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STUDY OF ARTERIAL HYPERTENSION AND ASSOCIATED RISK FACTORS FOR CARDIOVASCULAR DISEASES IN A LOT OF PATIENTS FROM KOSOVO AREA

Abstract

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Key words: blood pressure, arterial hypertension, cardiovascular diseases, risk factors, organ damage,ecocardiography, ambulatory blood pressure monitoring

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1. INTRODUCTION

Arterial hypertension is the most common risk factor for cardiovascular events, cerebrovascular accidents, end-stage renal disease, sudden death. Population of Kosovo region is classified among populations with increased cardiovascular risk in Europe. For this reason, we decided to study data related to the disease epidemiology and the impact of the disease with the highest prevalence at global level.

2. GENERAL DATA

An important chapter refers to arterial hypertension and associated cardiovascular risk factors (age, weight gain, the value of systolic and diastolic arterial pressure - SBP, DBP, lipid metabolism disorders, renin-angiotensin system, microalbuminuria, diabetes mellitus, metabolic syndrome, assessment of cardiovascular risk and organ damage). Framingham study showed that isolated high values of SBP are associated with high risk for cardiovascular disease (Franklin SS et al, 2012). About 40% of hypertensive people have also

hypercholesterolemia and genetic studies have established an association between arterial hypertension and dyslipidemia (Dalal J. et al, 2012). A certain atherogenic lipoprotein phenotype is highly correlated with endothelial dysfunction and atheromatous lesions (Ginghină C. et al, 2002). Asymptomatic organ damage represents an intermediate stage of the cardiovascular disease. There are four markers of organ injury: microalbuminuria, increased pulse wave velocity, left ventricular hypertrophy (LVH) and carotid intima-media atherosclerotic plaques. Increased pulse pressure may lead to endothelial dysfunction as a consequence of increasing wall shear stress at the level of localized areas of the vascular wall, especially in areas with vascular bifurcation, which are susceptible to the initiation and development of atherosclerotic lesion (Gusti S. et al, 1997; Davies PF, 2009). Global cardiovascular risk increases directly with the numbers of damaged organs (Volpe M., et al, 2012). A second chapter refers to left ventricular hypertrophy (LVH). An increase in cardiomyocytes size was proposed as a criterion *sine qua non* for the definition of LVH (Dorn GW. et al, 2003). Increasing ventricular muscle mass remains the most important compensatory mechanism against hemodynamic overload (Guyton A., Hall E., 2011). According to the European Society of Cardiology Guidelines for the management of arterial hypertension, LVH and in particular concentric LVH is associated with a cardiovascular risk higher than 20% at 10 years (Mancia G. et al, 2013). The third chapter covers left ventricular diastolic dysfunction in arterial hypertension. The main cardiac morphological and functional changes associated with diastolic dysfunction are: concentric geometry of left ventricle, left atrial enlargement and pulmonary arterial hypertension (Galderisi M., 2010). Isolated diastolic dysfunction may cause symptoms of heart failure (HF), diagnosed and assessed by Doppler echocardiography (Galderisi M., 2010). The last chapter of general part refers to vascular remodeling in HTA. Although it is considered that the vascular remodeling is accompanied by increased thickness of the intima, newer studies shows that are two specific forms of vascular remodeling: eutrophic and hypertrophic, depending on increasing or not of media cross-sectional area (Heagerty A.M., et al, 2003). Pathogenesis of vascular remodeling involves pressure dependent factors (Martinez-Lemus L.A. et al, 2004), renin angiotensin system (Sanz-Rosa D. et al, 2005), endothelin, reactive oxygen species (Intengam H D., Sciffrin E.L., 2001), nitric oxid (Marin E., Sessa W.C. 2007). Antihypertensive treatment (calcium antagonists, angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists and nitrates) may influence arteries mechanical properties (Davies P.F., 2009).

