 0.01$ = very significant, $P < 0.001$ = extremely significant, $P > 0.05$ = not significant. Statistical analysis and graphical representation were performed using GraphPad, InStat, and Excel software. The retrospective study of medical records was approved by our local institutional Ethics Committee (8046/2012), and the study was conducted following the principles of the Helsinki Declaration and good clinical practice.

## Results

Patient characteristics are shown in **Table 1** .

Following simple regression, we determined that there was no association between spinal BMD and the age at menopause, or between spinal BMD and the reproductive period (number of reproductive years). Conversely, there was a weak association between BMD of spine and each of the following factors: patient's age, age at menarche, number of

**Table 1.** Patient characteristics

| Variable | Min. | Max. | Mean ± SD |
|---|---|---|---|
| Age | 33 | 70 | 57.8 ± 7.6 |
| Age at menarche (y) | 10 | 19 | 13.9 ± 1.7 |
| Age at menopause (y) | 22 | 58 | 45.3 ± 5.8 |
| Reproductive period (y) | 5 | 44 | 31.4 ± 6.0 |
| Number of years after menopause (y) | 1 | 34 | 12.5 ± 12.5 |
| Stature (m) | 1.40 | 1.75 | 1.6 ± 0.1 |
| Weight (kg) | 36 | 98 | 63.7 ± 11.5 |
| BMI (kg/m$^2$) | 14.8 | 38.4 | 25.5 ± 4.5 |
| Bone mineral density in spine (g/cm$^2$) | 0.24 | 0.77 | 0.68 ± 0.08 |

years after the menopause, stature, and BMI. There was a moderate association between spinal BMD and weight. While associations were not very strong, there were very significant associations between spinal BMD and age, and the number of years after menopause. The associations between spinal BMD and each of the following independent variables were extremely significant: age at menarche, weight, stature, and BMI (**Figure 1, Table 2**). The spinal BMD variance was best explained by weight in 18.0% cases ($r^2$ = 0.1798).

We then performed multiple regressions, gradually increasing the number of independent variables and eliminating the situations of multicollinearity. This was done to determine how those variables influence spinal BMD and to develop a mathematical equation that describes the variance of spinal BMD related to those factors.

In multiple regressions with two independent variables, the highest coefficient of determination ($r^2$ =21.84%, $P$ < 0.0001) was recorded for the situation where the number of years after menopause and body weight represented independent variables, immediately followed age and body weight as independent variables ($r^2$ = 21.77%, $P$ < 0.0001).

Analysis with three independent variables found the highest coefficient of determination ($r^2$ = 24.93%) was for the age at menarche, weight, and number of years after menopause as independent variables, closely followed by the coefficient of determination ($r^2$ = 24.76%) for chronological age, age at menarche and body weight, in both cases the results being extremely significant ($P$ < 0.0001).

When four independent variables were examined, the highest coefficient of determination was 26.45%, and the independent variables were the age at menarche, BMI, number of years after menopause, and stature. The result was extremely significant ($P$ < 0.0001).

The highest coefficient of determination ($r^2$ = 27%, $P$ < 0.0001) was recorded when age at menarche, BMI, stature, age, and number of years after menopause the were considered as independent variables. The value of $r^2$ indicates that the obtained regression equation explains the variance of BMD at spine level in a proportion of 27%:

$$\mathbf{BMD = 0.1964 - 0.001128*X_1 - 0.008426*X_2 - 0.001149*X_3 + 0.3355*X_4 + 0.005931*X_5}$$

Where: $X_1$ = age, $X_2$ = age at menarche, $X_3$ = years after menopause, $X_4$ = stature, $X_5$ = BMI

## Discussion

Simple regressions indicate that spinal BMD did not associate with the reproductive period or the age at menopause. By contrast, a significant correlation between the number of reproductive years and BMD of the lumbar spine was found in an earlier study, but this showed no correlation between the number of reproductive years or age at menopause and BMD of femoral and radial regions [19].

