Original article

ASSOCIATION BETWEEN HYPERTENSION AND OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

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Hypertension is a frequent chronic cardiovascular disease with the prevalence between 20 and 40%. The prevalence of hypertension among women is lower than in men. Osteoporosis (OP) is characterized by decreased bone density with damages of bone tissue microarchitecture.

The aim of this study was to examine the association between hypertension and osteoporosis among postmenopausal women.

By means of densitometry, three hundred postmenopausal women were examined; none of them had suffered major cardiovascular event nor had clinically manifested atherosclerosis. Besides anamnestic data, the following was analyzed: body mass, body height, waist circumference, blood pressure (systolic blood pressure -SBP and diastolic blood pressure - DBP), cholesterol, triglycerides, HDL, LDL, glycemia, serum and urine levels of Ca and calculated ten-year risk of cardiovascular event using the SCORE system, bone mineral density on Hologic Discovery QDR-C densotometer, shown as T score on the lumbar part of the spinal column and left hip. The patients were divided into three groups based on the bone density measurements: patients with osteoporosis - bone density with T score less than 2.5 SD (100 examinees), patients with osteopenia - T score from -1 to -2,5 SD (100 examinees), and control group of patients with normal bone density - T score from +1 to -1 SD (100 examinees).

The mean age of postmenopausal women with normal bone density was 54.10±3.90 years (control group), 56.63±4.76 years in the group with osteopenia (group II) and 60.14±3.55 years in the group of postmenopausal women with osteoporosis.

The analysis of variance (ANOVA) and post hoc Dunett`s test showed that there was a statistically significant difference in age between the groups ($p<0.001$). In the control group hypertension was documented in 27 (27.0%) patients, in the group with osteopenia in 61 (61.0%) patients, and in the group with osteoporosis in 98 (98.0%) patients. Differences in distribution of hypertension among the examined groups were statistically significant ($p<0.001$). The average values of systolic blood pressure in the control group was 121.30±9.81 mmHg, in the group with osteopenia 136.40±13.37 mmHg, and in the group of postmenopausal women with osteoporosis it was 151.20±8.68 mmHg. Among these values, there was highly statistically significant difference $p<0.001$. The mean value of DBP among patients with normal bone density was 76.00±5.50 mmHg, in the group with osteopenia 80.90±8.05 mmHg, and in group with osteoporosis 89.00±6.74 mmHg, and these differences were considered statistically significant $p<0.001$.

Univariant linear regression analysis showed that every year of life, menopause duration and hypertension had a significant influence on the decrease in bone density among patients: each year of life by 0.012 g/cm^2, each year of menopause duration by 0.012 g/cm^2 , each year of hypertension by 0.014 g/cm^2 .

The rise in the values of SBP and DBP by one unit caused a significant decrease in the bone density of SBP by 0.005 g/cm^2 (0.005 to 0.006 g/cm^2); of DBP by 0.008 g/cm^2 (0.007 to 0.010 g/cm^2). Patients with hypertension had reduced bone density by 0.138 g/cm^2 (0.111 do 0.164 g/cm^2).

Osteoporosis and hypertension are two mass noninfectious diseases, the incidence of which increases with aging. Early menopause, lack of estrogen, age, smoking and physical inactivity pose significant risk factors, which stresses the necessity of preventive strategy for timely detection and treatment of these diseases. *Acta Medica Medianae 2009;48(2):8-13.*

***Key words**: hypertension, osteoporosis, postmenopause*

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Introduction

Arterial hypertension (HTA) is defined as a condition in which the value of systolic pressure is higher than 140 mm Hg and of diastolic pressure higher than 90 mm Hg (1).

Hypertension is a common chronic cardio-vascular disease occurring both in industrially developed and developing countries; the frequency

ranges from 20 to 40%. Hypertension is estimated to account for 7.1 million premature deaths and 4.5% of all diseases. Concerning that HTA also affects the working population, both social and medical aspects of HTA are considered. HTA is the cause of 64 million invalidity cases annually. As symptoms of HTA are mild or absent, the condition goes undetected or is detected accidentally during a systemic check-up, usually when complications begin (2).

Many studies have shown that hypertension plays a main role in developing of cardiovascular diseases, ischemic heart diseases, heart and renal failures. For the population aged 40 to 70 years, every increase of systolic blood pressure by 20 mmHg or diastolic pressure by 10 mmHg increases the risk of cerebrovascular diseases (3).

