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Risk factors for osteoporotic fractures and low bone density in pre and postmenopausal women

Fatores de risco para fratura por osteoporose e baixa densidade óssea em mulheres na pré e pós-menopausa

ABSTRACT

OBJECTIVE: To estimate the prevalence and analyze risk factors associated to osteoporosis and low-trauma fracture in women.

METHODS: Cross-sectional study including a total of 4,332 women older than 40 attending primary care services in the Greater São Paulo, Southeastern Brazil, between 2004 and 2007. Anthropometrical and gynecological data and information about lifestyle habits, previous fracture, medical history, food intake and physical activity were obtained through individual quantitative interviews. Low-trauma fracture was defined as that resulting from a fall from standing height or less in individuals 50 years or older. Multiple logistic regression models were designed having osteoporotic fracture and bone mineral density (BMD) as the dependent variables and all other parameters as the independent ones. The significance level was set at $p < 0.05$.

RESULTS: The prevalence of osteoporosis and osteoporotic fractures was 33% and 11.5%, respectively. The main risk factors associated with low bone mass were age (OR=1.07; 95% CI: 1.06;1.08), time since menopause (OR=2.16; 95% CI: 1.49;3.14), previous fracture (OR=2.62; 95% CI: 2.08;3.29) and current smoking (OR=1.45; 95% CI: 1.13;1.85). BMI (OR=0.88; 95% CI: 0.86;0.89), regular physical activity (OR=0.78; 95% CI: 0.65;0.94) and hormone replacement therapy (OR=0.43; 95% CI: 0.33;0.56) had a protective effect on bone mass. Risk factors significantly associated with osteoporotic fractures were age (OR=1.05; 95% CI: 1.04;1.06), time since menopause (OR=4.12; 95% CI: 1.79;9.48), familial history of hip fracture (OR=3.59; 95% CI: 2.88;4.47) and low BMD (OR=2.28; 95% CI: 1.85;2.82).

CONCLUSIONS: Advanced age, menopause, low-trauma fracture and current smoking are major risk factors associated with low BMD and osteoporotic fracture. The clinical use of these parameters to identify women at higher risk for fractures might be a reasonable strategy to improve the management of osteoporosis.

DESCRIPTORS: Fractures, Bone. Bone Density. Osteoporosis, Postmenopausal, epidemiology. Osteoporosis, epidemiology. Risk Factors. Cross-Sectional Studies. Women's Health.

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RESUMO

OBJETIVO: Estimar a prevalência e analisar os fatores de risco associados com osteoporose e fratura por baixo impacto entre mulheres.

MÉTODOS: Estudo transversal realizado com 4.332 mulheres acima de 40 anos de idade provenientes de atendimento primário de saúde na área metropolitana da Grande São Paulo, SP, entre 2004 e 2007. Dados antropométricos e ginecológicos e relativos a hábitos de vida, fratura prévia, antecedentes pessoais, ingestão alimentar e atividade física foram avaliados por meio de entrevista individual e quantitativa. Fratura por baixo impacto foi definida como decorrente de queda da própria altura ou menos em indivíduos com mais de 50 anos de idade. Modelos de regressão multivariada e logística analisaram, respectivamente, a densidade óssea e a fratura por osteoporose como variáveis dependentes e todas as outras como independentes. O nível de significância estatística estabelecido foi $p < 0,05$.

RESULTADOS: A prevalência de osteoporose e de fraturas por fragilidade óssea foi de 33% e 11,5%, respectivamente. Os principais fatores de risco associados com baixa densidade óssea foram idade (OR = 1,07; IC 95%: 1,06;1,08), menopausa (OR = 2,16; IC 95%: 1,49;3,14), fratura prévia (OR = 2,62; IC 95%: 2,08;3,29) e tabagismo atual (OR = 1,45; IC 95%: 1,13;1,85). Por outro lado, elevado IMC (OR = 0,88; IC 95%: 0,86;0,89), atividade física regular (OR = 0,78; IC 95%: 0,65;0,94) e terapia hormonal atual (OR = 0,43; IC 95%: 0,33;0,56) desempenharam papel protetor. Os fatores de risco significativamente relacionados com fratura por osteoporose foram idade (OR = 1,05; IC 95%: 1,04;1,06), menopausa (OR = 4,12; IC 95%: 1,79;9,48), história familiar de fratura de quadril (OR = 3,59; IC 95%: 2,88;4,47) e baixa densidade óssea (OR = 2,28; IC 95%: 1,85;2,82).