3. SPECIAL SECTION- PERSONAL CONTRIBUTION

The purpose of this study is to determine arterial hypertension prevalence in population from Kosovo region, associated cardiovascular risk factors and also to emphasize the role of arterial hypertension as a major independent risk factor, through high value of blood pressure and its consequences (left ventricular hypertrophy, vascular remodelling, endothelial dysfunction, etc).

The main objectives of this study were to establish HTA prevalence in the studied group and associated risk factors; assessment of cardiac remodelling (HVS) and endothelial dysfunction; to determine prevalence of diabetes mellitus and metabolic syndrome in the studied group; evaluation of organ damage (heart, vessels, brain, kidney); to emphasize associated clinical diseases (ischaemic cardiac disease, peripheral arterial disease, stroke, chronic kidney disease, retinal haemorrhages); to elaborate a a strategy of active prevention in clinical practice.

The clinical study was conducted in „Prim Dr. Daut Mustafa" Hospital Prizren-Kosovo and represents a prospective longitudinal observational study on an group of 457 hypertensive subjects selected from an initial group of 2000 patients admitted in internal medicine division, within 3 years, between 2009 - 2012.

In this group were 281 (61%) women and 176(39%) men, a majority of patients were included in group age of 50 -70 years, with a predominance of women and rural environment (77,89% of total patients). Depending of arterial hypertension grading, 66% of total patients were included in a subgroup with hypertension grade 2 and 3 (with values of BP over 160/110 mmHg), majority being women. Depending of personal hypertensive history we found that 167 of patients (36,54%) have over 10 years hypertensive history (70% women), 153 were diagnosed > 5 years and only 2,4% were newly diagnosed HTA. In the group with hypertensive history of 5 - 10 years, the majority were men (41,75 % of total hypertensive men included in the studied group).

Method of study: complete clinical examination (including calcul of body mass index, determination of waist circumference, standard office blood pressure measuring and also 24-h ambulatory BP monitoring), paraclinical examination: laboratory investigations (haemogram, fasting plasma glucose and haemoglobin A_{1c}, serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high - density lipoprotein (HDL) cholesterol, fasting serum triglycerides, serum creatinine and urea, protein C reactive, urine analysis with test for microalbuminuria), imagistic tests (ecg, ecocardiography M mode and Doppler color, fundoscopy, carotid ultrasound).

From the obtained results 124 patients (27%) have declared alcohol intake, mostly men; 225 patients (48%) had smoking habit. The majority of hypertensive patients (253, representing 55,36% of total patients included in the study) had low levels of HDL - cholesterol, a major part of them being smokers. More than a half of hypertensive patients, 255 (55,7%) had hypertriglyceridemia. A percent of 70,45% of men had hypertriglyceridemia, among them many are chronic alcohol consumers. 65,86% of total patients had high serum levels of LDL - cholesterol, of which 182 are women and 119 men. Presence of high LDL cholesterol is positively correlated and highly statistically significant with presence of HTA ($r = 0.2944$, $p < 0.001$). In the examined group, 42 patients presented with diabetes mellitus type 2 (9,19%) with a majority of women. Regarding prevalence of impaired glucose metabolism, we observed that a significant number of patients (34% of total patients) had either abnormal fasting plasma glucose level or altered glucose tolerance. Concerning the presence of obesity, statistical analysis showed that 242 patients had obesity, affecting equally both sexes. Family history for cardiovascular disease at a young age is positively correlated, highly statistically significant with presence of HTA ($r = 0.3983$, $p < 0.001$), and was found at 246 patients (54%).

Regarding age range analysis, 237 patients (52%) presented age as a risk cardiovascular factor, 32% of men included in the study were age > 55 years and a significant percent of women (64,4%) were age ≥ 65 years. Of total hypertensive patients studied, 44% had a high level of hs - CRP, with a preponderance of women and 183 patients (40,04%) were included in metabolic syndrome group with a preponderance of women 146 (31,95%).

