

POSTMENOPAUSAL BONE HEALTH MAY BE INFLUENCED BY THE PRESENCE OF ARTERIAL HYPERTENSION AND ANTIHYPERTENSIVE THERAPY

Radina Dimitrova, Kiril Hristozov, Mila Boyadzhieva

*Second Department of Internal Diseases, Faculty of Medicine,
Medical University of Varna*

*Clinic of Endocrinology and Metabolic Diseases, St. Marina University Hospital,
Medical University of Varna*

ABSTRACT

INTRODUCTION: Despite available evidence for a link between bone health and arterial hypertension (AH), the results of clinical trials remain conflicting. Thus, we conducted a cross-sectional study to analyze a possible association between blood pressure (BP), antihypertensive therapy and deteriorating bone health in postmenopausal women.

MATERIALS AND METHODS: The study included 84 women from Northeastern Bulgaria. Their mean age was 60.54 ± 7.07 years, and their mean duration of menopause was 11.45 ± 6.62 years. Bone health was assessed by dual-energy X-ray absorptiometry (DEXA) and by analysis of bone metabolic markers.

RESULTS: A significant negative correlation was established between bone mineral density (BMD) and diastolic BP. On the other hand, AH predominated in the studied population. However, among the subjects diagnosed with osteopenia and osteoporosis, a significantly higher proportion of AH was observed. In addition, differences were found according to the stage of AH and according to the intake of antihypertensive therapy, when assessing BMD and fracture risk. In subjects with newly diagnosed and respectively untreated AH as well as in the group of stage III AH, the lowest BMD and the highest fracture risk were found. Although we reported a significant difference in the mean age of women according to the presence of AH and its stages, after further analysis it was found that the presence of AH is an independent risk factor for bone health in postmenopausal women (OR=2.14 (0.686–6.703); $p=0.015$).

CONCLUSION: According to the obtained results, we assumed that AH was risk factor for bone health in postmenopausal women, as it was associated with lower BMD and higher fracture risk. In addition, we found differences according to the stage of AH and antihypertensive therapy, which might be considered in the prevention, prophylaxis and treatment of osteoporosis.

Keywords: *arterial hypertension, menopause, osteoporosis, fractures*

Address for correspondence:

Radina Dimitrova
Clinic of Endocrinology and Metabolic Diseases
St. Marina University Hospital
1 Hristo Smirnenski Blvd
9010 Varna
e-mail: dr.rsd1985@gmail.com

Received: October 7, 2021

Accepted: October 19, 2021

INTRODUCTION

It is known that the incidence of both arterial hypertension (AH) and osteoporosis increases with age. A number of researchers have suggested that the two diseases share certain similarities in etiology and pathogenesis, but the results of clinical observations on the relationship between bone health and blood pressure (BP) remain conflicting. Some studies have

found a negative correlation between AH and bone health (1,2,3,4). Much of the collected data suggest that AH could be a factor leading to a decrease in bone density and an increase in fracture risk (1,3). On the other hand, a study from Canada, conducted among a large group of men and women, found that AH was associated with an increase in bone mass and a decrease in the number of vertebral deformities. The effect is maintained after adjustment for age, weight, use of estrogens and thiazides (5). However, the results of other studies suggest that there is no correlation between AH and bone density (6,7). Javed et al., for example, in their retrospective study found that in patients with and without AH, the proportion of subjects with both osteopenia and osteoporosis was similar (6). Hijazi et al. also did not establish a link between osteoporosis and AH in postmenopausal women (7).

The presence conflicting data in the literature on the relationship between bone health and AH may be related to differences in the degree and stage of AH among the studied populations, as well as to the control of BP. It should be noted that not all studies clearly report whether subjects were receiving antihypertensive therapy. However, antihypertensive drugs, which have specific effects on various target organs, could also affect bone health. For example, thiazide diuretics, beta blockers (BBs), nitrates, and spironolactone are considered to have beneficial effects on bone (7,8). It has been suggested also that angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARBs) might be useful in patients with AH and impaired bone health, although there is different data on their effects on calcium-phosphorus metabolism and bone mass (8). Data on Ca-antagonists and bone health are limited and inconclusive, but it appears unlikely that these drugs have any clinically significant effect on bone (8). On the other hand, it is accepted that loop diuretics have a negative effect on bone integrity and are associated with an increased risk of fractures (8).

