Risk factors of low bone mineral density in premenopausal women

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Abstract
Aims: Osteoporosis is the most common metabolic bone disease, which is defined as a decrease in bone mass. This disease is known with the change and destruction or reduction of skeletal structure and increased risk of fracture. This study was conducted to investigate the risk factors in decreasing bone density in premenopausal women.

Methods: In a descriptive cross-sectional study, 644 premenopausal women of military families who were referred to bone densitometry center of a hospital in Tehran participated in the research. Then, based on bone densitometry results the participants were divided into two groups: bone density loss (case groups) and normal bone density (control group). The information associated with risk factors of bone density loss were collected by osteoporosis Canadian standard questionnaire and was analyzed with chi square test and T-test.

Results: Amount of spinal osteoporosis was 8.9% and the rate of osteopenia in these areas was 53.4%. There was significant difference between the case and control groups among the risk factors in calcium deficiency, lactose intolerance, history of corticosteroid drugs, methotrexate, anticonvulsants, disease of rheumatoid arthritis, hyperthyroidism, thalassemia minor and lower than 58kg weight.

Conclusion: The factors such as diet and the lack of consumption of dairy products, pharmaceutical parameters including corticosteroids and Methotrexate and glandular or rheumatologic diseases are among the important and effective factors in reduction of bone density in postmenopausal women.

Keywords: Bone Density, Osteoporosis, Osteopenia, Postmenopausal Women, Risk Factors

Introduction

Osteoporosis is the most prevalent metabolic bone disease (BMD) which is defined as a decrease in bone mass (density). This disease is known with change and destruction of skeletal structure and increased risk of fracture [1].

Osteoporosis literally means bone porosity [2]. World Health Organization has defined osteoporosis as a reduction in bone density with the rate of ±2.5 less than the average peak bone density in the population. To express the ratio of one's bone density compared to the baseline level, T score criteria are used. In other words, the individual is considered osteoporotic with T score< -2.5. Osteopenia is also defined as a decreased bone density between one to ±2.5 less than the average peak bone density (-1≥T score>-2.5) in young people and those who have (T score>-1) are considered normal [2, 3, 4].

with respect to the epidemiology of osteoporosis and osteopenia, about eight million women and 2 million men are suffering from osteoporosis and the bone density of more than 18 million people is to the extent that expose them to the risk of osteoporosis in the United States, and more osteoporosis occurs with age, because bone tissue is progressively lost [1].

In addition, it is statistically estimated that approximately 30-50% of women and 15-30% of men will be affected during their life by breakages related to osteoporosis [5]. Because of this disease, about 50% of these patients lose their activity and need long-term care at home, and even in terms of annual economic estimation about 13.8 billion dollars is spent on treatment and care of osteoporotic fractures [6]. Overall, the prevalence of osteopenia in menopausal women has been reported to be about 15 to 30%, while the prevalence of osteoporosis in this group differs from 0.1 to 3.2% [7, 8, 9, 10]. For instance, the study of Larijani et al. on 365 women aged 20-69 years living in Tehran, shows that the prevalence of osteopenia and osteoporosis in the age group of 40-49 years in the lumbar spine is, respectively, 3.2 and 29% and in the femoral region is 2.2 and 15.1%, respectively [10]. This rate, in the study of Amiri et al. on 558 women aged 20-69 years old living in Bushehr, in the age group of 40-49 years, the osteoporosis and osteopenia in the lumbar spine have been respectively, 1.2 and 12.5% and in femoral region, have been 0.5
and 7.5% respectively [11]. In Thailand, the prevalence of osteoporosis was reported to be 1% in spine, and in 0.1% in the femur region among 1796 women [7]. In addition, Chris et al., in their study in the United States, have reported the prevalence of osteopenia and osteoporosis in women, 0.6 and 15% respectively [8]. Risk factors specified for osteoporosis by the National Osteoporosis Society (NOF) include "non-adjustable factors" such as personal history of fracture in adulthood, family history of fracture, Caucasian race, old age, female gender, dementia and weakness, "poor general health" such as endocrine, neurological, rheumatic, digestive, bone tissue and hereditary disease and "adjustable factors" such as smoking, estrogen deficiency, decreased testosterone in men, low weight, reduced calcium intake, vitamin D absorption deficiency due to lack of sunlight, frequent falls, low mobility and poor hygiene [4, 12, 13, 14].