For estimating total cardiovascular risk we used SCORE (Systematic COronary Risk Evaluation) model, which estimates cardiovascular death risk within 10 years. We observed that 68,9% of patients have a total cardiovascular risk of death at 10 years, higher than 5%, which includes them in a group of population which require intensifying prevention and treatment strategies. Even more, almost a half 46,6% of total patients have a total cardiovascular risk, based on SCORE ≥ 10%. Statistic data shows that a risk of 10-14% of fatal cardiovascular disease at 10 years is positively correlated with feminine gender ($r = 0.1043$, $p = 0.025$). Stratification of total cardiovascular risk proposed by ESC guidelines showed that the highest percent of patients has an additional high risk associated with HTA (40,91%).

Men predominate among patients with moderate total cardiovascular risk (27.42% of men vs. women 23.13% of hypertension) and among patients classified as having very high additional risk (20% of males vs. 14.2% of hypertensive women). Regarding the number of

risk factors associated with hypertension, other than diabetes mellitus type II, we noticed that 65.2% patients have associated more than two cardiovascular risk factors, most patients (41,1 %) having 2 associated cardiovascular risk factors, followed by patients with ≥ 3 risk factors (24%), predominantly women.

There is a statistically significant correlation between the presence of two risk factors associated with HTA and the presence of hypertensive disease in the studied group (r = 0.1379, p=0.003). For all patients included in the study, diastolic and systolic blood pressure (SBP and DBP) was monitored diurnal and nocturnal with MESA Medizintechnik, a Holter device (ABPM). The histogram of the average daytime values of ABPM systolic blood pressure showed the existence of two peaks: most of the patients had mean value lying around 150 mmHg (35,66%) and respectively around 160 mmHg (33,47%). Regarding the mean values of diastolic blood pressure, 33.47% of the patients had values around 80 mmHg. 35,66 % of patients had average night - time systolic blood pressure values around 150 mm Hg. Night - time DBP values were therapeutically controlled for most of the patients. Peak-average values for night-time diastolic blood pressure is around 80 mm Hg (33.47% of patients). Day/night ratio of the blood pressure values of the established the "dipping" status of patients: 62.58% of them have a dipper type profile, the rest of 37.42% being non - dipper. Remarkably to notice an increasing number of hypertensive men non - dipper (55.68% of total men compared to only 25,97% of women with such profile). At ABPM only 120 patients have therapeutically controlled BP (27%) while for the remaining 337 patients (73%) antihypertensive medication has not controlled BP values; of them 190 were women (56.37%) and 147 men (43,62%). According to the ambulatory blood pressure monitoring follow-up visits, 236 patients (51.64% of all patients) had blood pressure controlled and the remaining 221 patients (48,35%) had uncontrolled blood pressure. We noticed that in between visits the number of uncontrolled patients decreased significantly. In the category of patients with therapeutically uncontrolled BP at visits were 127 women (57,46%) and 97 men (43,89%), while the group with achieved BP target was divided in 154 women (65,25%) and 82 men (34,74%). As the mirror control of blood pressure, ambulatory monitoring has more accuracy.

The most commonly used class of antihypertensive drugs in hypertensive patients was that of beta blockers (43,98% of patients, received a β - blocker). Almost as frequent use were renin-angiotensin - system antagonists (administered at 38.51% of patients). Diuretics are the third class of the most commonly used drugs in the treatment of hypertension (30.2% of the studied patients). Calcium antagonists have been using in 22,75% of the patients while 26,47% of patients did not have any sort of treatment at the time of inclusion into the study.

The most commonly used antihypertensive drugs in the present study were beta-blockers (25.5%) and angiotensin receptor blockers (22,33%). Among studied hypertensive patients, 13.56% had resistant blood pressure, predominantly being women (15.65% of women presented resistant hypertension vs. 10.22% of men). From the data collected has appeared that 136 patients (29.75% of patients) were not adherent to the treatment recommendations and lifestyle changes. Of those, 84 were male (61,7%) and 52 women (8.3%). Of patients non - adherent to treatment 85,69% are smokers, primarily men. There is a positive correlation between male patients, smoking and lack of adhesion to the antihypertensive treatment ($r = 0.4823$, $p < 0.001$). With regard to organ damage in hypertensive patients, we found electrocardiographic LVH in 101 patients (22,10% of the lot).