AIM

The aim of the study was to establish a possible association between BP, antihypertensive therapy and bone health in postmenopausal women.

MATERIALS AND METHODS

The study analyzed 84 women from North-eastern Bulgaria. Inclusion criteria: postmenopausal women with a missing menstrual cycle of ≥ 1 year. Exclusion criteria: 1. iatrogenic and premature menopause (< 40 years); 2. current or past use of drugs that affect bone metabolism (hormone therapy, corticosteroids, anticonvulsants, drugs for the treatment of osteoporosis); 3. malignancy; 4. acute and chronic inflammation; 5. thyroid and parathyroid dysfunction; 6. limited physical activity (immobilization, paralysis) 7. liver and/or kidney disease; 8. known diabetes mellitus.

After signing an informed consent, the participants underwent a structured medical interview and thorough medical examination. Systolic and diastolic BP measurements were taken with a calibrated sphygmomanometer on the dominant arm when the patients were in sitting position, 10 minutes after rest. The mean values of three measurements performed at an interval of 5 minutes were used for analysis.

Arterial hypertension was defined as systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg or a history of antihypertensive therapy. In the present study, these values are accepted in view of the categories of BP according to the 2017 ACC/ANA recommendations, where values of systolic BP 130–139 mmHg or diastolic BP 80–89 mmHg are classified as stage I AH (9). On the other hand, according to the 2018 ESC/ESH recommendations, BP values of systolic BP 130–139 mmHg and/or diastolic BP 85–89 mmHg are defined as high normal BP, but in some of the cases antihypertensive therapy may be considered (10). However, we took into account that BP has not been monitored to confirm AH in individuals with newly diagnosed AH. On the other hand, some of the subjects with newly diagnosed AH fell into the category of high normal BP according to the recommendations of 2018 ESC/ESH. In this regard, in subsequent analyses, we performed additional calculations after separating the group with newly diagnosed AH from patients with known AH. Depending on the presence and the degree of damage to the target organs, according to the WHO classification, the participants with AH were divided into 3 groups: Stage I AH—without organ damage; Stage II

AH—mild organ damage; Stage III AH—severe organ damage.

The measurement of BMD and T score at the level of lumbar spine and proximal femur by dual-energy X-ray absorptiometry (DEXA) was performed with a LUNAR PRODIGY BX-1L (GE MEDICAL, MEDISON, WI, USA). Blood samples for analysis of bone metabolic markers were taken in the morning in fasting state. The bone formation marker osteocalcin was determined by chemiluminescent immunoassay (Immulite 2000). The bone resorption marker Beta-crossLaps was determined by electrochemiluminescent immunoassay (Cabas 6000). The bone resorption marker Pyrilinks-D was determined by enzymatic chemiluminescent immunoassay (Immulite 2000). The method determines the amount of deoxypyridinoline in the urine. The results are presented as the ratio of Pyrilinks-D and creatinine in the first portion of morning urine. The 10-year probability of hip fractures (HF) and the 10-year probability of major osteoporotic fractures (MOF) were determined using the Fracture Risk Assessment Tool (FRAX). The fracture risk calculation was performed according to a formula for the Caucasian race using a femoral neck BMD (g/cm^2) (www.sheffield.ac.uk/FRAX/tool.aspx?country=9).

Statistical analysis

Data were processed with SPSS v.20.0 for Windows by performing dispersion analysis (ANOVA); variation analysis; correlation analysis (Pearson's R; Spearman correlation); risk assessment (OR) analysis; comparative analysis (hypothesis evaluation)— χ^2 , t-test. For all performed analyses, the statistical significance was set as $p < 0.05$ with a confidence interval of 95%.

