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## Time since menopause, but not age, is associated with increased risk of osteoporosis

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### ABSTRACT

**Objectives:** This study aimed to determine whether estrogen deficiency is a sole risk factor for osteoporosis or is also associated with age, through indicators such as gender, age, and time since menopause.

**Methods:** A cross-sectional study was conducted evaluating 938 postmenopausal women who underwent bone mineral densitometry. We collected the following data: age, ethnic group, body mass index, smoking, and time since menopause. These data were correlated to the presence of osteoporosis, according to the *T*-score of the femur and lumbar spine.

**Results:** The prevalence of osteoporosis was 37.8%. Ethnic group ( $p=0.47$ ) and smoking habits ( $p=0.19$ ) were not associated with osteoporosis. In the group of women with osteoporosis, mean age was significantly higher ( $p<0.001$ ), mean body mass index was significantly lower ( $p<0.001$ ), and time since menopause was significantly higher ( $p<0.001$ ) than in the group of women with no osteoporosis. After multivariate analysis was performed, the only variables that remained independently associated with osteoporosis were body mass index and time since menopause. Higher body mass index was a protective factor (odds ratio = 0.80 [95% confidence interval 0.76; 0.84],  $p<0.001$ ). Time since menopause represented a risk factor for osteoporosis (odds ratio = 1.04 [1.02; 1.06],  $p<0.001$ ). When divided into categories, the risk increased after 20 years of menopause and gradually every 5 years.

**Conclusion:** Time since menopause and body mass index were the most important factors associated with osteoporosis, confirming that estrogen deficiency, and not age, is the major cause of the disease.

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Osteoporosis; risk factors; time since menopause; bone mineral density

### Introduction

Osteoporosis is a chronic disease, characterized by loss of bone mass, tissue microarray deterioration, and impairment of bone resistance<sup>1</sup>. Its clinical importance is the increased susceptibility to fractures<sup>2</sup> and the significant morbidity and mortality that arises<sup>1-3</sup>. According to the American Association of Clinical Endocrinologists, in 2010 approximately 10 million people had been diagnosed with osteoporosis wherein more than 80% were elderly women<sup>4</sup>. In the United Kingdom, osteoporosis affects approximately 3 million people<sup>5</sup>. In Brazil, prevalence of the disease ranges from 22% to 33% in women older than 40 years<sup>6-8</sup>.

Population aging over the last decades has influenced the epidemiology of diseases. The 2017 United Nations report shows that the global population aged over 60 years has doubled since 1980 and is expected to double again by 2050<sup>9</sup>. As the mean age of the world population rises, chronic diseases such as osteoporosis have a bigger impact on public health<sup>8,10</sup>.

Bone mineral density is one of the factors that influence bone resistance and is associated with the bone mass peak

achieved in youth and on subsequent bone losses<sup>2</sup>. The bone mass peak is affected by several factors as gender, genetic predisposition, body mass index (BMI), dietary habits, smoking, alcohol abuse, medications, physical activity, and chronic diseases<sup>5,10-12</sup>. In women, the peak bone mass is achieved by the third decade of life, after which a process of slow bone loss begins<sup>2</sup>.

Bone homeostasis is controlled by a subtle balance between bone formation and bone absorption, and estrogen is one of the main regulators. In youth, normal estrogen serum levels are responsible for osteoblastogenesis and apoptosis of osteoclasts increasing bone formation<sup>13</sup>. After menopause, bone absorption is accelerated due to estrogen deficiency<sup>14</sup>.

Several studies have searched for the mechanism of estrogen deficiency-induced bone loss. The aging process is accompanied by a proinflammatory state, in which oxidative stress and cytokine production are increased. The lack of estrogen plays a major role in promoting the inflammatory microenvironment of the osteoporotic bone, through increased T-cell activity and production of cytokines<sup>15</sup>. Tumor necrosis factor alpha (TNF- $\alpha$ ) participates in this process,

inhibiting osteogenic differentiation of mesenchymal cells<sup>16</sup>; enhanced receptor activator of nuclear factor kappa-B ligand (RANKL) expression stimulates differentiation of bone marrow macrophages into osteoclasts; and TNF- $\alpha$ , interleukin (IL)-1 $\beta$ , IL-6, and IL-17 induce osteoclastogenesis through RANKL stimulation<sup>15</sup>.