Echocardiographic left ventricular hypertrophy was found at 192 patients (42%), most frequent in men, accounting for 68% of all men in the lot. Patients with LVH established either based on electrocardiograms or echocardiographic measurements were in total of 219. Of these, 97.7% had grade ≥ 2 hypertension. Prevalent type of left ventricular hypertrophy was concentric hypertrophy in 73 patients (38% of all patients with LVH) and respectively, 59,9% of the total of those with LVH, if we take into account also the patients with asymmetrical LVH. Only 37 patients (19% of all patients with LVH) had eccentric hypertrophy. More than half of the total hypertensive patients with echocardiographic LVH (51%) had age between 51 - 70 years. Of patients with LVH, 97.7% had grade ≥ 2 hypertension.

Comparing the total number of patients with gender analysis number we noticed that among the patients with grade 2 hypertension and associated LVH, men are more numerous (26.8% of total men with grade 2 hypertension and left ventricular hypertrophy). In hypertensive patients, 55.79% of them had a form of coronary heart disease (CHD). From total subjects diagnosed with CHD, 32.16% were women and 23.63% men. However, reporting the number of women with CHD to the total number of enrolled women and respectively men with CHD at men in total, we noted that coronary heart disease is more common among hypertensive men (61.71% of men have ischemic heart disease vs. just 52,31% of women with cardiac ischemia). Of the total of patients with CHD (255 patients) in the studied group, 187 (73.3%) have experienced acute coronary events (in medical history or during follow - up period in this study).

Of these, the majority (61%) had unstable angina, 23% have had non elevated ST myocardial infarction (NSTEMI) and 16% had ST elevation myocardial infarction (STEMI). We noted that more than half (54%) of patients with CHD had elevated blood pressure values ≥ 180

mmHg/110 (grade 3 hypertension). The presence of CHD is correlated statistically significant ($r = 0.3659$, $p < 0.001$) with the hypertension severity (more specifically with grade 3). A number of 283 patients (62% of all hypertensive patients) were diagnosed with heart failure, prevalent being women (184-65% of those with HF). Echocardiographically assessment revealed that 60,4% had heart failure with preserved ejection fraction (EF) and only 39.6% associated systolic dysfunction ($EF \leq 45\%$). In our group of hypertensive patients, atrial fibrillation (AF) was present at 141 patients, representing 31% of the studied group. From this group 85 were women (60%) and 56 men (40%). Although there is this percentage difference, reporting the presence of AF in men-women at total number of men-women we noted the presence of FA almost equal in both sexes: men (32%), women (30%). Left atrial enlargement was found in 84% of patients with AF. I noted that 187 patients (40.91% of the total) showed changes of intima-media thickness (IMT) at vascular Doppler ultrasound. Although the number of women with vascular changes (117) is greater than number of men (70), we found that the presence of atherosclerosis is almost in equal proportions in the group of women and respectively men.

In the studied group, 83 patients (18,16% total hypertensive patients) presented cerebrovascular events, women being more numerous. Of those with acute cerebrovascular events, the most numerous, 130 (80,72%) had ischemic stroke and only 31 (19,28%) had hemorrhagic stroke. We observed that 38.94% of the total patients had abnormal values of ankle - brachial index (ABI), 17.41% of them had arterial stiffness and in a similar percentage, ABI signaled the presence of peripheral artery disease. Of these, 82,58% presented advanced peripheral artery disease, as a result of screening programmes using the ankle - brachial index ($ABI \leq 0,9$), of which 71% were men and the rest women. The majority of patients (64,98%) had mild forms of hypertensive retinopathy (grade I - II predominantly women), 21,88% have experienced fundoscopic abnormalities type papilloedema or macular edema or retinal haemorrhages (advanced forms of hypertensive retinopathy), affecting both sexes similarly. A percentage of 57.33% of the total hypertensive patients presented reduced renal function, mostly (44,85%) having chronic kidney disease stage 2 (mild impaired renal function). Chronic kidney disease stage 3 (moderate renal dysfunction) was present at 12.25% of patients. The dipstick test has shown the presence of albuminuria at 214 patients (46.83% of patients).