CONCLUSÕES: Idade avançada, menopausa, fratura prévia por baixo impacto e tabagismo atual são os principais fatores de risco associados com baixa densidade óssea, a qual se associa com as fraturas por fragilidade óssea. O uso clínico desses parâmetros para identificar mulheres de maior risco para fraturas pode ser uma estratégia interessante para melhorar a abordagem da osteoporose.

DESCRIPTORIOS: Fraturas Ósseas. Densidade Óssea. Osteoporose Pós-Menopausa, epidemiologia. Osteoporose, epidemiologia. Fatores de Risco. Estudos Transversais. Saúde da Mulher.

INTRODUCTION

Osteoporotic fracture is an important public health problem worldwide. However, its impact varies considerably between countries, especially due to population differences and different use of public health resources.^{16,21} The prevalence of osteoporotic fracture increases with age and is associated with a deteriorated quality of life as well as greater mortality rate.¹¹ Studies carried out in Brazil have found that the annual (age-adjusted) incidence of hip fracture ranges between 5.59 to 13/10,000 inhabitants and 12.4 to 27.7/10,000 inhabitants in men and women, respectively.^{5,29,15} Clark et al⁶ found a prevalence of 11.18 morphometric vertebral fractures in a population sample of 1,922 postmenopausal women from five countries of Latin America,

of whom 415 patients (randomly stratified according to age) lived in the city of Vitória, Southeastern Brazil (95% CI: 9.23;13.4).

A number of strategies are available for the prevention and treatment of osteoporosis, offering an effective reduction in both vertebral and non-vertebral fractures. However, the best strategy for stratifying individuals at greater risk and selecting those that would most benefit from therapy or prevention remains a challenge for physicians.¹ In routine medical practice, it is used a combination of clinical risk factors^{2,4,8,30} together with the determination of bone mineral density (BMD).^{19,20} Based on this approach, Kanis et al¹³ have recently

proposed the use of FRAX™ as a useful, objective tool for assessing the risk of fracture in the next ten years, with direct implications for decision making and treatment costs. However, calculating the absolute risk of fracture depends on the population studied and this tool has not yet been approved for use in Brazil, as there is no reference database.²⁵ Therefore, further representative epidemiological data on the Brazilian population are needed.

The São Paulo Osteoporosis Study (SAPOS) is one of the most important studies on risk factors for low-trauma fracture and osteoporosis ever carried out in Brazil. It studied a large sample of women, including premenopause and postmenopause, from different areas of the Greater São Paulo attending primary care services rather than focusing on those receiving tertiary care or targeting high-risk populations.

The objective of the present study was to estimate the prevalence of and analyze factors associated to osteoporosis and low-trauma fracture among women.

METHODS

A cross-sectional study was conducted. More than 7,000 women over 40 years of age were recruited from primary care units in the metropolitan area of São Paulo, Southeastern Brazil, from January 2004 to December 2007. Almost 62% of the initial sample (N = 4,332) met the eligibility criteria and were included in the study. A little more than half (55%) were recruited from a primary care unit in the city of São Caetano do Sul and the rest (45%) were recruited from the metropolitan area of São Paulo.

All participants answered a questionnaire. The study questionnaire was developed based on a literature review on different clinical risk factors related to low BMD and fractures,^{2,4,8,30} which included details about demographic and anthropometrical data; gynecological and hormonal information; personal medical history based on the International Classification of Diseases (10th edition); previous fractures; family history of femur fracture after 50 years of age in first-degree relatives; and current lifestyle habits (smoking, regular physical activity in the previous 12 months and regular intake of dairy products).

Regular physical activity was defined as any physical activity performed for more than 30 min and during three or more times per week, excluding routine activities of daily living.²² Low-trauma fracture was defined as caused by a fall from one's own height or lower after 50 years of age.²⁴ The categorization of daily intake of dairy products was based on a frequency distribution of 200 mL (no serving, up to three servings, and three servings or more).²² The use of calcium supplements and vitamin D was also recorded.

Only individuals with cancer or cognitive impairment, such as neurological conditions or senile dementia, who were not able to provide adequate responses, were excluded from the study. The use of concomitant medications, including those related to mineral and bone metabolism, such as glucocorticosteroids, bisphosphonates, diuretics, selective estrogen receptor modulators and anticonvulsants, was not an exclusion criterion and these individuals were stratified and included in the statistical analysis.