BMD of the spine was associated with age, age at menarche, number of years after menopause, weight, stature and BMI. There is a positive correlation between BMD and stature in Japanese women [20].

Age at menarche and number of years after menopause as independent variables, show negative correlation coefficients, which indicates a reversed relationship between each of these factors and spinal BMD. This underlines that, with age and the increasing

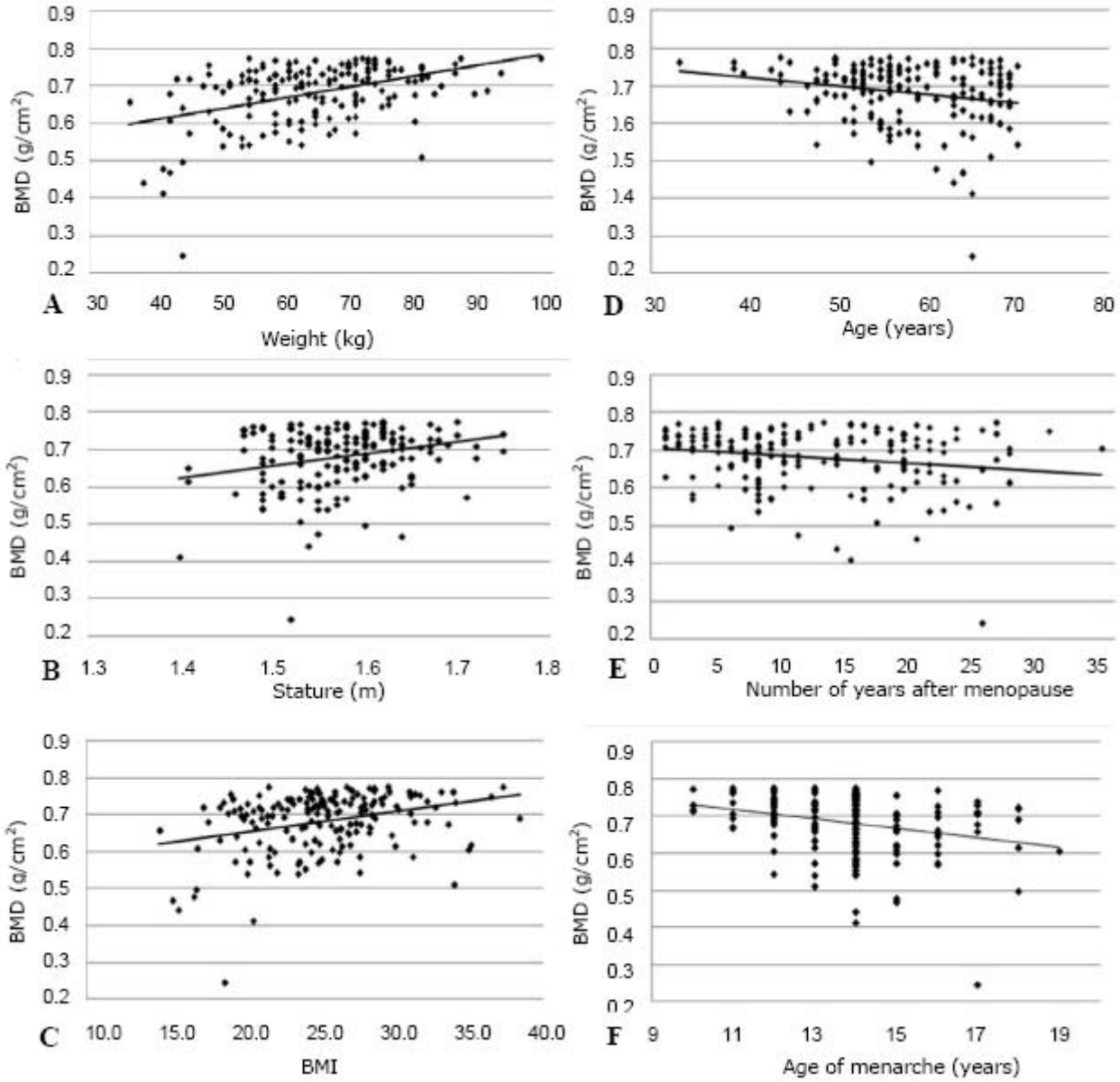


**Figure 1.** **A.** Correlation between spinal BMD and weight. **B.** Correlation between spinal BMD and stature. **C.** Correlation between spinal BMD and BMI. **D.** Correlation between spinal BMD and age. **E.** Correlation between spinal BMD and years after menopause. **F.** Correlation between spinal BMD and age at menarche.