37.85% of all patients had microalbuminuria and 8.97% had macroalbuminuria. 98,61% of patients presenting with albuminuria at the dipstick had uncontrolled blood pressure values therapeutic (strong correlation and highly statistically significant, $r = 0.6923$, $p < 0.001$)

Statistical analysis of the data reveals that at hypertensive patients, association between obesity and dyslipidemia was highly significant ($r = 0.3538$, $p < 0.001$). Increased urinary protein excretion correlates positively with hypertension severity, with a correlation coefficient ($r = 0.4527$, $p < 0.001$). Personal hypertensive history correlates positively with its severity ($r = 0.3872$, $p < 0.001$). Discussing the data of this study compared with those in the literature we concluded that at younger ages, the percentage of hypertensive men is higher, and once with increasing age there is an increase in the number of hypertensive women (similar to data from literature - SEPAR study). In the studied group most patients (38%) presented BP values above 160/110 mmHg, being distributed in the group with grade 2 hypertension; 28% of patients had grade 3 hypertension; 24.94% of patients with grade 1 hypertension. In a study (Markoglou NCh et al., 2005) more than half of the residents of Kosovo have had severe hypertension (51,2%), 31.5% moderate and 17.3% had mild HT, these data describing an improvement of blood pressure values. Comparing with data from the SEPHAR study, where grade 1 hypertension was seen in 55% of subjects, on medie 29% of the subjects, severe in 16% of subjects, we observed that the population of Kosovo examined in our study has in most cases moderate - severe hypertension, possibly due to the rural environment provenience, lack of education and, therefore, late presentation to the doctor and the lack of medication in the early stages of evolution of the disease.

In the studied group the frequency of smoking was 49%, higher than the one reported at european level (27%). The prevalence of diabetes in our group was 9,19%, somewhat higher than in SEPHAR study (5%). ABPM monitoring pointed out that night - time BP values are a better predictor for fatal cardiovascular events, than daytime BP values. It was found that a higher incidence of cardiovascular events is associated with a lower decrease in the blood pressure values during the night. We found 37.42% of patients with pattern "non dipper" were predominantly males (our data coincides with those of the literature). Heart failure was present in 62% of studied hypertensive patients (in the speciallity literature 70 - 80%). Of these, 60.4% had heart failure with preserved ejection fraction (EF) and only 39.6% had associated systolic dysfunction ($EF \leq 45\%$). In our study, 80,72 percent of the total strokes were ischemic . Of these, 96,96% occurred in patients with grade 2 and 3 hypertension, BP values $\geq 160/100$ mm Hg, compared with the percent of 75 - 80% found in the speciallity literature. In the present study, 38.94% of the total patients had abnormal ABI (ankle - brachial index), as follows: 17.41% had arterial stiffness, 17.41% had advanced peripheral artery disease ($ABI \leq 0,4$). In total, 82.58% of the patients had advanced atherosclerosis ($ABI \leq 0.6$), 71% of them being men, with similar findings in speciallity literature. I noted in most

patients (64,98%) mild hypertensive retinopathy (grade I - II) and for 21,88% the presence of advanced retinopathy. The dipstick test has shown the presence of albuminuria at 47% of patients (80.84% of the cases had microalbuminuria and 19.16% macroalbuminuria)