Timely diagnosis and treatment of hypertension will reduce the risk of cerebrovascular insult by 40% and of myocardial infarction by 15% (4).

Although the prevalence of hypertension among women is lower than in men, it reaches 70% to 80% among women above 70 years of age and is a strong predictor of cardiovascular risk. Risk increase is also reported in premenopausal women in whom hypertension is associated with a ten-fold increase of coronary mortality (5).

Because of statistical and epidemical causes, menopause is usually defined as the absence of menstrual periods during one year (6).

Menopause is characterized by ovarian atrophy with a lack of estrogen, progesterone and ovarian androgens. The loss of estrogen leads to vascular disorders, sleep disorders, mood disorders, depression, atrophy of urinary tract and vagina and increase in the risk of osteoporosis, hypertension, cardiovascular disease and loss of cognitive functions (7).

Osteoporosis (OP) is a systemic skeletal disorder with decreased bone mass and damages of bone tissue microarchitecture. The bone strength is determined by two basic characteristics: mineral bone density (BMD) and quality of bone (8).

BMD is measured in grams of minerals per surface (g/cm^2) or per volume (g/cm^3), and each person has its maximum bone mass (peak bone mass) and different intensity of bone loss. The measuring result of BMD can be shown as deviation (number of standard deviations) from the median bone density among the young, healthy population, which is called the T score, or as a deviation corresponding to the age of healthy subjects and is called the Z score (9).

The definition of OP according to the World Health Organization is (BMD)>2.5 of a standard deviation below average where T score is below -1 to -2.5. Normal bone density is BMD with T score from -1 to +1 (10).

According to the criteria of the World Health Organization, about 30% of postmenopausal women have osteoporosis. There are 10 million people with osteoporosis and about 34 million with low bone density in the USA (11). The risk of osteoporotic bone fracture (OP Fx) in women older than 50 years of age is 60%. There are 1.5 million osteoporotical bone fractures annually.

The seriousness of osteoporosis is also reflected through the risk of bone fractures, increase in hospital mortality after sustaining fracture, significant decrease in functional capacity as well as high treatment costs. One year after sustaining an osteoporotic hip fracture, every fifth patient dies (12).

Aims

The aim of the study was to analyze the correation between hypertension and osteoporosis among postmenopausal women.

Patients and methodology

The paper presents the clinical, randomized prospective study conducted in the cabinet for densitometry at the "Treatment and Rehabilitation Institute Niška Banja – Niš" in the period from June 2008 until April 2009.

Inclusion criteria

Clinical trial involved three hundred postmenopausal women who came for densitometry examination; none of them had a major cardiovascular event (myocardial infarction, cerebrovascular insult) nor ischemic heart disease. Personal data, personal and family anamnesis were taken.

Exclusion criteria

Women older than 65 suffering from cardiovascular disease (ischemic coronary disease, cerebrovascular insult, peripheral arterial disease), patients with secondary osteoporosis caused by endocrine disorders (hyperparathyroidism, hypercorticism or hyperthyroidism) as well as patient's taking drugs which influence bone metabolism (glucocorticoids, anticonvulsives).

The parameters used in further analysis:

- body mass, body height and waist circumference (in the middle between the lowest rib and spina illiaca. According to this parameters, body mass index (BMI) was calculated.

- blood pressure measurements were taken on both arms, when the patients were in the sitting posture, half an hour after rest. Higher mean value obtained after three measurements on one hand would be used for further statistical calculations.

-laboratory analyses: cholesterol, triglycerides, HDL, LDL, glycemia, serum Ca and P, and urine Ca

-Analysis of life habits: physical activity, smoking, alcohol consumption

- calculation of ten-year risk of fatal cardiovascular event according to the SCORE system using tables for high risk. The following variables were considered: sex, age, systolic blood pressure, smoking, level of cholesterol in mmoll/l.

According to bone density, the examinees were divided into three groups: examinees with osteoporosis - T score <-2.5; examinees with osteopenia - T score from -1 to -2,5 SD; control group of patients with normal bone density - T score from +1 to -1 SD

Anamnestic data related to ischemic heart disease, cerebrovascular disease and osteoporosis were collected for all examinees.

Statistical methods

Quantitative statistical analysis was performed by computer. Excel Microsoft Office 2003 was used for registration, rating, grouping, table and graphic data presentation. For the analyses of the

research results, statistical package SPSS (10.0 for Windows) was used.

The following statistic parameters were presented: arithmetic mean (Xsr), standard deviation (SD), median (Med), minimal (Min) and maximal (Max) values, structure index (%) and 95% confidence interval (CI).