RESULTS

The mean age of participants was 60.54 ± 7.07 (46–75) years, and the mean time from the onset of menopause was 11.45 ± 6.62 (1–24) years. After the results of DEXA, the patients were divided into three groups according to the lowest BMD at the lumbar spine, the mean value from total neck and/or femoral neck: healthy controls with T-score ± 1 SD; osteopenia with T-score from -1.1 to -2.5 SD; osteoporosis with T-score ≤ -2.5 SD (Fig. 1).

There was a significant difference in age (healthy controls 56.6 ± 6.58 y, osteopenia 60.21 ± 6.19

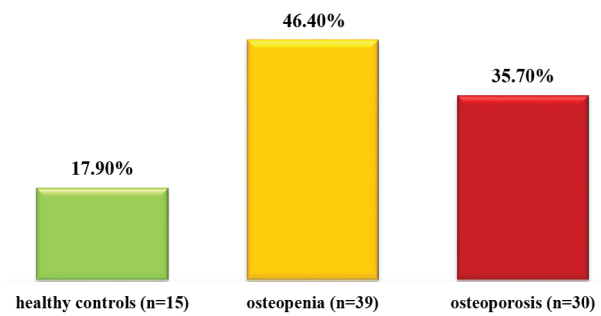


Fig. 1. Distribution of the subjects according to T-score

y, osteoporosis 62.93 ± 7.59 y; $p = 0.015$) and the duration of menopause (healthy controls 7.56 ± 4.79 y, osteopenia 9.92 ± 5.72 y, osteoporosis 15.03 ± 6.99 y, $p < 0.001$) between the three groups, but no significant difference was found in terms of smoking and alcohol consumption. The results of the subsequent analysis showed a strong proportional relationship ($r = 0.836$; $p < 0.001$) between age and duration of menopause in the studied groups. As a threshold value of the age above which the risk of osteoporosis increases, we defined 62.5 years ($\text{AUC} = 0.647$ (0.518–0.775); $p = 0.027$) with a sensitivity of 56.7% and a specificity of 70.4%. As a threshold value for the duration of menopause, above which the risk of osteoporosis increases, we defined 12.5 years ($\text{AUC} = 0.738$ (0.616–0.860); $p < 0.001$) with sensitivity of 63.3% and specificity of 72.2%. From the analysis we can say that 70% of the changes in bone density are due to the long duration of menopause and the advanced age of the patients.

Nevertheless, a negative correlation was found in the whole group between diastolic BP and BMD at the level of lumbar spine and femoral neck (respectively T-score L1-L4 $r = -0.311$, $p = 0.004$; BMD L1-L4 $r = -0.284$, $p = 0.009$; T-score neck $r = -0.219$, $p = 0.045$; BMD neck $r = -0.232$, $p = 0.034$). This relationship was maintained after considering age (respectively T-score L1-L4 $r = -0.307$, $p = 0.005$; BMD L1-L4 $r = -0.280$, $p = 0.01$; T-score neck $r = -0.213$, $p = 0.05$; BMD neck $r = -0.226$, $p = 0.04$), body mass index (BMI) (respectively T-score L1-L4 $r = -0.303$, $p = 0.005$; BMD L1-L4 $r = -0.275$; $p = 0.012$; T-score neck $r = -0.208$, $p = 0.05$; BMD neck $r = -0.221$, $p = 0.04$) and waist circumference (respectively T-score L1-L4 $r = -0.302$, $p = 0.005$; BMD L1-L4 $r = -0.224$, $p = 0.012$; T-score neck $r = -0.206$, $p = 0.06$; BMD neck $r = -0.220$, $p = 0.046$). The negative correla-

tion between diastolic BP and BMD remained significant, but only at the level of lumbar spine after considering the duration of menopause (T-score L1-L4 $r=-0.276$, $p=0.012$; BMD L1-L4 $r=-0.245$, $p=0.026$) and body weight (respectively T-score L1-L4 $r=-0.280$, $p=0.01$; BMD L1-L4 $r=-0.250$, $p=0.023$).