Concerning the risk factors of bone density loss, most studies have reported that factors such as nutrition, lifestyle and consumption of supplemental calcium reduce the probability of fracture in elderly women by 500-1000 mg/day and vitamin D by 800 IU/day. Of course, the higher the age, the higher the need to the supplemental vitamin D will be [15]. Given that decrease in 25-hydroxy vitamin D or hypovitaminosis D with physiological, pathological and clinical manifestations of vitamin D deficiency will lead to increase in PTH secretion and bone turn-over, mild osteoporosis and osteomalacia and the increased risk of hip fracture; therefore, taking 1500 ml grams of calcium daily in shape of calcium containing foods or drug supplements is recommended for osteoporotic women [16]. A study by Sasaki et al in Japan on 243 pre-menopause women, showed a significant relationship between the mean daily dietary calcium and BMD [17]. In another study by Guthrie and colleagues in Australia on 224 women aged 46-56 years, risk factors has been reported as follows: calcium absorption lower than 800 mg/day 52%, caffeine intake higher than 360 mg/day 56%, exercising less than an hour and a half per week 29%, body mass index (BMI) under 20 5%, current cigarette use 14%, smoking history 23% and family history of fractures 25%. Also in this study, BMD has had a positive correlation with weight, BMI and calcium uptake [18]. In a study by Sa’adati et al. in Iran on 52 patients with rheumatoid arthritis that had been using corticosteroids for at least six months, the patients with BMD should be looked after [19]. In another study by Khalvat et al., on 63 Iranian women aged 45-55years, a positive relationship was found between BMI and BMD values and BMI has been posed as a predictive factor of BMD [20]. Furthermore, in the literature, in addition to adjustable risk factors of osteopenia and osteoporosis, lack of ovarian activity and menopause is posed as an influential factor of the osteoporosis high prevalence among postmenopausal individuals. Therefore, this study attempted to investigate the causes that make bone density loss prevalent among pre-menopause women. These are mainly controllable and preventable risk factors in the appearance of osteoporosis, such as poor diet, lack of physical activity, excessive alcohol and coffee consumption, smoking, the weight less than normal or weight loss of more than 10% compared to age 25 that most of them are modifiable. Since most studies have been conducted in the field of osteopenia and osteoporosis on menopausal women and considering the fact that identifying the risk factors may lead to preventing this disease and its high financial costs and disability especially after menopause, this study was conducted with the aim of investigating the risk factors affecting bone loss in premenopausal women referred to bone densitometry center of a hospital in Tehran.

**Methods**

In a descriptive cross-sectional study in 2006-2007, among postmenopausal women of military families who referred to the bone densitometry center of a hospital in Tehran, 644 individuals were selected by purposive sampling method. Women with three or more months of amenorrhea or the history of hysterectomy or oophorectomy or suspicion to pregnancy were not enrolled.

In order to collect data, first the demographic questionnaire was completed for individuals. Then densitometry was done using DXA method (Norland XR-63; USA) of femoral neck and second to fourth lumbar vertebrae and the results was determined according to the World Health Organization’s T-score scale. Based on the results of bone mass densitometry, participants were divided into two groups (with reduced bone density as osteoporosis or osteopenia) and control (with normal bone density).

The data related to risk factors for bone loss was gathered by a 38-section questionnaire of the simple osteoporosis risk estimation (SCORE), which was the Canadian osteoporosis standard and included the medical history, drug history, dietary habits and lifestyle factors. Validity and reliability of this questionnaire has been confirmed with respect to the investigation of risk factors of bone loss in various
Results

The mean age of participants was 43.07±2.02 years, their average height was 157.78±52.5 cm, their mean weight was 70.05±9.82 kg, their mean BMI was 18.28±4.78 and the mean BMD in the spinal and femoral regions were 0.85±0.12 and 1.05±0.14, respectively (Table 1). The prevalence of osteopenia and osteoporosis in the femur neck was respectively 50.2 and 8.7% and in the spinal region was 21.6 and 0.3%, respectively. The overall prevalence of osteopenia and osteoporosis in femoral neck and spinal region was 53.4% and 8.9% respectively.