The interview was performed by health professionals at primary care units after receiving specific training from a rheumatologist with ample experience with this type of methodology.

Spine and femur bone densitometry (DPX NT, GE-Lunar) was performed in all women, using the acquisition and analysis protocol proposed by the International Society of Clinical Densitometry, recently validated by the Brazilian Society of Clinical Densitometry.³ The reference database and osteoporosis classification criteria used were from the Third National Health and Nutrition Examination Survey¹⁷ and World Health Organization,¹² respectively.

Descriptive analysis was carried out and data were expressed as percents (%), means and standard deviations. The chi-square test was used to estimate the individual effect of each variable studied, with BMD as the dependent variable. In a complementary analysis, low-trauma fracture after 50 years of age was also used as a dependent variable in the logistic regression model. The routine procedure was adopted for the multivariate regression for which BMD was considered as dependent variable in each final model. All p-values lower than 0.05 were considered statistically significant. Statistical analysis was performed by the SPSS, version 12.

All participants signed a written informed consent form prior to their participation in the study and the Research Ethics Committee of the Universidade Federal de São Paulo/Escola Paulista de Medicina approved the protocol.

RESULTS

Table 1 displays patient age and anthropometrical data according to the presence of low-trauma fracture. Women with previous osteoporotic fracture were older and thinner than those with no history of fracture. The majority of participants were Caucasians (75.2%) and the rest was classified as non-Caucasians (24.8%), of whom 17.1% were mixed, 6.9% were of African descent and 0.8% was of Asian descent. The vast majority of the sample (90.9%) was in menopause, but only 444 women (10.2%) used regular hormonal replacement therapy in the 12 months prior to the interview, with

Table 1. Age and anthropometrical data according to the presence of low-trauma fracture. Greater São Paulo, Southeastern Brazil, 2004–2007.

| Variable | No fracture N = 3835 % (SD) | Previous fracture N = 497 % (SD) | p |
|--------------------------------------|-----------------------------------|--|---------|
| Age (years) | 59.4 (9.9) | 65.5 (10.0) | < 0.001 |
| Weight (kg) | 66.4 (13.3) | 64.5 (11.6) | 0.013 |
| Height (m) | 1.54 (0.06) | 1.53 (0.06) | < 0.001 |
| Body mass index (kg/m ²) | 27.8 (5.2) | 27.5 (4.9) | 0.521 |

an average duration of nearly four years. Hysterectomy and oophorectomy prior to menopause were reported in 18.3% and 10.4% of the women studied, respectively.

Regular physical activity and current smoking habits were reported in 27.3% and 8.7% of the sample, respectively. Current use of calcium supplements was reported in 618 women (14.3%), with an average duration of a little more than two years. Current regular intake of dairy products was reported in 78%; 63.9% of whom reported low daily intake (up to two servings – equivalent to 500 mg of calcium) and only 14.1% reported adequate daily intake (more than three servings – more than 800 mg of calcium).

Associated diseases were reported in 2,382 women (55%), whereas 45% reported no health conditions. Diseases of the circulatory system were reported in 1,586 women (66.6%), of which arterial hypertension was the most frequent (63.4%). A total of 963 women (40.4%) reported having musculoskeletal-joint disease, such as fibromyalgia (14.6%), osteoarthritis (12.2%) and osteoporosis (10.3%). A total of 876 women (36.8%) reported endocrine, nutritional and metabolic diseases, the most prevalent of which were dyslipidemia (13.1%), diabetes mellitus (12.5%) and thyroid diseases (9.2%). Digestive tract conditions were reported in 54.6% of the sample, mostly dyspeptic symptoms. However, chronic diarrhea was only reported in 5% of the sample.

Nearly 90% of the sample was using some concomitant medication. Regular use of anti-hypertensive medication was reported in over 50% of the women, especially angiotensin-converting enzyme inhibitors (39.3%), thiazide diuretics (29.7%), beta-blockers (13.2%)

and calcium channel blockers (3.4%). The use of oral bisphosphonates and glucocorticosteroids was reported in 8% and 4% of the women, respectively. Statins and thyroid hormone replacement therapy were reported in 11.2% and 11.5% of the women, respectively. Approximately 10% of the women chronically used non-steroid anti-inflammatory agents (9.4%) and oral anti-diabetic agents (9.7%).