Subsequent analysis of BP values and the presence of AH revealed that patients with AH predominated. Women with known AH, who received antihypertensive therapy, were 61% of the total cases. They were with optimal BP levels (mean systolic BP 126 ± 12 mmHg; mean diastolic BP 77 ± 7 mmHg). Women with newly diagnosed and respectively untreated AH were 8% of the cases and were classified as stage I AH. Their mean systolic (136 ± 8 mmHg) and diastolic BP (8 ± 6 mmHg) were significantly higher compared to the patients with known AH (respectively $p=0.039$ and $p<0.001$). In addition, a positive correlation was found between age ($r=0.395$; $p<0.001$) and duration of menopause ($r=0.249$; $p=0.022$) with the stages of AH. However, a significant increase was found in the age of women according to the presence of AH and its stages (from 57.76 ± 6.57 y in subjects without AH to 67.6 ± 4.25 y in the group of stage III AH, $p=0.001$), but the trend to increase the duration of menopause according to the presence of AH and its stages did not reach statistical significance ($p=0.06$).

Although AH predominated in the studied population, in subjects with changes in bone density (osteopenia and osteoporosis) a significantly higher proportion of women with AH was observed (Fig. 2). When performing additional analyses, it was found that the presence of AH was an independent risk factor for bone health in postmenopausal women (OR=2.14 (0.686–6.703); $p=0.015$). Because there was a significant difference in age between patients with and without AH (61.76 ± 6.99 y vs. 57.76 ± 6.57 y; $p=0.015$, respectively), and in the groups—according to BMD, we suggested that the established negative impact of AH on bone health could be age-modulated. This was confirmed by the calculated higher cumulative risk to bone health after considering the age (OR=5.66 (0.839–6.462); $p=0.017$).

The analysis of the mean values of T-score and BMD according to the stage of AH revealed several differences, although not significant. In women

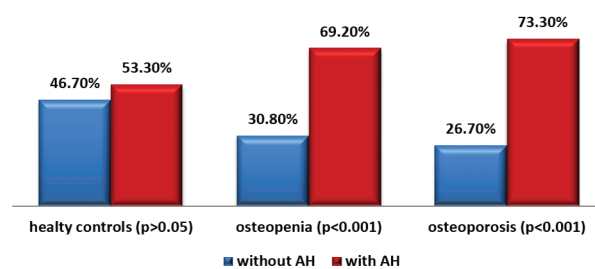


Fig. 2. Distribution of arterial hypertension by groups

with stage III AH the lowest bone indices were observed at the level of L1-L4 (T-score -1.46 ± 1.50 SD; BMD 1.00 ± 0.18 g/cm² for L1-L4), femoral neck (T-score -1.77 ± 1.11 SD; BMD 0.78 ± 0.15 g/cm²) and total neck (T-score -1.20 ± 1.16 SD; BMD 0.85 ± 0.15 g/cm²). These results could be associated with a negative impact on the bone of the target organ damage, as well as the older age of patients in this group. The established better parameters in stage II AH in the femoral region (femoral neck T-score -1.42 ± 0.83 SD, BMD 0.85 ± 0.12 g/cm²; total neck T-score -0.61 ± 1.00 SD, BMD 0.93 ± 0.13 g/cm²) compared to subjects without AH (femoral neck T-score -1.60 ± 0.68 SD, BMD 0.82 ± 0.09 g/cm²; total neck T-score -0.95 ± 0.81 SD, BMD 0.89 ± 0.10 g/cm²) and compared to subjects with stage I AH (femoral neck T-score -1.55 ± 0.78 SD, BMD 0.82 ± 0.11 g/cm²; total neck T-score -0.77 ± 1.03 SD, BMD 0.91 ± 0.13 g/cm²) suggested the presence of a protective effect in the group of stage II AH. Therefore, we hypothesized that the use of antihypertensive drugs could explain the observed differences, as women without AH and individuals with newly diagnosed AH, who are in the group of stage I AH, did not receive antihypertensive therapy.