<table>
<thead>
<tr>
<th>Group</th>
<th>Natural</th>
<th>Osteopenic</th>
<th>Osteoporotic</th>
<th>Total subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>37.7</td>
<td>53.4</td>
<td>8.9</td>
<td>100</td>
</tr>
<tr>
<td>Femur</td>
<td>0.98±0.09</td>
<td>0.80±0.09</td>
<td>0.65±0.04</td>
<td>0.85±0.12</td>
</tr>
<tr>
<td>Spine</td>
<td>1.14±0.12</td>
<td>1.004±0.12</td>
<td>0.89±0.11</td>
<td>1.05±0.14</td>
</tr>
</tbody>
</table>

Discussion

Osteoporosis is the most common type of metabolic bone disease that is defined as the reduced bone mass. In the studied population, too, the bone mass loss as osteopenia and osteoporosis is respectively 53.4 and 8.9%. This bone loss is 58.9% in the femur site and 21.9% in vertebrae. This finding is consistent with the results of Kouhi et al. study which was conducted on Asian women and reported the rate of osteoporosis in Chinese women as 19% and in women of other countries as 7% [25]. But it is not consistent with some other studies that the prevalence of osteopenia and osteoporosis has been reported to be 0.1-4.1% and 15-27.3% and with that of Bayat et al. on 200 postmenopausal women in Tehran that the prevalence of osteoporosis came out to be 26% and that of osteopenia 52.5% [7, 8, 9, 22].

The difference in prevalence of low BMD can be attributed to two main reasons. One reason is the difference in the research community that certainly menopause and ovarian inactivity are the main causes of osteoporosis high frequency; the second reason is that in this study samples were patients referred to densitometry by rheumatology clinic and most of them had some risk factors and this issue has been considered as a limitation in measuring the frequency of osteopenia and osteoporosis and cannot be generalized to the population, but at least justifies the necessity of individuals' screening before being obliged to refer rheumatology clinic and the necessity of early diagnosis and treatment of those who have the risk factors of low BMD.

Regarding the prevalence of risk factors of bone mass loss among studied samples, a statistically significant difference was obtained between nutritional factors including calcium intake of less than 400 mg/d and the dairy products intolerance in both of case and control groups, no statistically significant difference was observed (p<0.05; Table 2). The prevalence of other risk factors affecting the bone loss such as the history of fractures 5.1%, smoking 1.6%, weight change 3.4%, chronic inactivity 0.5%, BMI below 0.619% and weight under 58 kg was11.5% respectively. Among these factors, only between the frequency of weight under 58 kg in both groups, a significant difference was observed (p<0.001; Table 2).

Table 1- Mean and standard deviation of BMD in the studied population

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent</th>
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<th>Spine</th>
</tr>
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<td>Natural</td>
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</tr>
<tr>
<td>Osteoporotic</td>
<td>8.9</td>
<td>0.65±0.04</td>
<td>0.89±0.11</td>
</tr>
<tr>
<td>Total subjects</td>
<td>100</td>
<td>0.85±0.12</td>
<td>1.05±0.14</td>
</tr>
</tbody>
</table>

Table 2- Relative Frequency Distribution and Comparing the Factors Affecting Bone Loss (Chi Square test)

<table>
<thead>
<tr>
<th>Group Agents</th>
<th>Control (Percent)</th>
<th>Case (Percent)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium Deficiency</td>
<td>7.5</td>
<td>17.1</td>
<td>***0.03</td>
</tr>
<tr>
<td>Lactose Intolerance</td>
<td>4.2</td>
<td>9</td>
<td>*0.02</td>
</tr>
<tr>
<td>Medicinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>3.6</td>
<td>12.9</td>
<td>***0.001</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>0</td>
<td>1.2</td>
<td>***0.02</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2.6</td>
<td>6.6</td>
<td>*0.02</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>2.6</td>
<td>8.2</td>
<td>***0.01</td>
</tr>
<tr>
<td>History of Underlying Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor Thalassemia</td>
<td>4.0</td>
<td>4.3</td>
<td>**0.002</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2.0</td>
<td>5.6</td>
<td>**0.011</td>
</tr>
<tr>
<td>Other</td>
<td>Weighing Less Than 58 Kg</td>
<td>1.7</td>
<td>9.8</td>
</tr>
</tbody>
</table>

Between nutritional factors including calcium intake of less than 400 mg/d and dairy products Intolerance in both of case and control groups, no statistically significant difference was observed (p<0.05; Table 2). The prevalence of other risk factors affecting the bone loss such as the history of fractures 5.1%, smoking 1.6%, weight change 3.4%, chronic inactivity 0.5%, BMI below 0.619% and weight under 58 kg was11.5% respectively. Among these factors, only between the frequency of weight under 58 kg in both groups, a significant difference was observed (p<0.001; Table 2). Therefore it can be concluded that low calcium intake...
is the most important risk factor for reduced bone density in women and this finding is consistent with that of other studies in this field. Honkanen et al. concluded, studying 896 women of 38-57 years of age with lactose intolerance, that the calcium intake of this group (570 mg/d) was less than the control group (850 mg/d). In addition, the rate of lower limb fracture is strongly associated with lactose intolerance [30] and overall the dairy intolerance is a factor of bone mass loss in the study group that poses the necessity of appropriate training and administration of lactose free milk products or other diaries in people with lactose intolerance. Among the other findings of this study was the statistical difference between the frequency of using some pharmaceutical agents such as corticosteroids in two groups so that the difference for the femoral area came out to be \(p=0.001\) and for vertebral area came out to be \(p=0.024\). In this regard, in the study of Sa’adati et al., it has been mentioned that patients should be under care by BMD evaluation [31]. Therefore, it can be concluded that steroids are of most important pharmaceutical factors affecting bone mass loss, as it has been mentioned in this study and other studies.