A total of 497 women (11.5%) reported a history of low-trauma fracture, with a mean age of 65.5 (SD=10) years at the time of the event. Vertebral fractures were reported in 44 women (6%) and non-vertebral fractures were reported in 616 (86%), which included the humerus, distal forearm (Colles), metacarpal, ribs and hip. Femur fracture was reported in 55 women (8%). Family history of hip fracture after 50 years of age in first-degree relatives was reported in 15% of the women, especially those with a previous fracture ($p < 0.001$).

Just over 33% of the postmenopausal women had osteoporosis in the lumbar spine or femur, based on World Health Organization criteria¹⁷ (Table 2). Radiographic analysis revealed structural abnormalities in the lumbar spine in 8% of the tests. In these cases, the affected vertebra was excluded from the analysis. Table 3 displays the characteristics of bone mass measurements according with the presence or absence of fracture. Women with a history of low-trauma fractures had significantly lower BMD in all the skeletal sites studied.

The final multivariate regression model showed that the main risk factors significantly associated with low BMD in the lumbar spine or femur were advanced age, menopause and current smoking habits. In contrast,

Table 2. Prevalence of osteopenia and osteoporosis in postmenopausal women according to bone mineral density and WHO criteria. Greater São Paulo, Southeastern Brazil, 2004–2007.

| Variable | Normal n (%) | Osteopenia n (%) | Osteoporosis n (%) |
|--------------|-----------------|---------------------|-----------------------|
| Lumbar spine | 1579 (36.4) | 1674 (38.6) | 1079 (24.9) |
| Femoral neck | 1446 (33.4) | 2001 (46.2) | 885 (20.4) |
| Trochanter | 2014 (46.5) | 1646 (38.0) | 672 (15.5) |
| Total hip | 2491 (57.5) | 1462 (33.7) | 379 (8.7) |

Table 3. Descriptive analysis of bone mass measurements (spine and femur bone mineral density) according to the presence of low-trauma fracture. Greater São Paulo, Southeastern Brazil, 2004–2007.

| Variable | No fracture N = 3835 | Previous fracture N = 497 | p ^a |
|--|-------------------------|------------------------------|----------------|
| Lumbar spine (g/cm ²) (SD) | 1.018 (0.18) | 0.913 (0.15) | < 0.001 |
| Femur (g/cm ²) (SD) | | | |
| Neck | 0.865 (0.15) | 0.775 (0.12) | < 0.001 |
| Trochanter | 0.743 (0.13) | 0.668 (0.13) | < 0.001 |
| Total hip | 0.925 (0.18) | 0.827 (0.14) | < 0.001 |

^a Student's t-test

higher body mass index (BMI), regular intake of dairy products and regular physical activity in the previous year and hormone therapy played a protective role against fractures (Table 4). After adjustments, ethnic background, family history of hip fracture and concomitant medications and diseases were not significantly associated with low bone mass.

In the final logistic regression model for low-trauma fracture, the main clinical risk factors were menopause, advanced age and family history of hip fracture. Regular physical activity in the previous year was the only factor with a significant association to lower risk of fracture (Table 5). The model was adjusted for ethnic background, BMI, hormone therapy, current smoking, regular intake of dairy products intake and concomitant medications and diseases.

DISCUSSION

The present study showed high prevalence of osteoporosis among women over 40 years of age, which is similar to findings from other studies carried out in North America^{7,30} and Europe.¹⁴ Moreover, 11.5% of the sample had a past history of fracture due to bone frailty, which is consistent with recently published data from studies of representative samples of the Brazilian population.^{6,24}

The SAPOS study also revealed that menopause, family history of hip fracture, low BMD and advanced age were the main risk factors associated to low-trauma fracture. In contrast, regular physical activity in the previous 12 months was the only factor that played a protective role against osteoporotic fracture. Likewise, menopause, advanced age and previous fracture were significantly associated with greater likelihood of having low BMD, whereas higher BMI, hormonal replacement therapy and regular physical activity in the previous year had a positive effect on BMD, which corroborates previous studies.^{4,31}

Being underweight is considered an important risk factor for low bone mass and fracture,^{2,4,28,30} especially in populations at high risk for osteoporosis. In the present study, however, no harmful effect of being

Table 4. Final multivariate regression model for low bone density. Greater São Paulo, Southeastern Brazil, 2004–2007.