For comparison of mean numerical values between two groups of examinees Student's t test and Mann Whitney U test were used when the distribution of values did not meet the requirements of normal distribution. The comparison of values between the three groups was done by ANOVA Dunnet post hoc test.

Results

Out of 300 examinees, 100 examinees suffered from osteoporosis, i.e. T score was less than 2.5 SD; 100 examinees suffered from osteopenia - T score ranged from -1 to -2,5 SD; 100 examinees had normal bone density - T score from +1 to -1 SD (Table 1).

Table 1. Bone density presented by groups (g/cm^2)

Parameter	Group			Total
	Control	Osteopenia	Osteoporosis	
Xsr	1.00	0.85	0.71	0.85
SD	0.07	0.04	0.06	0.13
Median	0.98	0.85	0.74	0.85
Minimum	0.93	0.76	0.51	0.51
Maximum	1.25	0.94	0.80	1.25

The age of postmenopausal women with normal bone density was on average 54.10 ±3.90 years (age range from 44 to 62). In the group of examinees with osteopenia (group II) the mean age was 56.63±4.76 years (age range from 44 to 65). Mean age of the group of postmenopausal women with osteoporosis was 60.14±3.55 years (age range from 50 to 65). Variance analysis (ANOVA) and post hoc Dunnett's test showed that age differences between all examined groups were statistically significant (p<0.001) (Table 2).

Table 2. Age of the examinees presented by groups

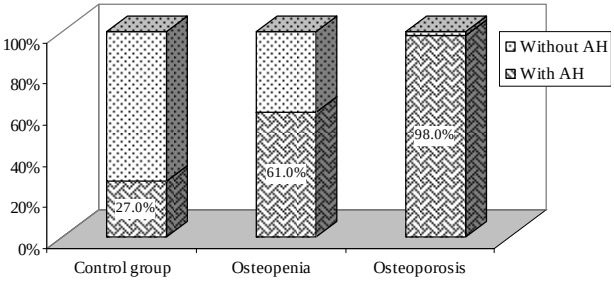
Parameter	Group			Total
	Control	Osteopenia	Osteoporosis	
Xsr	54.10	56.63	60.14	56.96
SD	3.90	4.76	3.55	4.78
Median	54.00	57.50	60.00	58.00
Minimum	44.00	44.00	50.00	44.00
Maximum	62.00	65.00	65.00	65.00

Postmenopausal period in the control group was on average 4.64±3.36 years, in the group with osteopenia 9.11±4.92 and in the group with osteoporosis 14.68±5.64 years. Differences in postmenopausal period duration between all examined groups were highly statistically significant (ANOVA and post hoc test :p<0.0001) (Table 3).

Table 3. Duration of postmenopausal period presented by groups (years)

Parameter	Group			Total
	Control	Osteopenia	Osteoporosis	
Xsr	4.64	9.11	14.68	9.48
SD	3.36	4.92	5.64	6.26
Median	4.00	8.00	14.00	9.00
Minimum	1.00	1.00	4.00	1.00
Maximum	15.00	21.00	38.00	38.00

In the control group hypertension was found in 27(27.0%) examinees, in the group with osteopenia in 61(61.0%) examinees, and in the group with osteoporosis in 98 (98.0%) examinees. Chi-square test confirmed that the differences in the distribution of HTA among all examined groups were statistically significant (p<0.001) (Graph 1).

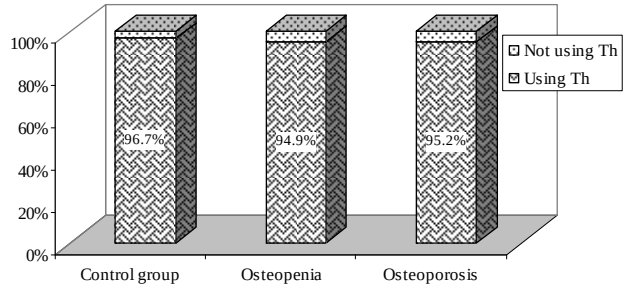


Graph 1. Distribution examinees by groups in respect to distribution of hypertension

Duration of hypertension in the control group was on average 3.19±2.30 years, in the group with osteopenia 4.54±2.89 years, and in the group with osteoporosis 9.37±5.61 years. Differences in hypertension duration between all examined groups were highly statistically significant (ANOVA and post hoc test:p<0.001) (Table 4).