Moreover, the high frequency of using methotrexate had significant difference in normal and abnormal group. Saarto et al. also have come to the conclusion that chemotherapy with methotrexate can cause accelerated bone mass loss [32]. Also, Jordan et al. have obtained the same finding in relation with tamoxifen [33]. It can be concluded that pharmaceutical agents are among the factors affecting bone mass loss in premenopausal women that shows the necessity of prescribing correct medications and post medical treatment cares. In the field of underlying diseases, the results of this study showed that the prevalence of rheumatoid arthritis disease in both groups, there is significant difference in femoral area. Lee et al., in their study on 39 women with SLE have obtained lower BMD and T score means [34]. One reason for bone mass loss in patients with rheumatoid arthritis can be the disease itself (lack of physical activity and inflammatory factors) and taking steroids; therefore, the early diagnosis of bone mass loss in patients with rheumatoid arthritis and its timely and appropriate treatment is necessary. In Sa’adati et al study, also the necessity of controlling BMD status of these patients has been recommended [31].

This study also showed that the frequency of Hyperthyroidism had significant difference in two studied groups. In other studies in this area, it has been concluded that long-term treatment with levothyroxine can cause osteoporosis [35, 36]. But Larijani, Bayat et al. have not reported a significant correlation in this field [24, 37]. What is certain, in patients with hyperthyroidism due to increased bone turn-over, bone density will decrease that necessitates early screening and more studies in this regard. Among the other results is the statistical significant difference between the frequency of minor thalassemia in the two groups (\(p=0.002\)). However, little studies have been reported in this field, but Matteo et al. have found more femoral fractures and bone complications in patients with major thalassemia [38]. Therefore, a study with larger number of minor thalassemia patients is recommended in this field. Regarding the weight under 58 kg, the results showed that the difference has been statistically significant between the two groups (\(p=0.001\)). In Adami et al study on 2727 premenopausal women in Italy, also a direct relationship between the current weight and weight at 25 years old with osteoporosis has been obtained [27]. In another study, it has been concluded that higher weight in women is a protective factor for bone density [39]. Bayat et al have reported a statistical significant difference between the osteopenia and osteoporosis prevalence and older age and lower BMI [40], that the findings of this study are quite consistent with other studies in this field. Overall, the most common risk factors for bone mass loss which were significant between two groups included "calcium deficiency", "lactose intolerance", "corticosteroid use", "taking methotrexate", "history of arthritis Rheumatoid", "hypothyroidism", "thalassemia minor" and "less than 58 kg weight" respectively, and since a high percentage of these risk-factors are eating disorders, medical complications and diseases that are modifiable by dietary modification and preventive treatments, the importance of the present study and similar complementary population-oriented studies is confirmed. Moreover, in field of other risk factors such as glandular, hematopoietic, renal and gastrointestinal factors that were not observed in this study shows the necessity of conducting studies with higher number of samples is.

Despite the promotion in dairy products’ use in Iran, necessary measures and strategies should be taken in order to produce calcium enriched dairy products and increase the subsidy access to these products. Also more comprehensive research should be conducted in the field of identifying the risk-factors in different social groups, especially women of premenopausal ages to control the osteoporosis and osteopenia modifiable factors in different geographical regions of the country with different life styles.
Conclusion

Low calcium intake, lactose intolerance, use of methotrexate and corticosteroids, hyperthyroidism, rheumatoid arthritis, minor thalassemia and weight less than 58 kg can cause metabolic bone disease, but factors such as hyperthyroidism, diabetes, hyperthyroidism and hematopoietic problems such as leukemia, lymphoma, multiple myeloma and renal factors such as kidney stone, chronic renal failure, dialysis and renal transplantation, and gastrointestinal factors including mal-absorption, inflammatory bowel disease, primary biliary cirrhosis and gastrectomy and other factors such as fracture, smoking, chronic immobility, weight change and body mass index of less than 19, although being considered as risk factors, doesn’t have any impact on incidence of metabolic bone diseases.

References

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