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Osteoporosis – A Risk Factor for Cardiovascular Diseases: A Follow-Up Study

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SUMMARY

Introduction Cardiovascular (CV) diseases and bone fractures due to osteoporosis are the leading causes of death in the elderly.

Objective The aim of this study was to demonstrate a correlation between the overall risk for CV events, and low bone density in postmenopausal women, and its impact on the incidence of serious CV events.

Methods Our prospective study involved 300 postmenopausal women. All the examinees were divided into three groups based on their measured bone density: Group I – 84 examinees with osteoporosis; Group II – 115 examinees with osteopenia; and Group III – 101 examinees with normal bone density. In all examinees the overall ten-year risk for a fatal CV event was calculated using the SCORE system tables.

Results After a 36-month follow-up, CV events occurred in 19 (6.3%) examinees. Significant differences in the incidence of CV events were demonstrated between the patients with osteoporosis, osteopenia, and normal bone density (χ^2=28.7; p<0.001), as well as between those with a high and low CV risk (χ^2=22.6; p<0.001). Multivariate logistic regression analysis showed that smoking (OR: 2.23; 95% CI: 1.02 to 6.19; p=0.035), and increase of overall CV score (OR: 1.36; 95% CI: 1.17 to 1.58; p<0.001) are associated with increased CV event risk, while the increase of T score value is associated with decreased risk of CV event (OR: 0.42; 95% CI: 0.25 to 0.73; p=0.002).

Conclusion Measurement of bone density with a standard assessment of the total CV risk could be useful for selecting women who need intensive prevention and treatment of atherosclerosis.

Keywords: osteoporosis; cardiovascular risk; SCORE system

INTRODUCTION

Cardiovascular diseases and bone fractures due to osteoporosis are the leading causes of death in the elderly. Some recent studies and observations in the fields of pathogenic phenomena and treatment approaches have indicated a possible substantial association between osteoporosis and atherosclerosis. The association is based upon their elevated incidence rates in more advanced age and the existence of numerous mutual risk factors [1].

A concept proposed has been proposed that cardiovascular diseases and osteoporosis are linked by a common factor acting on both vascular and bone cells. Arterial calcification is common in atherosclerosis, being associated with a higher risk for cardiovascular events. Vascular calcification is similar to any bone formation, both being estrogen regulated [2].

Atherosclerosis and osteoporosis commonly have atypical presentations in their early phases, which necessitate the identification of individuals at high risk and identification of various independent predictors of overall risk. Two thirds of women die suddenly of a cardiovascular disease or experience bone fractures without any antecedent, warning disease signs. Identification of individuals at high risk would have an immense significance in clinical practice, since it would enable adequate prevention of both cardiovascular diseases and complications of osteoporosis.

OBJECTIVE

The aim of this study was to establish the association between overall risk for cardiovascular events determined by the SCORE system and low bone density in postmenopausal women, and to determine their common impact on the incidence of serious cardiovascular events.

METHODS

Study population

Our prospective study involved 300 women referred to the Department of Densitometry, Institute for Treatment and Rehabilitation "Niška Banja", for densitometric examination, since they belonged to the risk group of postmenopausal women.

All examinees were postmenopausal (defined as the absence of a menstrual cycle in the period of one year). The study did not enroll

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examinees with documented cardiovascular disease, diabetes, secondary osteoporosis caused by various endocrine disorders, systemic diseases, and those on therapy, which could have an impact on bone metabolism (glycocorticoids and anticonvulsives).

Based on their measured bone density, all the examinees were divided into three groups:

- I group – 84 examinees with osteoporosis, i.e. T score ≤ -2.5 standard deviations (SD);
- II group – 115 examinees with osteopenia, i.e. T score from -1 to -2.5 SD; and
- III group – 101 examinees with normal bone density, i.e. T score ≥ -1 SD.
- The following parameters were used in the study:

1. Clinical work-up of patients involved the patient's history.

2. Bone density was measured in the lumbar spine using a DEXA densitometer Hologic Discovery QDR-C, and the results were presented as absolute values (gr/cm^2) and T scores. According to the WHO recommendations, the gold standard for bone density measurements is dual (photon)-energy x-ray absorptiometry (DEXA), measuring bone density in the vertebral bodies and the left hip [3].