Table 4. Duration of hypertension presented by groups (years)

Parameter	Group			Total
	Control	Osteopenia	Osteoporosis	
Xsr	3.19	4.54	9.73	7.08
SD	2.30	2.89	5.61	5.29
Median	2.00	5.00	10.00	5.00
Minimum	0.00	0.00	0.00	0.00
Maximum	10.00	10.00	30.00	30.00



Graph 2. Distribution of examinees by groups in respect to antihypertensive drugs

In the control group of examinees with HTA, 25 (96.7%) of them was on antihype-

rtensive therapy; 59 (94.9%) examinees in the group with osteopenia; 93 (95.2%) in the group with osteoporosis. Differences among these values were not statistically significant (Graph 2).

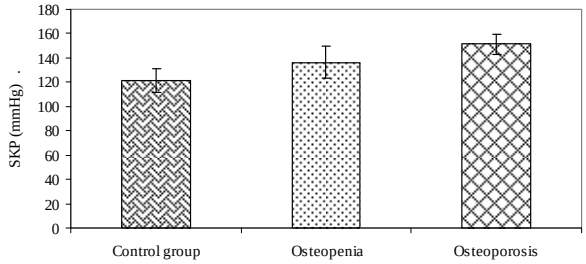
The average value of SBP in the control group was 121.30±9.81 mmHg, in the group with osteopenia 136.40±13.37 mmHg, and in the group of postmenopausal women with osteoporosis it was 151.20±8.68 mmHg. Between all these values there were highly statistically significant differences (ANOVA) and post hoc test: $p<0.0001$.

High values of SBP were obtained in the control group in 9 (9.0%) examinees; in the group with osteopenia in 66 (66.0%) examinees; in the group with osteoporosis in 99 examinees (99.0%). Chi square test confirmed that the differences between all statistically examined groups in the distribution of elevated SBP were highly statistically significant ($p<0.001$),(Table 5).

Table 5. Distribution of examinees by groups in respect to the value of SBP

Altitude of SBP	Group			Total
	Control	Osteopenia	Osteoporosis	
As far as 140 mmHg	91 91.0%	34 34.0%	1 1.0%	126 (42.0%)
Over 140 mmHg	9 9.0%	66 66.0%	99 99.0%	174 (58.0%)

The value of DBP among the patients with normal bone density was on average 76.00±5.50 mmHg, in the group with osteopenia 80.90±6.74 mmHg, and in the group with osteoporosis 89,00±6.74 mmHg. Differences among these values were highly statistically significant (ANOVA and post hoc test :$p<0.001$) (Graph 3)



Graph 3. Values of DBP in examinees by groups (mmHg)

Univariant linear regression analysis showed that each year of life, menopause duration and hypertension had a significant influence on the decrease in bone density among patients in the following way: each year of life by 0.012 g/cm²; each year of menopause duration by 0.012 g/cm²; each year of hypertension by 0.014 g/cm².The increase in the values of SBP and DBP for one unit caused a significant decrease in bone density by 0.005 g/cm²(0.005 to 0.006 g/cm²), in DBP by 0.008 g/cm²(0.007 to 0.010 g/cm²). Patients with hypertension had reduced bone density by 0.0138 g/cm² (0.111 to 0.0164 g/cm²) (Table 7).

In the control group, elevated DBP was found in 3 (3.0%) examinees; in the group with osteopenia among 21 (21.0%) examinees; and in the group with osteoporosis among 75 (75.0%) examinees. Differences between these groups in the distribution of DBP were statistically significant (χ^2 test and Fishers test: $p<0.001$) (Table 6)

Table 6. Distribution of examinees by groups in respect to the value of DBP

Value of SBP	Group			Total
	Control	Osteopenia	Osteoporosis	
Up to 90 mmHg	97 (97.0%)	79 (79.0%)	25 (25.0%)	201 (67.0%)
Over 90 mmHg	3 (3.0%)	21 (21.0%)	75 (75.0%)	99 (33.0%)

Table 7. The influence of age, menopause and hypertension on bone density; results of univariant linear regression analysis

Factor	B	t	p	borders 95% IP for B	
				lower	upper
Age	-0.012	8.28	<0.001	-0.015	-0.009
Duration of menopause	-0.012	12.56	<0.001	-0.014	-0.010
HTA	-0.138	10.18	<0.001	-0.164	-0.111
Duration of HTA	-0.014	12.52	<0.001	-0.017	-0.012
SBP	-0.005	15.16	<0.001	-0.006	-0.005
DBP	-0.008	11.32	<0.001	-0.010	-0.007

Univariant linear regression analysis showed that each year of life, menopause duration and hypertension had a significant influence on the risk of osteopenia and osteoporosis in the manner that each year of life the decrease was by 25% (17 to 33%); each year of a menopause duration by 42% (30 to 54%), each year of hypertension by 62% (41 to 86), DBP by 20% (14 to 25 %).