The potential pleotropic effect of antihypertensive drugs on bone was supported by the established mean values of T-score and BMD after separation of women with newly diagnosed (respectively untreated) AH. After recalculations in subjects with treated stage I AH the best values of BMD were reported (L1-L4 T-score -0.90 ± 1.05 SD; BMD 1.07 ± 0.12 g/cm²; femoral neck T-score -1.35 ± 0.73 SD; BMD 0.85 ± 0.10 g/cm²; total neck T-score -0.55 ± 1.12 SD; BMD 0.94 ± 0.14 g/cm²). On the other hand, in persons with newly diagnosed AH the lowest BMD was observed (L1-L4 T-score -1.85 ± 1.04 SD, BMD 0.94 ± 0.13 g/cm²; femoral neck T-score -1.96 ± 0.62 SD, BMD 0.76 ± 0.09 g/cm²; total neck T-score -1.05 ± 0.78

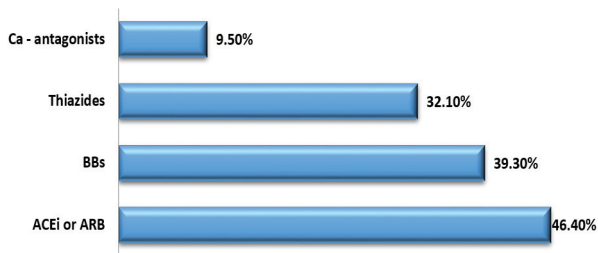


Fig 3. Distribution according to the intake of antihypertensive drugs

SD, BMD 1.01 ± 0.10 g/cm²). These results are comparable with the established parameters in stage III AH. Additionally, we found a significant difference

in the duration of menopause between women with newly diagnosed AH and subjects with treated stage I A (14.14 ± 6.09 y vs. 8.18 ± 5.56 y, $p=0.048$) in the absence of a significant difference in age (60.43 ± 6.65 y vs. 58.27 ± 5.33 y, $p>0.05$). On the other hand, significant difference in age was observed between the subjects with newly diagnosed AH and women with stage III AH (60.43 ± 6.65 y vs. 67.6 ± 4.25 y, $p=0.016$) in the absence of significant difference in the duration of menopause (14.14 ± 6.09 y vs. 14.9 ± 5.36 y, $p>0.05$). These results suggest that untreated AH is associated with worsening BMD parameters, especially in older women and in those with longer duration of menopause.

Table 1. Mean value of T-score and BMD according to the intake of some antihypertensive drugs in the studied groups

		Healthy Controls			Osteopenia			Osteoporosis		
		L1-L4	Neck	Total	L1-L4	Neck	Total	L1-L4	Neck	Total
T-score (\pm SD)										
ACEi or ARB	Without	0.21	-0.64	0.04	-1.08	-1.67	-0.89	-2.30	-2.01	-1.25
	With	0.15	-0.38	0.45	-0.72	-1.41	-0.64	-2.42	-2.08	-1.49
	P	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Thiazides	Without	0.19	-0.54	0.21	-1.02	-1.63	-0.89	-2.18	-1.93	-1.26
	With	0.16	-0.44	0.36	-0.73	-1.42	-0.55	-2.72	-2.28	-1.60
	P	> 0.05	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
BBs	Without	0.02	-0.44	0.31	-1.13	-1.70	-0.96	-2.40	-2.10	-1.47
	With	0.42	-0.60	0.18	-0.65	-1.36	-0.54	-2.29	-1.94	-1.19
	P	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Ca-antagonists	Without	0.16	-0.58	0.18	-0.97	-1.59	-0.82	-2.35	-2.08	-1.42
	With	0.18	-0.51	1.40	-0.60	-1.30	-0.47	-2.47	-1.70	-1.37
	P	> 0.05	< 0.05	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
BMD (g/cm ²)										
ACEi or ARB	Without	1.21	0.95	1.01	1.05	0.81	0.89	0.88	0.76	0.85
	With	1.19	0.98	1.06	1.09	0.84	0.93	0.89	0.77	0.82
	P	> 0.05	> 0.05	< 0.05	< 0.05	> 0.05	< 0.05	> 0.05	> 0.05	> 0.05
Thiazides	Without	1.20	0.96	1.03	1.06	0.81	0.89	0.90	0.77	0.85
	With	1.19	0.97	1.05	1.09	0.83	0.93	0.85	0.76	0.81
	P	> 0.05	> 0.05	> 0.05	< 0.05	> 0.05	< 0.05	< 0.05	> 0.05	< 0.05
BBs	Without	1.18	0.97	1.05	1.04	0.80	0.88	0.87	0.75	0.82
	With	1.23	0.95	1.03	1.10	0.84	0.94	0.91	0.80	0.86
	P	< 0.05	> 0.05	> 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Ca-antagonists	Without	1.19	0.96	1.04	1.06	0.82	0.90	0.88	0.76	0.83
	With	1.24	1.11	1.19	1.11	0.85	0.95	0.88	0.81	0.89
	P	< 0.05	< 0.05	< 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05	< 0.05