**Table 2.** Correlation coefficient (*r*) and significance of simple linear regression between bone mineral density (BMD) in spine and age, anthropometric, and reproductive factors.

| Independent variable | *r* | *P* |
|---|---|---|
| Age | –0.22 | 0.004** |
| Age at menarche | –0.27 | 0.0003*** |
| Age at menopause | –0.02 | 0.715 |
| Reproductive period | 0.05 | 0.506 |
| Number of years after menopause | –0.19 | 0.0093** |
| Weight | 0.42 | <0.0001*** |
| Body mass index | 0.31 | <0.0001*** |
| Stature | 0.26 | 0.0004*** |

**$P < 0.01$ = very significant, ***$P < 0.001$ = extremely significant, $P > 0.05$ = not significant. Reproductive period is number of reproductive years between menarche and menopause.

number of years after menopause, there is a decrease in BMD, and that, as the age of occurrence of menarche is higher, the BMD is less. Our results are similar to those obtained in other studies showing a negative correlation between BMD and age [21], and between BMD and menopausal status [20]. For simple regressions using body weight and BMI as independent variables, the correlation coefficients were positive, indicating that an increase in weight, and BMI, leads to an increase in spinal BMD. This finding is consistent with other studies that have shown a positive association between body weight and BMD in women after menopause [22], between BMI and BMD, and between weight and BMD in men [16], and between BMI and BMD regardless of age, sex, or race [23].

The most extremely significant correlation that we have obtained from simple regressions was between spinal BMD and weight, followed by a correlation between spinal BMD and BMI, and between spinal BMD and the age at menarche. These findings are in accordance with another finding of a higher correlation between weight and BMD in the lumbar spine, than between BMI and lumbar BMD [24]. In another study, weight, BMI, and age were found to have the strongest correlation with BMD, both at the lumbar spine and hip level [25]. The enhancement of mechanical load by a larger body mass, providing an osteogenetic stimulus, can explain the association between weight and BMD that we have found. Moreover, fat reserves provide a place for aromatization of androgen hormones into estrogens [26]. After menopause there is an increased conversion of estrogen from adrenal precursors in adipose tissue [27].

The plurifactorial influences on osteoporosis explain, in part, the relatively small correlations between spinal BMD and single independent variables. Performing multiple regressions is important because it is possible to determine the extent to which several variables considered together account for a decrease of spinal BMD. The resulting equation more closely models the real situation in which more factors can act simultaneously, and has a better predictive value.

Comparing the coefficients of determination obtained from multiple regressions with different numbers of independent variables, we observed, as expected, that with an increase in the number of independent variables included in the analysis, the coefficients of determination tended to increase and were extremely significant in all cases. The independent variables, which in association best explained the variance of spinal BMD, were age, age at menarche, number of years after menopause, BMI, and stature. Our finding highlight the plurifactorial influences on the disease, the development of which implies several etiopathogenic factors. Consequently, as more such factors are included in the analysis, the explanation of spinal BMD variance improves. Identifying the variables that influence BMD is important because they may help in assessing the risk of osteoporosis and subsequent fractures.

## Conclusions

Weight, BMI, and stature have a protective effect on spinal BMD, while increasing age, greater age at menarche, and increasing number of years after menopause onset have a negative effect on spinal BMD.

Multiple regression analysis showed that spinal BMD variance is better explained by increasing the number of independent variables considered together. The variance of spinal BMD was best explained in this study by the association of age, age at menarche, number of years after the menopause, stature, and BMI.

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