Discussion

Hypertension and osteoporosis are two mass noninfectious diseases the incidence of which increases with aging, smoking and physical inactivity.

The basic mechanism of association between hypertension and osteoporosis has not been clarified yet.

The latest researches have shown that renin-angiotensin system (RAS) plays a main role in the blood pressure control and has an influence on the bone density. Researches of Asaba J. et al. on transgenic RAS mice have pointed to the role of angiotensin II in the occurrence of osteoporosis. Angiotensim II act on cytokines RANKL and vascular endothelial growth factor (VEGF), thereby stimulating the formation of osteoclasts, and also decreasing in bone density. Their conclusion is that the application of drugs that inhibit synthesis of angiotensin II may be more effective in the treatment of hypertension end osteoporosis (13).

It is well-known that high blood pressure is associated with calcium metabolism disorder witch affects increased secretion of calcium through urine depending on the intake of Na; secondary increase of parathyroid hormone activity has been confirmed as well (14).

Perez - Castrillon et al. have shown that women with hypertension and osteoporosis have increased values of body mass index, calciuria

and Ca/cretinine ratio compared to women without osteoporosis (15).

Among the examinees, osteoporosis was more frequently documented in older women compared to examinees with normal bone density p< 0.001 (Table 2). Prolonged postmenopausal period was more frequently found in examinees with osteoporosis compared to women with normal bone density and osteopenia; statistical significance was p<0.001.

Numerous studies have shown that female sex, advanced age and early menopause are fundamental and invariable risk factors affecting development of osteoporosis (16).

Age is also a very important risk factor for hypertension development. The Framinghamsk study involved 1289 women and men aged between 55 and 65 years .The study showed that in the next 22 years 90% of examinees would be suffering from hypertension (17).

Among our examinees with osteoporosis, the distribution of hypertension was significantly higher (p<0.001) than in women with normal bone density (Graph 1).

There was statistically significant association between duration of arterial hypertension and prevalence of osteoporosis, p<0.001 (Table 4). The examinees suffering from osteoporosis had higher values of systolic and diastolic blood pressure than women with normal bone density, with statistical significance of p<0.001 for systolic blood pressure, and p<0.001 for diastolic blood pressure, though the values of diastolic blood pressure were within the range of prehypertensive values (Tables 5 and 6, Graph 3).

A univariant linear regression analysis has shown that each year of life, menopause duration and hypertension significantly affected the fall in bone density among patients: each year of life by 0.012 g/cm²(0.009 to 0.015 g/cm²), each year of menopause duration by 0.012 g/cm²(0.010 to 0.014), each year of hypertension by 0.014 g/cm² (0.012 to 0.017). The increase in the values of SBP and DBP by one measuring unit caused a significant fall in bone density: SBP by 0.005 g/cm² (0.005 to 0.006 g/cm²), DBP by 0.008 g/cm² (0.007 to 0.010 g/cm²). Patients with hypertension had reduced bone density by 0.0138 g/cm² (0.111 to 0.0164 g/cm²) (Table 7).

The study of F.Cappucino et al. conducted in 1999 involving 3676 women older than 65 showed the association between systolic and diastolic blood pressure and osteoporosis. The study also showed that annual decrease in femoral neck bone density was 2.26 mg/cm²in the group with the lowest blood pressure values, and 3.79 mg/cm²in the group with the highest blood pressure values, which corresponds to the average annual change in bone density of 0.34% and 0.59% (18).

The Third National Health and Nutrition Examination Survey (NIHANES) involved 2739 postmenopausal women aged between 50 and 74 years. The obtained results did not show the association between the values of systolic and diastolic blood pressures on the one hand and bone density on the other. The aforesaid survey could not be taken as a referent one to be compared with our investigation, as it involved different race groups (Afro Americans, whites, and Latin Americans). Numerous studies have shown that white women have high independent risk for osteoporosis (19).

Conclusion

Osteoporosis and hypertension are two mass noninfectious diseases, the incidence of which increases with aging. Early menopause, lack of estrogen, age, smoking and physical inactivity pose significant risk factors, which stresses the necessity of preventive strategy for timely detection and treatment of these diseases.