3. Anthropometric measurements involved body mass (BM) and body height (BH) measurements. Based on that, body mass index (BMI) was calculated using the following formula: BMI(kg/m^2) = BM(kg)/BH^2(m^2). Obesity was defined as BMI>30 kg/m^2. Waist circumference was measured in the middle between the lowest rib and spina iliaca, and the values obtained were assessed using the WHO criteria. The normal value for women was <88 cm.

4. Measurement of arterial blood pressure was performed in a sedentary position on both arms, half-hour after rest, utilizing the auscultation method by Korotkoff and a mercury sphygmomanometer. The highest average value of three measurements on one arm was used for further statistical calculations.

5. Life style habits were analyzed, such as physical activity, smoking, and alcohol intake. The examinees reporting any physical activity (daily rapid walking, riding a bicycle, swimming, aerobic exercise) undertaken for 30 to 45 minutes, 4 to 6 times a week were taken to be physically active, with intensity amounting to 60-75% of a corresponding heart frequency [4]. Smokers were defined as individuals reporting everyday smoking. Non-smokers were taken to be ex-smokers (for more than 2 years) and those who never smoked.

6. The following biochemical parameters were measured in all examinees: total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, glycemia, and serum values of Ca and P.

- Total cholesterol (Hol) was measured using the enzymatic color test (PAP method), with reference laboratory values of 3.9-5.5 mmol/l;
- Triglycerides (TG) were measured using the enzymatic color test, with reference laboratory values of 0.7-2.0 mmol/l;
- HDL cholesterol (HDL-C) was measured using the enzymatic color test (PAP method), with reference laboratory values of 1.0-1.7 mmol/l for women;
- LDL cholesterol (LDL-C) was determined using the indirect calculation method and formula: LDL-C=Hol – Tg/2.2-HDL-C, with reference laboratory values of 2.8-3.9 mmol/l;
- Glycose (Gly) was measured using the GOD-PAP method, with reference laboratory values of 3.6-6.1 mmol/l;
- Serum calcium (Ca) was measured using the spectrophotometric method, with reference laboratory values of 2.2-2.65 mmol/l;
- Serum phosphorus (P) was measured using the spectrophotometric method, with reference laboratory values of 0.81-1.45 mmol/l.

7. Determination of overall ten-year risk for a fatal cardiovascular event. Overall ten-year risk for a fatal cardiovascular event was determined using the SCORE system tables for the countries with a high cardiovascular risk [5].

The examinees were followed for 36 months and the presence of all significant cardiovascular events were evaluated (death of any cause and type of death; cardiac, cardiovascular, or non-cardiovascular), hospitalization due to exacerbated coronary disease in the form of unstable angina pectoris (NAP), fatal and non-fatal myocardial infarction (MI), and fatal and non-fatal ischemic brain stroke, revascularization procedures (percutaneus coronary intervention or coronary artery bypass grafting). The data were obtained by a telephone interview after 36 months of follow-up.

Statistical methods

Quantitative statistical analysis was performed using a personal computer. MS Excel from the Microsoft Office 2007 software package was used for registration, ranking, grouping, and tabular and graphical display of data. Calculations were performed using the SPSS 10.0 software package.

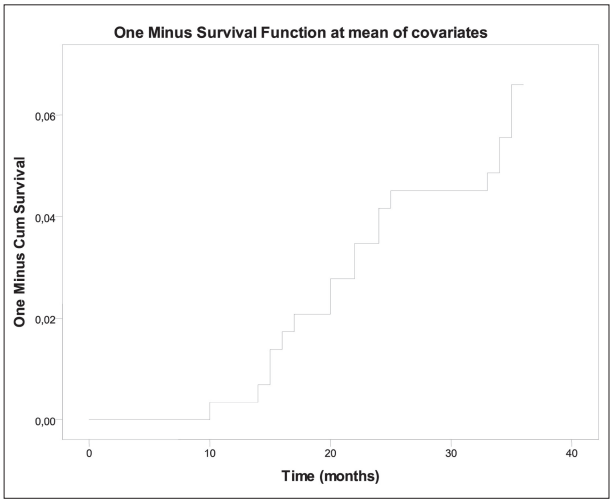
The following statistical parameters were presented: arithmetic mean ($\bar{X}$), standard deviation (SD), minimum (Min) and maximum (Max) value, structure index (%), and 95% confidence interval (95% CI).

Mean values of numerical characteristics between the two groups of examinees were compared using the Student's t-test for independent samples, and the Mann-Whitney U-test was used when the distribution of values for particular characteristics did not fulfill the requirements of normal distribution. The Mantel-Haenszel chi-square test and Fisher's test of exact probability of the null hypothesis were employed in the comparison of frequencies of particular characteristics, when any of the expected frequencies were below 5.