4. CONCLUSIONS

1. The present research was realized on a group of 457 hypertensiv patients, selected from 2000 patients admitted in internal medicine department of „Prim Dr. Daut Mustafa" Hospital Prizren -Kosovo (22,8% of total admitted patients).The distribution of cases regarding gender was: 61,48% women and 38,52% men. Rural environment was found in 77,89% of cases. Average age for our group was 55,16 years, a majority of patients had age between 41 and 70 years. In young age group, arterial hypertension was prevalent in men (38% men vs 31,31% women) and in over 70 years group we found prevalence of women (12% of total women vs. 11,36% of total men). Depending on the hypertension grading, 38% of patients were distributed in grade 2 hypertension group; 28% in grade 3 HT group and 24,94% were patients with grade 1 hypertension. 28% of patients follow had the HSI, their average age being 67.7 years. Over 70% of the patients in our study had more than five years of arterial hypertension history. 55.36% of patients had low HDL - cholesterol, 55.7% had hypertriglyceridemia, 65.84% had hypercholesterolemia with high LDL - cholesterol and 45.6% had mixed dyslipidemia. 53% of hypertensive patients had abdominal obesity. Diabetes mellitus was associated with arterial hypertension in 9.19% of patients, the other 34% of total patients studied had impaired glucose tolerance.
2. Assessment of global cardiovascular risk had established that 46,6% of patients have a death risk at 10 years $\geq$ 10, calculated conform SCORE. Men had frequently a high and very high global cardiovascular risk. On our studied group , the presence of at least 2 cardiovascular risk factors influence the appearance of HTA (63,67% of patients had 2 risk factors associated with HTA). Only 32,3% of women and 16,47% of men achieved target blood pressure values with antihypertensive medication. Resistant HTA was presented in 13,57% of patients. Our researches showed that a proportion of 29,75% of patients were non adherent at treatment and diet recommendation.
3. Ambulatory blood pressure monitoring showed a good control of BP values in 32,2% of women and 16,47% of men, day/night raport values established that 62,58% of patients had a dipper type profile while the rest of 37,42% were non-dipper type. We noticed an increased number of hypertensive patients in the group of non-dipper: 56% of total men, while 25,97%

of women had this profile. This results draw attention to the fact that the prognostic is less favorabile in patients with low decrease of nocturnal blood pressure. Left ventricular hypertrophy was ecocardiographically assess in 42% of cases (predominant patttern was concentrical hypertrophy), with a dominancy of men and 50 - 60 group of age. CHD prevalence between hypertensive patients included in the study was 55,79%, in this subset prevalence of coronary syndromes was 73,3%. Ischemic cardiac disease is more frequently in patients with grade 3 - 4 hypertension (high and very high risk) in the studied group. Heart failure was encountered in 62% of total patients, from them 60,4% had heart failure with preserved ejection fraction. Atrial fibrillation was diagnosed at 31% of patients. Left atrial enlargement was diagnosed at 85% of hypertensive patients with FiA.

4. Acute cerebrovascular events were prevalent in a percent of 18,1% among studied hypertensive patients (80,8% being ischemic). In our study, arterial hypertension increased the risk of stroke by 4 times, ischemic cardiac disease was associated with a relative risk for acute cerebrovascular events of 2 times, left ventricular hypertrophy and heart failure have been associated with a relative risk of 3 times. 38,94% of total patients had abnormal values of ankle-brachial index. We noticed a statistically significant correlation between the male sex and the presence of peripheral arterial disease in the study. Advanced forms of hypertensive retinopathy were present at 21,88% of patients. 57,33% of total hypertensive patients had renal dysfunction. Albuminuria was detected by dipstick test at 47% of patients. Therapeutically uncontrolled values of blood pressure were correlated strongly and statistically significant with presence of microalbuminuria.
5. **The originality of this study:** The present study is one of few, regarding epidemiology and prevalence of arterial hypertension in Kosovo region. Beyond epidemiological data offered by our research, this study was design as observational, to appreciate the importance of arterial hypertension and other associated risk factors in the appearance and evolution of cardiovascular diseases. The results of this study suggest that diagnostic procedures and therapeutic management of arterial hypertension should be intensified in Kosovo region and hypertensive patients to be treated in accordance with individual evaluation of total cardiovascular risk.

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