The aim of this study was to investigate whether estrogen deficiency is a sole risk factor for osteoporosis or is also associated with age, through indicators such as gender, age, and time since menopause.

## Materials and methods

We conducted a cross-sectional study at Hospital das Clínicas of the Universidade Federal de Minas Gerais, evaluating 938 women who underwent bone mineral densitometry (BMD) between November 2014 and April 2015. All participants came from the community, were referred from several different centers, were included in a government program for elderly health care, and were referred to this program due to risk factors or suspected ongoing disease. The study was approved by the Research Ethics Committee (COEP/UFMG – No. 576.150). Data were obtained from patients' medical records, including age, ethnic group, BMI, smoking, and time since menopause. These data were correlated to the presence or absence of osteoporosis, according to *T*-scores of the femur and lumbar spine at BMD. Patients were diagnosed with osteoporosis when *T*-scores were less than or equal to  $-2.5$  standard deviations<sup>17</sup>.

### Bone mineral densitometry

All BMD was performed by the same examiner using the same equipment (Discovery W; Hologic Inc., Marlborough, MA, USA). The effective coefficient of variation is 0.5%. All X-ray incidences were obtained from the hip and lumbar spine, with patients in a supine position.

### Statistical analysis

For this a convenience sample, we used analysis of variance for comparison between means, the Wilcoxon test for medians, and the chi-square test for comparison of proportions. Multinomial logistic regression was applied to calculate the odds ratio (OR). We performed multivariate analysis to exclude potential confounders and define independent risk

factors, using the variables that remained significant ( $p < 0.05$ ) in the Wald test. The likelihood of association between osteoporosis and the study variables was calculated using the OR adjusted for variables that remained significant.

Significant variables ( $p < 0.05$ ) were submitted to multivariate analysis to exclude potential confounders and define independent risk factors. Risk of osteoporosis was calculated using the OR adjusted for variables that remained significant.

## Results

The mean age was  $75.5 \pm 7.2$  years (range 60–103 years) and the prevalence of osteoporosis was 37.8%. When we compared the results of women with and without osteoporosis, we observed no differences concerning ethnic group ( $p = 0.47$ ) and smoking habits ( $p = 0.19$ ). Only 18% of all women reported being smokers and none of them used hormone therapy previously. In the group of women with osteoporosis, mean age was significantly higher ( $p < 0.001$ ), mean BMI was significantly lower ( $p < 0.001$ ), and time since menopause was significantly higher ( $p < 0.001$ ) than that observed in the group of women with no osteoporosis (Table 1).

A multivariate analysis was performed to exclude confounding factors. In this model, ethnic group, age, and smoking were not associated with osteoporosis. The only variables that remained independently associated with osteoporosis were BMI and time since menopause. Higher BMI was a protective factor (OR = 0.80,  $p < 0.001$ ). Overweight (BMI = 25–30) patients presented a 64% lower risk of osteoporosis, while obese (BMI > 30) patients had a 92% lower risk. Time since menopause represented a risk factor for osteoporosis (OR = 1.04,  $p < 0.001$ ). When divided into categories, the risk increased after 20 years of menopause and gradually every 5 years (Table 2).

## Discussion

This study showed that BMI and time since menopause, but not age, were associated with osteoporosis. Most of the patients were elderly women, overweight, Hispanic, and with a long time since menopause. As none of the patients reported the use of hormone therapy previously, exogenous estrogen did not interfere with the results. However, as this was a retrospective analysis, some women might have used hormone therapy without reporting, thus creating a recall bias.

**Table 1.** Clinical characteristics of women with osteoporosis and with no osteoporosis.

Variable	Osteoporosis (N = 355)	No osteoporosis (N = 583)	p-Value
Ethnic group <sup>a</sup>			
White	26 (41.9%)	36 (58.1%)	0.47
Black	14 (30.4%)	32 (69.6%)	
Hispanic	315 (38%)	515 (62%)	
Age (years) <sup>b</sup>	77.3 $\pm$ 6.9 (60–96)	74.4 $\pm$ 7.1 (60–103)	<0.001
Body mass index (kg/m <sup>2</sup> ) <sup>b</sup>	24.3 $\pm$ 4.2 (13.5–39)	29.1 $\pm$ 5.3 (15.9–49.7)	<0.001
Time since menopause (years) <sup>b</sup>	29.9 $\pm$ 9.5 (1–63)	26.1 $\pm$ 9.0 (5–50)	<0.001

<sup>a</sup>Data expressed in absolute numbers.