Assessment of the significant predictors of cardiovascular events was done by way of logistic regression analysis. We calculated the approximate relative risk (odds ratio – OR) for cardiovascular events under the impact of cardiovascular score, T score, and traditional risk factors for cardiovascular events. The chi-square based Wald test was used to evaluate the statistical significance of calculated OR values. After univariant logistic regression analysis,

multivariant analysis was performed. The factors demonstrated by univariant regression to significantly influence the values of dependent variables were included in multivariant regression models. Using the backward stepwise method by Wald, all factors with non-significant influence were excluded from our multivariant analysis. The coefficient values represented the changes of dependent variables caused by the changes of independent variables by one measurement unit. For category independent variables, the coefficient of regression represented the change of value of a dependent variable for a single modality of characteristic compared to another modality.

In all analyses, the statistical significance cut-off was taken to be the assessment error of less than 5% ($p<0.05$). The results of statistical analysis were presented as tables and graphs.



Graph 1. Kaplan-Meier analysis with log-rank survival test of the examinees followed for 36 months

RESULTS

Out of 300 examinees, 84 (28.0%) had osteoporosis, i.e. T score below -2.5 SD; 115 examinees (38.3%) had osteopenia, i.e. T score from -1 to -2.5 SD, and 101 examinees (33.7%) had normal bone density. The examinees were followed for three years. During the period of follow-up, 12 examinees (4%) were excluded from the study due to the lack of compliance. All significant cardiovascular events were recorded: death, unstable angina pectoris (UAP), myocardial infarction (MI), revascularization procedures (percutaneus coronary intervention or coronary artery bypass grafting) and ischemic brain stroke (IBS). After a 36 month follow-up, significant cardiovascular events were observed in 19 (6.3%) out of 300 examinees. The mean time until the occurrence of a cardiovascular event was 23.7±8.4 months. One patient (0.3%) died of brain stroke; she had a T score value of -4 and a cardiovascular score of 9. Three examinees (1%) had MI, UAP was observed in 10 examinees (3.3%), while IBS was observed in 8 (2.7%). Two examinees (0.7%) had both IBS and UAP.

Time to event comparisons were performed using the Kaplan-Meier analysis with log-rank testing. The test showed a significant difference in the incidence of cardiovascular events between the examinees with osteoporosis, osteopenia, and normal bone density (chi-square 28.7; $p<0.001$), as well as in those with high and low cardiovascular risks (chi-square 22.6; $p<0.001$) (Graph 1).

The examinees that experienced a cardiovascular event were statistically significantly of a more advanced age than those without any cardiovascular events, and their menopause duration was significantly longer. They had a significantly lower bone density, expressed as a T score value. All risk factors included in the SCORE system charts were significantly more common in these examinees. Total cholesterol level, LDL cholesterol, and triglycerides were significantly higher in the group with cardiovascular events.

Hypertension and physical inactivity, reported in patients' histories, were significantly more common in the group of examinees who experienced cardiovascular events.

Table 1. Values and distribution of relevant characteristics of the examinees with and without past cardiovascular (CV) events

Parameter	Examinees		p value
	Without CV event	With CV event	
Age (years)	56.6±4.7	61.5±4.4	<0.001
Duration of menopause (years)	9.0±6.1	14.8±5.9	<0.001
T score (SD)	-1.6±1.2	-2.9±0.7	<0.001
BMI (kg/m^2)	26.4±3.5	27.2±4.0	0.309
SBP (mmHg)	135.2±16.1	151.6±9.0	<0.001
DBP (mmHg)	81.3±6.7	89.5±6.2	<0.001
Cholesterol (mmol/L)	5.8±1.1	7.0±0.8	<0.001
HDL cholesterol (mmol/L)	1.5±0.3	1.4±0.3	0.746
LDL cholesterol (mmol/L)	3.7±1.3	4.4±0.7	<0.001
Triglycerides (mmol/L)	1.5±0.6	2.5±1.6	<0.001
Glucose (mmol/L)	5.0±0.5	5.0±0.5	0.971
Ca (mmol/L)	2.3±0.2	2.3±0.1	0.685
P (mmol/L)	1.1±0.2	1.1±0.1	0.474
Hypertension	160 (59.5%)	18 (94.7%)	0.002
Dyslipidemia	124 (46.1%)	18 (94.7%)	<0.001
Smoking	105 (39%)	12 (63.2%)	0.039
High CV risk	84 (31.2%)	16 (84.2%)	<0.001
Osteoporosis	65 (24.2%)	15 (78.9%)	<0.001
Physical inactivity	86 (32.0%)	13 (68.4%)	0.002
Inheritance of CV diseases	122 (45.4%)	12 (63.2%)	0.133

The values are expresses as mean value with standard deviation, and the number of patients with percentage.