Mean T-score and BMD were further adjusted for antihypertensive therapy (Fig. 3 and Table 1), which included drugs from the groups of thiazide diuretics, ACEi, ARB, BBs and/or Ca-antagonists. Only two patients with osteopenia were receiving a loop diuretic.

Analysis of the data showed better BMD parameters at the level of femoral neck and total neck in healthy controls taking ACEi or ARB. In the group of patients with osteopenia, the intake of these drugs was associated with a higher BMD, both in the femoral region and at the level of the lumbar spine. However, no positive effect was found in the group of patients with osteoporosis. Similar results were observed according to thiazides. On the other hand, BBs intake was positively associated only with lumbar BMD in healthy controls. In patients with osteopenia and osteoporosis, better BMD parameters were observed, both in the femoral region and at the level of lumbar spine. Ca-antagonist intake was positively associated with BMD, both in the femoral region and at the level of lumbar spine in healthy controls and in patients with osteopenia. In patients with osteoporosis, there was a positive association with BMD only at the level of femoral neck and total neck.

Initial analysis showed no difference between the levels of bone metabolic markers and the values of BP, the presence of AH or its stage. This was found after considering the use of antihypertensive drugs in women with osteoporosis (Fig. 4). The results showed that women with osteoporosis taking the discussed antihypertensive drugs had significantly lower levels of osteocalcin ($p < 0.05$). The same trends were maintained for Beta crossLaps and intake of ACEi or ARB, BBs and/or Ca-antagonists, as well as for the ratio of Pyrilinks D/creatinine in urine and intake of ACEi or ARB, thiazide diuretic and/or BBs. However, there was no significant difference ($p > 0.05$) in the levels of

Beta crossLaps according to the intake of thiazide diuretic and in the ratio of Pyrilinks D/creatinine in the urine according to the intake of a Ca-antagonist.

In the analysis of fracture risks, a positive correlation was found between diastolic BP and both the 10-year risk of MOF ($r = 0.252$; $p = 0.021$) and the 10-year risk of HF ($r = 0.282$; $p = 0.009$). This relationship was maintained for the two fracture risks after considering age (respectively $r = 0.272$; $p = 0.013$ for MOF,

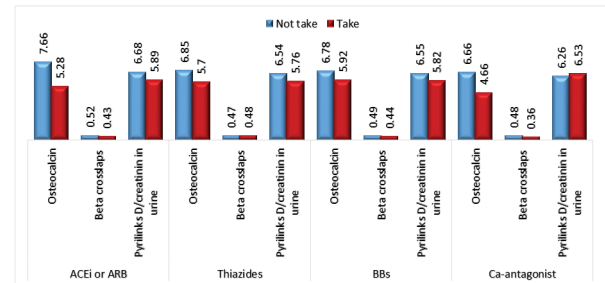


Fig. 4. Comparative analysis of the levels of osteocalcin (ng/mL), Beta crossLaps (ng/mL) and Pyrilinks D/creatinine in urine (nmol/mmol) according to medication intake in women with osteoporosis

and $r = 0.285$; $p = 0.009$ for HF), body weight (respectively $r = 0.224$; $p = 0.042$ for MOF, and $r = 0.251$; $p = 0.022$ for HF), BMI (respectively $r = 0.249$; $p = 0.023$ for MOF and $r = 0.275$; $p = 0.012$ for HF) and waist circumference (respectively $r = 0.245$; $p = 0.025$ for MOF and $r = 0.274$; $p = 0.012$ for HF). After considering the duration of menopause, only the correlation between diastolic BP and HF remained positive ($r = 0.235$; $p = 0.033$).