<sup>b</sup>Results expressed as mean  $\pm$  standard deviation (range).

**Table 2.** Impact of clinical characteristics on the risk of osteoporosis in women.

Type of independent variable	Variable	Risk of osteoporosis, OR (95% CI)	p-Value
Model 1 – continuous variables	BMI	0.80 (0.76; 0.84)	<0.001
	Time since menopause (years)	1.04 (1.02; 1.06)	<0.001
Model 2 – categoric variables	BMI		
	<25	1.00	
	25–30	0.36 (0.23; 0.55)	<0.001
	>30	0.08 (0.05; 0.15)	<0.001
	Time since menopause (years)		
	<20	1.00	
	20–24	1.88 (0.89; 3.99)	0.099
	25–29	2.14 (1.12; 4.09)	0.022
30–34	2.34 (1.17; 4.68)	0.016	
>35	3.28 (1.81; 5.94)	<0.001	

Multivariate analysis for *p*-value and multinomial logistic regression to calculate the OR. BMI, body mass index; CI, confidence interval; OR, odds ratio.

We found no association between osteoporosis and ethnic group. This result is in agreement with another Brazilian study<sup>18</sup>, but different to those described by others from Europe and the USA<sup>19,20</sup>. This finding might be explained by the fact that the majority of the patients were Hispanic, with few Caucasians, who are usually depicted as the most affected population. Our results also demonstrated lack of association between osteoporosis and current smoking, and are not in agreement with other studies<sup>21,22</sup>. This difference can be explained by the low incidence of smokers observed in our study group.

As previously described, we also observed that overweight and obesity had a protective effect against osteoporosis<sup>23,24</sup>. This association can be explained by the conversion of androgens to estrogens in adipose tissue, which is the major source of estrogens in postmenopausal women, thus collaborating for the maintenance of bone mass<sup>25</sup>.

Time since menopause was identified as an independent risk factor for osteoporosis. The stratification according to age categories demonstrated that women with more than 20 years since menopause have an increased risk for osteoporosis. Moreover, we describe an increase in the risk every 5 years since the onset of menopause. To our knowledge, this is the first study that describes this association. Yoldemir *et al.*<sup>26</sup> analyzed 27 women with osteoporosis and concluded that time since menopause was not associated with osteoporosis. This difference can be explained by the small number of patients with osteoporosis that they analyzed. Silva *et al.*<sup>25</sup> also concluded that women with more than 5 years since menopause had higher prevalence of osteoporosis after studying 99 patients; however, they did not evaluate the effect after time periods. Although time since menopause might not be easy to obtain, due to a possible lack of memory, in our study the data (last menstrual period) were obtained from the patient's charts and not from a questionnaire during the BMD examination – therefore, possible patient's lack of memory was not considered a problem or bias.

Shorter periods of exposure to estrogen were used to explain low bone mineral density and higher risk of fractures in a study where late onset of menarche was associated with osteoporosis<sup>13</sup>. Estrogen exposure was also assessed through age of menopause in studies that showed positive association between early menopause and osteoporosis<sup>23,27</sup>,

including genetic polymorphisms that are common to both<sup>28</sup>. Sioka *et al.*<sup>29</sup> described a decreased bone mineral density in female patients with less than 30 years of fertility (time between age at menarche and age at menopause), concluding indirectly that shorter exposure to estrogen contributes to the risk of osteoporosis.

Although the aging process is commonly related to osteoporosis<sup>10,30,31</sup>, in our study age was not an independent risk factor. This difference can be explained by the fact that the others did not evaluate time since menopause as a risk factor. The fact that time since menopause, and not age itself, was an independent risk factor for osteoporosis suggests that the role of hypoestrogenism in the development of osteoporosis in women is more important than aging. Also, time since menopause could be used as a marker of estrogen deficiency.

In conclusion, our study demonstrated that, for the sample analyzed, time since menopause and BMI were the most important factors associated with osteoporosis, confirming that estrogen deficiency, and not age, is the major cause of the disease.

### Author contributions

All authors participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting/revising the manuscript, and approving the final version and agreed that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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