SD – standard deviation; BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, Ca – calcium, P – phosphorus; p – statistical significance

In women who experienced cardiovascular events, the family history of cardiovascular diseases was significantly more common. Women with a high cardiovascular risk and osteoporosis had a significantly higher incidence of cardiovascular events.

Glycemia (there were no diabetics among the examinees), alcohol consumption, BMI, and HDL cholesterol level did not differ significantly between the examinees (Table 1).

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Univariate logistic regression analysis shows that an increase in T score value is associated with a decreased risk of a cardiovascular event (OR: 0.38; 95% CI: 0.25 to 0.58; p<0.001), while an increase in cardiovascular score (OR: 1.35; 95% CI: 1.22 to 1.50; p<0.001) and an increase in age (OR: 1.34; 95% CI: 1.16 to 1.54; p<0.001) is associated with an increased risk of a cardiovascular event. Also, increase in systolic blood pressure (SBP), diastolic blood pressure (DBP), cholesterol, LDL cholesterol, triglycerides, and smoking, are associated with an increased risk of a cardiovascular event (Table 2).

The examinees with a history of arterial hypertension (AH) had 11.57 times higher incidence of cardiovascular events compared to those without AH, smoking increased incidence of cardiovascular events by 2.6 times, physical inactivity by 1.9 times, and family history of cardiovascular disease doubled the incidence of cardiovascular events. Values of BMI, HDL, glycemia, levels of Ca and P, and alcohol consumption did not show any significant influence on the incidence of cardiovascular events.

In patients with a cardiovascular risk exceeding 5%, cardiovascular events were 10 times more common, while in those with osteoporosis, cardiovascular events were 7 times more common in the follow-up period of three years.

Multivariate logistic regression analysis shows that smoking (OR: 2.23; 95%; CI: 1.02 to 6.19) and an increase in overall cardiovascular score (OR: 1.36; 95%; CI: 1.17 to 1.58) are associated with an increased risk of a cardiovascular event, while an increase in T score value is associated with a decreased risk of a cardiovascular event (OR: 0.42; 95%; CI: 0.25 to 0.73) (Table 3).

Table 2. Values of overall risk (OR) in the assessment of association of the studied risk with incidence of cardiovascular (CV) events – results of univariant logistic regression analysis

Parameter	OR	95% CI for OR		p value
		Lower	Upper	
Age	1.34	1.16	1.54	<0.001
Duration of menopause	1.11	1.05	1.17	<0.001
Hypertension	11.58	1.55	86.71	0.017
BMI	1.06	0.94	1.20	0.308
SBP	1.07	1.03	1.10	<0.001
DBP	1.10	1.05	1.15	<0.001
Smoking	2.68	1.02	7.02	0.039
Cholesterol	1.83	1.37	2.43	<0.001
HDL cholesterol	0.74	0.13	4.22	0.738
LDL cholesterol	1.18	1.01	1.38	0.034
Triglycerides	2.69	1.90	3.81	<0.001
SCORE risk	1.35	1.22	1.50	<0.001
T score	0.38	0.25	0.58	<0.001
Physical activity	1.90	1.09	3.33	0.025
Inheritance of CV diseases	2.03	0.80	5.17	0.136
Alcohol	0.05	0.00	223.90	0.578

CI – confidence interval

Tabela 3. Values of overall risk (OR) in the assessment of association of the studied risk with incidence of cardiovascular (CV) events – results of multivariant logistic regression analysis

Parameter	OR	95% CI for OR		p value
		Lower	Upper	
Smoking	2.23	1.02	6.19	0.035
T score	0.42	0.25	0.73	0.002
CV SCORE	1.36	1.17	1.58	<0.001

DISCUSSION

In the light of the ever-growing life expectancy rates, a large number of women will spend about one-third of their lives in menopause, and it is the period of life when various disorders occur, among which cardiovascular diseases and osteoporosis have a prominent place.

