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## ORIGINAL PAPER

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# The Influence of Non-preventable Risk Factors on the Development of Osteoporosis in Postmenopausal Women

Radojka Bijelic<sup>1</sup>, Snjezana Milicevic<sup>2</sup>, Jagoda Balaban<sup>3</sup>

<sup>1</sup>Health Center Banja Luka, Banja Luka, Bosnia and Herzegovina

<sup>2</sup>Urology Clinic, University Clinical Center of RS, Banja Luka, Bosnia and Herzegovina

<sup>3</sup>Clinic for Dermato-Venerology, University Clinical Center of RS, Banja Luka, Bosnia and Herzegovina

**Corresponding author:**  
Ass. prof. Radojka Bijelic,  
MD, PhD. Health Center  
Banja Luka, Bosnia and  
Herzegovina. E-mail:  
[rada.bijelic@gmail.com](mailto:rada.bijelic@gmail.com).  
ORCID ID: <http://www.orcid.org/0000-0001-9148-1230>.

## ABSTRACT

**Introduction:** Scientific studies show that many genetic factors can significantly contribute to the onset of osteoporosis in women. **Aim:** The aim of our study was to determine whether non-preventable risk factors (certain genetic predisposition - positive parameters of family and personal history, i.e. family history of osteoporosis, family history of fractures, osteoporotic fractures, previous fractures, menopause duration) can affect the occurrence of osteoporosis in women in postmenopausal age. **Methods:** The study was performed as matched case and controls study. A group of cases consisted of 100 female postmenopausal women in whom by the DEXA method was newly diagnosed osteoporosis at the Clinic for Endocrinology, Diabetes and Metabolism of the University Clinical Center of Republic Srpska during 2015-2016, while the control group consisted of 100 female postmenopausal women without diagnostic signs of osteoporosis. Groups were matched by age ( $\pm 2$  years). In order to collect demographic data and data on risk factors for osteoporosis and life habits of patients, the Bone Mineral Density Questionnaire for females of the Irish Society for Osteoporosis was used. **Results:** The results of the univariate logistic regression in our study did not show that early loss of the menstrual cycle before 50 years of age was a significant factor for osteoporosis in postmenopausal women ( $p=0.421$ ,  $OR=0.966$ ,  $95\% CI=0.889-1.051$ ). The analysis of the data of a positive family history of osteoporosis as a risk factor by the model of the multivariate of logistic regression shows that the presence of osteoporosis in close relatives (usually the mother) represents a significant and independent risk factor for the development of osteoporosis ( $p=0.003$ ,  $OR=4.567$ ,  $95\% CI=1.674-12.460$ ). The results of the study show that the presence of earlier fractures in the

tested subjects is a significant independent risk factor for osteoporosis ( $p=0.015$ ,  $OR=2.464$ ,  $95\% CI=1.195-5.084$ ). **Conclusion:** The results of our study show that the presence of osteoporosis in close relatives (usually the mother) and the existence of previous fractures are significant risk factors for the occurrence of osteoporosis. The presence of these factors may be the reason for the selection of patients for further preventive or curative procedures.

**Keywords:** family history, risk factors, osteoporosis, menopause.

## 1. INTRODUCTION

Osteoporosis, Greek *osteum* – bone, *poros* – pore, „hollow bone“ is a metabolic bone disease characterized by a progressive reduction in bone mineral density and bone tissue microarchitecture disorder resulting in increased bone fragility, which makes them more susceptible to physical stress, falls and impact, increased risk of fracture (1). Osteoporosis is a multifactorial disease in which many factors are involved. According to the results of recent studies, the genetic component of osteoporosis is responsible for 75%, while external factors for 25% of bone mineral density (2). Positive family history of osteoporosis and fractures represent risk factors for osteoporosis. In many studies, they are presented as one of the most important risk factors (3). It is believed that genetic factors affect the achievement of bone density maximum up to 25 years of age. Many authors have shown polymorphisms of genes responsible for genetic predisposition for osteoporosis (4,5). Numerous studies have also confirmed that genetic factors have a dominant influence on bone mineral density (6) and several gene locuses, potentially

involved in osteoporosis, have been identified. Vitamin D receptor (VDR) gene is the most widely studied since this vitamin plays a central role in calcium metabolism and homeostasis, regulating calcium absorption, bone resorption and mineralization, bone cell differentiation and parathyroid hormone secretion (PTH) (7). With the help of modern molecular diagnostic methods today, people with genetic predisposition to osteoporosis can be identified, which can significantly influence these people in timely instruction on screening osteodensitometry, the FRAX model of fracture risk calculation, and timely advice on prevention measures and adequate treatment (8).