| Variable | OR (95%CI) |
|--|------------------|
| Time since menopause | 2.16 (1.49;3.14) |
| Current smoking | 1.45 (1.13;1.85) |
| Age | 1.07 (1.06;1.08) |
| Regular physical activity in the previous year | 0.67 (0.57;0.79) |
| Hormone replacement therapy | 0.43 (0.33;0.56) |
| Body mass index | 0.88 (0.86;0.89) |
| Regular intake of dairy products | 0.93 (0.87;0.99) |

Table 5. Final logistic regression model for low-trauma fracture. Greater São Paulo, Southeastern Brazil, 2004–2007.

| Variable | OR (95%CI) |
|--|------------------|
| Time since menopause | 4.16 (1.81;9.56) |
| Family history of hip fracture | 3.59 (2.88;4.47) |
| Age | 1.05 (1.04;1.06) |
| Regular physical activity in the previous year | 0.79 (0.63;0.99) |

underweight was seen on the risk of osteoporotic fracture, although care was taken to investigate anthropometrical data accurately in all the subjects. This finding may be explained by the greater prevalence of overweight and obesity in the present sample, as was also recently reported in the BRAZOS study.²⁴ Similarly, other studies have been unable to demonstrate the role of body weight regarding the risk of hip fracture and low BMD.²⁶

The present study found that the majority of women had some concomitant diseases, especially related to the cardiovascular system. The statistical analysis showed no significant association between concomitant diseases and low-trauma fracture. Likewise, the use of concomitant medications was not significantly associated with greater risk of fracture or low BMD. Although hormone replacement therapy has a positive effect on BMD and reduces osteoporotic fracture risk, it may increase

the risk of cardiovascular events in older women, as suggested by the Women's Health Initiative.²⁷ Regular use of thiazide diuretics was considerably prevalent in the present sample (29.7%), but was not significantly associated to a greater risk of fracture or low BMD, as has been reported elsewhere.⁹ Moreover, although used by 4% of the participants, long-term corticosteroid therapy was also not significantly associated with low bone mass or fractures.

Although more than 30% of the sample had osteoporosis and half had a history of low-trauma fracture, only a small subsample was taking medications with beneficial action on bone tissue (10% were receiving hormone replacement therapy, 8% bisphosphonates and 14% calcium supplements, even with low dietary intake of calcium). The lack of a diagnosis following a fracture event is a major problem in many countries, including Brazil.^{10,23,24} It is highly concerning since osteoporotic fracture, especially hip fracture, is associated to higher mortality rate (23.2%) and prevalence of disability (30%).¹⁰ Furthermore, it should be stressed that the current treatment of osteoporosis can reduce the risk of vertebral (50% to 65%) as well as non-vertebral fractures (25% to 40%). Therefore, it is unacceptable that individuals with a previous event and those at a high risk of fracture be deprived of safe, effective and cost-efficient treatment for the prevention of bone loss and further events.²³

The present study has limitations that should be addressed. One of them is failure to assess other extra-skeletal conditions directly related to fractures, such as falls, visual and hearing impairment, gait velocity and balance. Furthermore, biochemical markers of bone remodeling were not measured, and radiographies of the thoracic and lumbar spines were not taken to detect fractures with little or no symptoms. Thus, the

prevalence of fractures could be higher than that found in the present study.

The results of the present study indicate that the prevalence of clinical risk factors for low BMD and fracture are similar to those reported in previous studies in Caucasian populations. Furthermore, spine and femur BMD is also similar to that from two large international cohorts: the European Vertebral Osteoporosis Study (EVOS)¹⁸ and the Latin America Vertebral Osteoporosis Study (LAVOS).⁶ However, the prevalence of fracture found in the present study is lower than that reported in populations in the United States, Europe and Asia using the FRAX™ assessment tool.¹³ The impact and importance of clinical risk factors as well as their interactions, particularly with gender, age, BMD and type of fracture, have a crucial epidemiological importance to our understanding of these population differences and to explain the different fracture risks between populations that share similar clinical risk factors and BMD. Besides, longitudinal and prospective studies should be carried out and the FRAX™ tool should be validated for use in Brazil.²⁵

Due to its high prevalence and association with mortality and disability, osteoporosis and its main consequence – fracture due to bone frailty – should be considered public health problems in Brazil. The implementation of educational actions is extremely important to prevent high prevalence of osteoporosis related to aging, such as quit smoking, alcohol consumption abuse and promotion of regular physical activities and intake of dairy products. The results of the present study should be into taken consideration while formulating public health policies for prevention and early treatment strategies for this disease and resource allocation, thereby minimizing the direct and indirect costs associated with osteoporotic fractures.

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