Cardiovascular diseases and osteoporosis are more prevalent with increased age, and they are influenced by numerous common pathophysiologic mechanisms. Age, dyslipidemia, oxidative stress, inflammation, hypertension, hyperhomocysteinemia, diabetes, and lifestyle are associated with an increased risk of cardiovascular diseases and bone density reduction [1]. Elevated LDL and low HDL cholesterol are associated with reduced bone density, bone remodeling, and atherosclerotic processes [6]. Antilipemics, especially statins, in addition to their impact on lipids, also have an effect on bone metabolism, while biphosphonates, medicaments with antiresorptive effects on bone tissue also influence the process of osteoporosis. Statins and biphosphonates share a common action pathway – the mevalonate pathway of cholesterol synthesis [7].

Nitric oxide, in addition to its atheroprotective effect, favorably acts on the function of osteoblasts and bone metabolism [8]. Estrogens, as natural cardioprotectors, also have protective effects on bone tissue [9]. Osteoprotogerin serves as an inhibitor of bone resorption, being an independent risk factor for the progression of atherosclerosis [10]. Homocystein is regarded as a risk factor for cardiovascular events, being at the same time an independent risk factor for the onset of osteoporosis and subsequent bone fractures [11]. Physical inactivity and smoking are the main common risk factors for cardiovascular diseases and osteoporosis [12].

Oxidated lipids in serum, in addition to their confirmed role in atherogenesis, act under experimental conditions on osteoblasts and osteoclasts as well. It appears that numerous cellular and molecular elements, such as collagen 1, osteonectin, osteopontin, osteoprotogerin, and oxidated lipids, regulate the process of mineralization in both bone structures and vasculature, which can explain the observed association of osteoporosis and atherosclerotic calcifications independent of age [13, 14, 15].

The results of our study of 300 patients, interviewed after 36 months of follow-up, showed that major cardiovascular events were more common in postmenopausal women with a higher cardiovascular risk and low bone density.

Numerous studies have shown that bone density reduction can have a significant impact on increased mortality from cardiovascular diseases in postmenopausal women. Supporting this was the study by Tanko et al. [16], who studied 2,576 postmenopausal women without any evi-

dent cardiovascular disease in the period of four years, and observed that postmenopausal women with osteoporosis had a 3.9 times higher risk of adverse cardiovascular events compared to age-matched women with osteopenia, and that women with osteopenia had a 2.1 times higher risk of cardiovascular events compared to those with normal bone density.

Elevation of SCORE risk by 1% caused a bone mineral density (BMD) decrease of 0.033 g/cm^2 (0.029 to 0.036 g/cm^2). Multivariate logistic regression analysis showed that the following factors caused a significant increase in the risk of decreasing BMD: every year of life by 20%, menopause duration by 26%, increase in systolic blood pressure (BP) by 1 mmHg by 7%, increase in SCORE risk by 1% by 5.31 times, physical inactivity by 5.96 times, and osteoporosis in the family history by 3.91 times [17].

Calculations of cardiovascular risk can prove useful in the identification of individuals with low BMD. In 3,881 women and men aged 56 to 74 years, without any cardiovascular disease and cerebrovascular insults in their histories, Broussard et al. examined the association of BMD and 10-year cardiovascular risk, calculated using the Framingham cardiovascular risk model. In the group of women with a cardiovascular risk ≥20%, the probability of low BMD was 73% higher [18].

Arterial calcification is common in atherosclerosis and is associated with an increased risk of ischemic heart disease and myocardial infarction. Schulz et al. [19] have found that patients with vascular calcifications commonly have low bone density, and that substantial bone loss correlates with a more rapid progression of calcification of the abdominal aorta, while lower BMD values correlate well with calcified but not with non-calcified plaques.

In their follow-up of 236 postmenopausal women aged 45 to 57 years, Hak et al. [20] have shown an inverse correlation between aortic calcification and bone density of the metacarpal bone.

In 467 examinees (339 women), Choi et al. [21] have demonstrated that a low BMD value is associated with a higher calcium score in the coronary arteries and atherosclerotic plaques in women.

In 946 women and 963 men, Hyder et al. [22] have shown that low BMD is associated with more prominent arterial calcifications in both men and women, with the observation that in women, there is an association between low BMD and prominent arterial calcification in the coronary blood vessels.

Seo et al. [23] have found in their study of 152 postmenopausal women that osteoporosis is associated with increased arterial rigidity and presence of coronary atherosclerosis.