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HIPERTENZIJA I OSTEOPOROZA KOD ŽENA U POSTMENOPAUZI

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Hipertenzija (HTA) je često hronično kardiovaskularno oboljenje sa prevalencom 20-40%. Prevalenca kod žena je niža nego kod muškaraca. Osteoporoza se karakteriše smanjenom koštanom masom i oštećenjem mikroarhitekture koštanog tkiva. Koštanu snagu determinišu dve osnovne karakteristike: mineralna gustina kostiju (BMD) i kvalitet kosti.

Cilj ove studije bio je ispitivanje postojanja veze između hipertenzije i osteoporoze kod žena u postmenopauzi.

Metod rada: Denzitometrijski je analizirano 300 žena u postmenopauzi, koje nisu preživele veliki kardiovaskularni događaj i nemaju klinički manifestnu aterosklerozu. Pored anamnestičkih podataka analizirani su: telesna masa, telesna visina, obim struka; krvni pritisak, holesterol, trigliceridi, HDL, LDL, glikemija, Ca i P u serumu i Ca u urinu; izračunavan je desetogodišnji rizik od fatalnog kardiovaskularnog događaja po SCORE sistemu; osteodenzitometrija na aparatu Hologic Discovery QDR-C, a rezultati su prikazivani kao T scor na lumbalnom delu kičmenog stuba i levom kuku. Ispitanice su podeljene na osnovu izmerene koštane gustine u tri grupe: grupa sa osteoporozom (100 bolesnica), grupa sa osteopenijom (100 bolesnica), kontrolna grupa sa normalnom koštanom gustinom (100 bolesnica).

Starost ispitanica u postmenopauzalnom periodu u kontrolnoj grupi iznosila je 54.10±3.90 godina, u grupi ispitanica sa osteopenijom 56.63±4.76 a kod žena u postmenopauzi sa osteoporozom 60.14±3.55 godina. Analiza varijanse i post hoc Dunnett-ov test pokazuju da su razlike u starosti između svih ispitivanih grupa statistički značajne ($p<0.001$). U kontrolnoj grupi je HTA bila ispoljena kod 27 (27.0%) ispitanica, u grupi sa osteopenijom kod 61 (61.0%), a u grupi sa osteoporozom kod 98 (98.0%)

ispitanica. Razlike u zastupljenosti HTA između svih ispitivanih grupa statistički su značajne ($p<0.001$). Prosečna visina sistolnog krvnog pritiska (SKP) je u kontrolnoj grupi iznosila 121.30±9.81 mmHg, u grupi sa osteopenijom 136.40±13.37 mmHg, a kod žena sa osteoporozom 151.20±8.68 mmHg i između svih ovih grupa razlike su značajne ($p<0.001$). Visina izmerenog dijastolnog krvnog pritiska (DKP) kod ispitanica sa normalnom koštanom gustinom u proseku je iznosila 76.00±5.50 mmHg, u grupi sa osteopenijom 80.90±8.05 mmHg, a kod žena sa osteoporozom 89.00±6.74mmHg i razlike između svih ovih vrednosti su značajne ($p<0.001$).

Univarijantna linearna regresiona analiza je pokazala da su svaka godina starosti, trajanja menopauze, HTA značajno uticale na pad koštane gustine kod ispitanica i to: starosti za 0.012 g/cm^2 (0.009-0.015 g/cm^2), menopauze takođe za 0.012 g/cm^2 (0.010-0.014 g/cm^2), HTA za 0.014 g/cm^2 (0.012-0.017 g/cm^2). Povećanje vrednosti SKP, DKP, za jednu mernu jedinicu uzrokovali su značajan pad koštane gustine: SKP za 0.005 g/cm^2 (0.005- 0.006 g/cm^2), DKP za 0.008 g/cm^2 (0.007-0.010 g/cm^2). Ispitanice sa HTA imale su umanjenu koštanu gustinu za 0.138 g/cm^2 (0.111 do 0.164 g/cm^2).

Osteoporoza i hipertenzija su masovne nezarazne bolesti i incidenca im se povećava sa starenjem populacije. Rana menopauza i deficit estrogena, životno doba, pušenje i fizička neaktivnost predstavljaju značajne faktore za obe bolesti, što nameće pitanje preventivne strategije za pravovremeno otkrivanje i lečenje ovih bolesti. *Acta Medica Medianae 2009;48(2):8-13.*

***Ključne reči**: hipertenzija, osteoporoza, postmenopauza*