Osteoporosis is a systemic skeletal disorder characterized by decreased bone mass and changes in bone structure, resulting in increased bone fragility and increased tendency of bone tissue to fractures (9,10). It is a disease of impressive proportions that affects almost a tenth of the world's population, estimated to be around 200 million people worldwide suffering from this disease in Europe, the United States and Japan (11). Reasons for the occurrence of the disease itself are numerous: first of all, the world population is getting older, medical science is becoming more advanced, allowing longer life, and technological innovations provide early diagnosis of osteoporosis. The proportion of patients is progressively increasing, and millions of fractures are diagnosed annually around the world. Hip fractures are the biggest public health problem especially in the elderly because they significantly reduce the quality of life and increase the morbidity and mortality of this population (12,13). There are certain risk factors (early menopause, positive family history of osteoporosis, earlier fractures) for the onset of osteoporosis whose postmenopausal association can lead to loss of bone mass and increased risk of fractures (10,14).

## 2. AIM

The aim of our study was to determine whether certain non-preventable risk factors and their association contribute to accelerated reduction in mineral bone density and the occurrence of osteoporosis in postmenopausal women.

## 3. METHODS

The study was carried out for a period of two years from 2015 to 2016. Experimental group (a group of cases) consisted of 100 females in the post-menopausal age (at least two years after the last menstruation) in whom was newly diagnosed osteoporosis in the Osteodensitometry Unit (Clinic for Endocrinology, diabetes and metabolic disease UKC RS) by determining the bone mineral density, the DEXA method on the lumbar spine (L2-L4) and the hip, and the upper part of the thigh bone, using the "LUNAR DPX" densitometer Product Division American GE Healthkare (GENERAL Electric Computer 2006)..

The control group (group of controls) consisted of 100 females in the postmenopausal age, in which after the determination of bone mineral density by DEXA method osteoporosis was not diagnosed. Data collection period was April 2015 to May 2016.

The exclusion criteria were malignant diseases, diabetes, thyroid diseases, diseases of parathyroid and adrenal glands, chronic renal failure, inflammatory arthritis, use of statins in the treatment of dyslipidemia, corticosteroids, hormones or diuretics for more than three months, secondary osteoporosis due to

endocrine disorders, peptic ulcers surgery, chronic liver disease, and drug-induced osteoporosis.

For the purpose of collecting demographic data, the data on risk factors for osteoporosis and the patient's habitual habits, a questionnaire on mineral bone density was used in women of the Irish Association of Osteoporosis, which contains five parts. The first concerns physical activity issues, other on eating habits, and parts of three to five of the menstrual cycle, personal and pharmacological anamnesis. The questionnaire is publicly available on the Internet. Descriptive and analytical statistics were used in the analysis. To test the differences between the groups the chi-square test, independent sample t-test, paired t-test, and ANOVA analysis were used. The correlation between dependent and independent variables was investigated by an appropriate bivariate as well as multivariate logistic regression.

## 4. RESULTS

Observing both groups in our study, from the demographic point of view, we find that in the experimental group the mean age of the respondents was 64 years, and in the control group 63 years, which statistically does not represent a significant difference. Regarding the level of education, both groups were dominated by respondents with elementary or secondary school (78% in the experimental group and 84% in the control group), without statistically significant difference between the groups.

Variable	Experimental group N= 100	Control group N= 100	p
Osteoporosis			
Yes	20	8	0.025 *
No	80	92	
Family history of fractures			
Yes	26	11	0.013 *
No	74	89	
Osteoporotic fractures			
Yes	16	3	0.002*
No	84	97	

Table 1. Parameters of family history associated with osteoporosis. \* Chi-square test

In terms of testing the differences between the groups in relation to unprecedented risk factors such as the presence of osteoporosis and traumatic/osteoporotic bone fractures in the family history, from the Table 1, we note that these factors are more present in the experimental group (osteoporosis 20%, osteoporotic fractures 16%) compared to the

Variable	Experimental group N= 100	Control group N= 100	p
Previous fractures			
Yes	43	21	0.001 *
No	57	79	
Age of menopause onset			
< 50 years	41	19	0.000 *
≥ 50 years	59	81	

Table 2. Parameters of personal history associated with the onset of osteoporosis. \* Chi-square test

control group (osteoporosis 8%, osteoporotic fracture 3%), and the obtained differences were statistically significant.

In terms of personal history data (previous fractures and menopause onset), we can notice that there is a statistically significant difference between the observed groups. Namely, in the experimental group, the previous fractures in personal history was statistically significantly more frequent (43%) than in the control group (21%). Menopause onset (before 50 years of age) occurred in 41% of women in the experimental group compared to women in the control group 19%, which statistically represents a significant difference ( $\chi^2=10.13$ ,  $p<0.05$ ) (Table 2).

Investigation of risk factors for the occurrence of osteoporosis by logistic regression model included all investigated factors. By univariate logistic regression, it was found that statistically significant relation with osteoporosis exist between: earlier fractures and family history of osteoporosis (Table 3).

All factors that were statistically significantly related to osteoporosis in univariate regression were incorporated into the multivariate model. The results of multivariate logistic regression show that independent risk factors for the occurrence of osteoporosis in women in menopause are earlier fractures (OR=2.464;  $p=0.015$ ) and family history of osteoporosis (OR=4.567;  $p=0.003$ ) (Table 4).