Kadu et al. [24] have demonstrated that a drop in BMD value by one standard deviation increases the risk of mortality from ischemic heart disease or other forms of atherosclerosis by 1.2 to 1.3 times. Von Der Recke et al. [25] have shown that the lowest value of bone mass in women is associated with a 2 times higher risk of adverse cardiovascular events compared to the women with thehighest bone mass values.

The confirmation that low bone density independently predicts coronary disease has been reported after performed coronary angiography and determined bone density values. Bone density was measured in the lumbar spine using a DEXA densitometer. Significant coronary stenosis was observed in 62% of the examinees with osteopenia and in 75% of those with osteoporosis [26].

Women with the lowest bone mass values have a 1.9 times higher risk of brain stroke compared to those with the highest BMD values. A study has stressed that low BMD is a predictor of brain stroke in women [27].

Univariant logistic regression analysis of our study demonstrated that age, duration of menopause, hypertension, dyslipidemia, smoking, physical inactivity, and inheritance significantly influenced the occurrence of cardiovascular events. A cardiovascular SCORE increase of 1% caused an increased incidence of cardiovascular events by 35% (21.9 to 49.5%). The patients with cardiovascular risks exceeding 5% were ten times more likely to experience cardiovascular events in the follow-up period of three years, while those with osteoporosis were seven times more likely to experience cardiovascular events in the same period.

Multivariate logistic regression of our study singled out smoking, overall cardiovascular risk, and decreased T score values as statistically significant factors for cardiovascular events. All these factors caused a significant increase in the incidence of cardiovascular events: smoking (OR: 2.23; 95% CI: 1.02 to 6.19) increased CV risk (OR: 1.36; 95% CI: 1.17 to 1.58) and decreased T score (OR: 0.42; 95% CI: 0.25 to 0.73).

Limitations of the study

In relation to previous studies, this study included a relatively small number of participants and the duration of participant monitoring was relatively short, only 36 months. This study did not consider whether participants were adhering to the prescribed treatments for cardiovascular risk factors and/or osteoporosis, which could impact cardiovascular events.

CONCLUSION

Osteoporosis and atherosclerosis have a profound impact on human health, especially on the elderly and on postmenopausal women. Our study suggests that in women with osteoporosis, adverse cardiovascular events are more common, and the obtained results indicate that bone density measurements can be very useful in the selection of women in whom extensive prevention and treatment of atherosclerosis should be initiated in order to prevent adverse cardiovascular events.

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Остеопороза – фактор ризика за кардиоваскуларна обољења: студија клиничког праћења

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КРАТАК САДРЖАЈ

Увод Кардиоваскуларне (КВ) болести и преломи костију због остеопорозе су водећи узроци смрти људи старије животне доби.

Циљ рада Циљ истраживања био је да се утврди веза између укупног ризика за КВ обољења и мале густине кости код жена у постменопаузи, те њихов утицај на инциденцију КВ догађаја.

Методе рада Проспективним истраживањем обухваћено је 300 жена у постменопаузи. Све испитанице су на основу измерене густине кости сврстане у три групе: прву групу чиниле су 84 испитанице са остеопорозом, другу групу чинило је 115 жена са остеопенијом, док је у трећој групи била 101 жена нормалне густине кости. Свим испитаницама израчунат је укупни десетогодишњи ризик за настанак КВ смрти применом систем-таблице *SCORE*.

Резултати После 36 месеци клиничког праћења испитаница, КВ догађаји наступили су код 19 жена (6,3%). Установљена је значајна разлика у инциденцији КВ обољења међу испитаницама са остеопорозом, остеопенијом и нормалном густином кости (χ^2=28,7; p<0,001), као и код жена с високим и ниским КВ ризиком (χ^2=22,6; p<0,001). Мултиваријантна логистичка регресиона анализа је показала да су пушење (*OR*: 2,23; *95% CI*: 1,02–6,19; *p*=0,035) и повећање КВ ризик-скора (*OR*: 1,36; *95% CI*: 1,17–1,58; *p*<0,001) удружени с повећаним ризиком од КВ догађаја, док је повећање Т скора удружено са смањеним ризиком од развоја КВ обољења (*OR*: 0,42; *95% CI*: 0,25–0,73; *p*=0,002).

Закључак Мерење густине кости уз стандардну процену укупног КВ ризика може бити веома корисно у одабиру жена код којих треба започети интензивну превенцију и лечење атеросклерозе.

Кључне речи: остеопороза; кардиоваскуларни ризик; *SCORE* систем

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