In addition, a significant difference in fracture risk was found according to the presence of AH and its stage, both in terms of the 10-year risk of MOF and the 10-year risk of HF (Table 2). Recalculation of fracture risks after separation of women with newly diagnosed (respectively untreated) AH

Table 2. Mean values of the 10-year risk of MOF and HF according to AH stages (mean \pm SD)

Fracture risk	Without AH	AH Stages			F	P value
		First	Second	Third		
10-year risk of a major osteoporotic fracture (MOF) (%)	8.45 \pm 3.65	9.58 \pm 4.20	9.34 \pm 4.39	13.70 \pm 7.30	3.39	0.026
10-year risk of hip fracture (HF) (%)	1.23 \pm 0.92	1.66 \pm 2.34	1.58 \pm 1.50	3.29 \pm 3.44	3.22	0.039

revealed the lowest 10-year risk of MOF and HF in subjects with stage I AH and in those without AH (respectively MOF $7.78 \pm 3.28\%$, HF $0.70 \pm 0.78\%$ and MOF $8.45 \pm 3.65\%$, HF $1.23 \pm 0.92\%$, $p > 0.05$), while in women with newly diagnosed AH the fracture risks were comparable to those in stage III AH (respectively MOF $12.4 \pm 4.12\%$, HF $3.16 \pm 3.21\%$ and MOF $13.70 \pm 7.30\%$, HF $3.29 \pm 3.44\%$, $p > 0.05$). No additional relationship between the intake of antihypertensive drugs and fracture risks was established.

DISCUSSION

It is well known that older age and longer duration of menopause are the leading unmodifiable risk factors for the development of osteoporosis in postmenopausal women. According to the present study, changes in bone density were determined in about 70% of these two risk factors. However, our results identified AH as an additional determinant of postmenopausal bone health. Our data are comparable to the results of a number of other clinical studies and meta-analyses (1,3,4,11), but do not overlap with the conclusion of Hanley et al. that AH is associated with an increase in bone mass (5), as well as with the conclusion of Hijazi et al., who did not establish a link between osteoporosis and AH in adult postmenopausal women (7).

The negative correlation found between diastolic BP and BMD, with established positive correlation between diastolic BP and fracture risks, corresponds to the results of Jeon et al. (12), while other authors also report a negative impact of systolic BP on bone health (2). In addition, we found that not only higher diastolic BP but also the presence of AH as well as its stage could be relevant to postmenopausal osteoporosis, as subjects with treated stage I AH presented the best BMD values at the level of lumbar spine, femoral neck and total neck, as well as the lowest fracture risks. On the other hand, in women with newly diagnosed (respectively untreated) AH and in the group of stage III AH, the lowest BMD and the highest fracture risk were reported. These results suggest that untreated AH is associated with worsening BMD parameters, especially in older women and in those with longer duration of menopause. In addition, our data support assertions about the potential pleotropic effects of antihypertensive drugs on bone (7,8). The established better BMD values in

the different skeletal regions in the group of healthy controls and among women with osteopenia taking ACEi/ARB, thiazide diuretic, BBs and/or Ca-antagonists raise the question of the importance of these antihypertensive drugs in prevention and prophylaxis of osteoporosis. On the other hand, the lack of such observations in the group of women with osteoporosis taking ACEi/ARB and/or thiazide diuretics suggests a loss of protective effect in case of osteoporosis or a negative impact of additional factors such as older age, longer duration of menopause or concomitant comorbidities. In addition, we found that the intake of the discussed antihypertensive drugs in the group of osteoporosis was associated with a lower level of bone metabolism.

Based on the obtained results, we assume that the timely inclusion of antihypertensive drugs is essential, as their presumed pleotropic effects on bone probably depend on the duration of their intake and on the initial bone parameters at which antihypertensive treatment was started. We also believe that properly selected and timely initiated antihypertensive therapy could be useful in preventing potential fractures.