## 5. DISCUSSION

With the help of modern molecular diagnostic methods, people with genetic predisposition for osteoporosis can now be identified, which can significantly affect such persons being promptly directed to screening osteodensitometry, FRAX model for calculating fracture risk, and timely advice on preventive measures and adequate treatment (14). The results of our study show that the presence of earlier fractures in the subjects is a significant independent risk factor for osteoporosis, which is in line with other scientific studies (9, 15). Danndan Xie and associates in their research find that among other specified risk factors for osteoporosis, a positive family history of earlier fractures and falls represent a significant risk factor for the onset of this disease (1). Also, other scientific studies suggest that previous falls and fractures in family or personal history increase the risk of osteoporosis/osteoporotic fractures several times and that in postmenopausal women they represent strong predictors for the first - incident fracture, especially hip fracture (15-17).

In our study, the family history of osteoporosis was found in a significantly larger number of subjects in the group of cases compared to the control group. Examination of this factor by the model of the multivariate of logistic regression shows that the presence of osteoporosis in close relatives (usually the mother) represents a significant and independent risk factor for the occurrence of osteoporosis, which is in agreement with other studies (9, 18) and points to the important role of genetic predisposition to the emergence

Risk factor	B*	SE	p	OR†	95% CI for OR ‡	
					Lower limit	Upper limit
Previous fractures	1.104	0.321	0.001	3.018	1.607	5.665
Family history of osteoporosis	1.056	0.445	0.018	2.875	1.201	6.883
Age of menopause onset	-0.034	0.043	0.421	0.966	0.889	1.051

Table 3. Risk factors for the emergence of osteoporosis identified by the univariate logistic regression. \* coefficient; † odds ratio; ‡ confidence interval

Risk factor	B*	SE	p	OR†	95% CI for OR ‡	
					Lower limit	Upper limit
Previous fractures	0.902	0.369	0.015	2.464	1.195	5.084
Family history of osteoporosis	1.519	0.512	0.003	4.567	1.674	12.460
Constant	-2.953	1.420	0.038	0.052		

Table 4. Risk factors for the emergence of osteoporosis identified by multivariate logistic regression. \* coefficient; † odds ratio; ‡ confidence interval

of osteoporosis. Seeman and associates find that daughters whose mothers suffer from osteoporosis have reduced bone mass on the lumbar spine and femur, which places them in a group of increased risk of fracture and osteoporosis (19). Scientific studies investigating inheritance for reduced mineral bone density and the occurrence of osteoporosis through three generations (mothers, daughters and grandmothers) indicate a significant correlation between mineral bone density on the proximal forearm, especially between mothers and grandmothers. A slightly lower correlation of mineral bone density on the proximal forearm was found between mothers and daughters (20). It is known that genetic components strongly affect bone mineral density, its architecture and processes within the bone itself, playing an important role in determining the risk of osteoporosis and fracture sensitivity. Newer scientific studies on dual and family cohabitation have confirmed the importance of genetic factors in individual variants of bone peak, bone mineral density, and bone metabolism, and therefore predispositions for osteoporosis and fracture (21).

Mineral bone density decreases rapidly in years immediately after the onset of menopause, and the reason for this is a sudden drop in estrogen levels in the organism which, through its receptors (ER- $\alpha$  and ER- $\beta$ ), affects the growth of the skeleton and its maturation (12). Estrogen deficiency has a direct anabolic effect on bone tissue and affects bone loss, although the deficit of sex hormones, both in women and men, is not sufficient to lead to osteoporosis, as osteoporosis does not develop in all postmenopausal women (22). When we analyze the years of menopause in our study, we can see that in the majority of subjects in the experimental group menopause occurred before 50 years of age, versus control group. The results of the univariate logistic regression in our study did not show that the early

loss of the menstrual cycle before the age of 50 represents a significant factor for osteoporosis in postmenopausal women, which is consistent with studies showing that the duration of menopause and the year of its occurrence are not correlated with the onset of osteoporosis. The presence of risk factors for the development of osteoporosis associated with different lifestyles and habits (smoking, excessive alcohol consumption) and the duration of menopause, more than the year of menopause, can significantly affect the development of the disease (23-25). On the other hand, the results of the study by Francuccia and associates (26), as well as other scientific studies (1, 6, 27), show that early loss of the menstrual cycle (before 50 years of age) can be an important independent risk factor for the development of osteoporosis and osteoporotic fracture (28), which is due primarily to the lack of estrogen as an important factor for the formation of bone reserves.

This study has certain limitations. Our database consists of respondents living in urban areas (urban population) and perhaps the results of the study may be inappropriately applied to women living in rural environments that have different lifestyles.

## 6. CONCLUSION

Many genetically related risk factors have a significant effect on bone mineral density in postmenopausal women. The results of our study show that the presence of earlier fractures and positive family history of osteoporosis in close relatives (most often mother) are significant predictors of risk for osteoporosis in postmenopausal women. Through education and certain methods of screening, risk groups can be identified in a timely manner in order to further prevent the osteoporosis.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms
- **Author's contribution:** RB and SM gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. Each author had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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