LIMITATIONS

Several limitations should be considered in the interpretation of our data. The small sample size might attenuate the strength of the established associations between bone health, AH and the considered antihypertensive drugs. In addition, the duration of AH and the duration of antihypertensive treatment have not been analyzed. On the other hand, we did not evaluate bone microarchitecture, which is an additional determinant of bone strength. Due to the cross-sectional nature of the study, the causal relationship between bone health and BP, AH or antihypertensive treatment cannot be determined.

CONCLUSION

According to the obtained results, we assumed that AH is risk factor for bone health in postmenopausal women, as it is associated with lower BMD and higher fracture risk. In addition, we found differences according to the stage of AH and antihypertensive therapy, which might be considered in the prevention, prophylaxis and treatment of osteoporosis.

Funding: This work was supported by the Science Fund at the Medical University of Varna, Bulgaria (research project № 18017; protocol № 110-1939 / 05.12.2018)

REFERENCES

1. Yang S, Nguyen ND, Center JR, Eisman JA, Nguyen TV. Association between hypertension and fragility fracture: a longitudinal study. *Osteoporos Int*. 2014;25(1):97–103. doi: 10.1007/s00198-013-2457-8.
2. Cappuccio FP, Meilahn E, Zmuda JM, Cauley JA. High blood pressure and bone-mineral loss in elderly white women: a prospective study. *Study of Osteoporotic Fractures Research Group*. *Lancet*. 1999;354(9183):971. doi: 10.1016/s0140-6736(99)01437-3.
3. Li C, Zeng Y, Tao L, Liu S, Ni Z, Huang Q, Wang Q. Meta-analysis of hypertension and osteoporotic fracture risk in women and men. *Osteoporos Int*. 2017;28(8):2309–18. doi: 10.1007/s00198-017-4050-z.
4. Ye Z, Lu H, Liu P. Association between essential hypertension and bone mineral density: a systematic review and meta-analysis. *Oncotarget*. 2017;8(40):68916-27. doi: 10.18632/oncotarget.20325.
5. Hanley DA, Brown JP, Tenenhouse A, Olszynski WP, Ioannidis G, Berger C, et al. Associations among disease conditions, bone mineral density and prevalent vertebral deformities in men and women 50 years of age and older: Cross-sectional results from the Canadian Multicentre Osteoporosis Study. *J Bone Miner Res*. 2003;18(4):784-90. doi: 10.1359/jbmr.2003.18.4.784.
6. Javed F, Khan SA, Ayers EW, Aziz EF, Akram MS, Nadkarni GN, et al. Association of hypertension and bone mineral density in an elderly African American female population. *J Natl Med Assoc*. 2012;104(3-4):172–8. doi: 10.1016/s0027-9684(15)30140-1.
7. Hijazi N, Alourfi Z. Association between hypertension, antihypertensive drugs, and osteoporosis in postmenopausal Syrian women: A cross-sectional study. *Adv Med*. 2020; 2020:7014212. doi: 10.1155/2020/7014212.
8. Ghosh M, Majumdar SR. Antihypertensive medications, bone mineral density, and fractures: a review of old cardiac drugs that provides new insights into osteoporosis. *Endocrine*. 2014; 46(3):397-405. doi: 10.1007/s12020-014-0167-4.
9. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):e13-e115. doi: 10.1161/HYP.0000000000000065.
10. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). *Eur Heart J*. 2018; 39(33):3021–104.
11. Chai H, Ge J, Li L, Li J, Ye Y. Hypertension is associated with osteoporosis: a case-control study in Chinese postmenopausal women. *BMC Musculoskelet Disord*. 2021;22(1):253. doi: 10.1186/s12891-021-04124-9.
12. Jeon YK, Lee JG, Kim SS, Kim BH, Kim SJ, Kim YK, et al. Association between bone mineral density and metabolic syndrome in pre- and postmenopausal women. *Endocr J*. 2011;58(2):87-93. doi: 10.1507/endocrj.k10e-297.