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Biochemical and Paraclinical Evaluation of Organ Damage in Arterial Hypertension with Associated Chronic Kidney Disease

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Abstract. *Organ damages, which contribute to the overall cardiovascular risk of hypertensive patients, should be early detected, prevented and treated. The study evaluated organ damage in a hypertensive study group with chronic kidney disease (CKD), compared with a study group of hypertension without CKD. Albuminuria was present in 41.2% and reduced estimated glomerular filtration rate <60 ml/min/m^2 was present in 72.5% of hypertensive with CKD. The comparison of organ damage revealed in the CKD group a statistical significant higher prevalence of organ damage as follows: intima-media thickness >0.9 mm in 39.9% vs 10.5%, carotid plaques in 28.2% vs 12.6%, left ventricular hypertrophy in 39.9% vs 31%, ankle brachial index in 6.2% vs 3.5%. Early detection and treatment of additional cardiovascular risk factors as dyslipidaemia and hyperglycaemia, that have significant role in the pathogenesis of organ damage, contribute to the better prevention of cardiovascular and renal complications in hypertension with CKD.*

Keywords*: hypertension; chronic kidney disease; organ damage; biochemical evaluation;*

1.Introduction

Hypertension induces multiple structural and functional changes in the vasculature of the heart, brain, kidney and the retina. Hypertension mediated organ damages (HMOD) progress to more severe cardiovascular diseases, which contribute to the grown cardiovascular morbidity and mortality characteristic for chronic kidney disease evolution [1]. As patients with mild and moderate degree of hypertension are usually treated in primary care, it results as necessary to include at this level a better routine detection and evaluation of risk factors and of target organ damages.

Studies have demonstrated that the prevalence of arterial essential hypertension is 30-40% of the adult population, of which 10-20% develop chronic kidney disease (CKD), expressed by reduced estimated glomerular filtration rate (eGFR) <59 mL/min/m^2 and/or the presence of albuminuria [2-4]. The appearance of CKD will aggravate hypertension, including a worse response to treatment and will rise significantly the incidence of cardiovascular events [5].

At the heart level, ventricular hypertrophy (LVH) develops due to the mechanical stress of pressure overload and secondary to various neurohormonal substances that are elevated in hypertension and have effects on the structures of the heart, including aldosterone, angiotensin II, insulin and noradrenaline. LVH is detected in 25-35% of the hypertensive population, but its prevalence is much higher in the presence of associated CKD, ranging to 50-70% and contributing to the nearly triple cardiovascular morbidity and mortality of these patients [6-7].

The wall thickening of the common carotid artery, expressed as intima-media thickness (IMT) ≥0.9 mm indicate hypertrophy of the carotid walls induced by hypertension, while the presence of carotid plaques reflect especially atherosclerosis. Both IMT and carotid plaques are associated with future risk

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of ischemic stroke and myocardial infarction. IMT >0.9 mm is met in hypertensive subjects in 6-15%, but its prevalence reaches nearly 35-40% when CKD is present [8].

Studies have demonstrated that LVH, IMT, microalbuminuria and reduced eGFR can be positively influenced by early detection and treatment, the most important intervention being the reduction of BP to targets and the correction of risk factors [9].

There are few Romanian studies [10-12] on essential arterial hypertension associating CKD and about hypertension mediated organ damage (HMOD) in CKD patients. As the epidemiology and characteristics of hypertension with CKD differs, it is important to have national studies to evaluate the local situation and to elaborate on this basis prevention, diagnosis and therapy strategies [13, 14]. The aim of the present study was to evaluate in hypertension with CKD (1) the induced vascular damage, evaluated with carotid intima-media thickness, carotid plaques and ankle brachial index (ABI); (2) the heart response to hypertension, respectively the left ventricular hypertrophy and (3) to establish the correlation between these organ damage, hypertension, CKD and associated clinical and biochemical cardiovascular risk factors.

2. Materials and methods

The study is an observational cross-sectional one, conducted between January 2017 and December 2019 in twelve primary health care centres of Timis Country, Romania. At the study participated 14 general practitioners (GPs), 16 medicine family residents, cardiologists and internal medicine specialists from the Victor Babes University of Medicine and Pharmacy of Timisoara. In conformity with the World Medical Association Declaration of Helsinki, at the beginning of the study all participants signed a written informed consent.

CKD was diagnosed in 131 cases (13.32%) of 984 evaluated adult hypertensive subjects. The repartition in CKD groups [15] was: group I. corresponded to stage 1 CKD (MAU/albuminuria present, normal eGFR between 120-90 mL/min/1.73 m^2); group II corresponded to stage 2. CKD (MAU/albuminuria present, eGFR between 89-60 mL/min/1.73 m^2); group III corresponded to stage 3 CKD (eGFR between 59-30 mL/min/ m^2, albuminuria not required ±) and group IV included stages 4 and 5 CKD (eGFR 29-15 mL/min/1.73 m^2 / eGFR <15 mL/min/ 1.73 m^2, albuminuria not required ±).

The laboratory analyses consisted of total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), triglycerides (TG), fasting plasma glucose (FPG), serum uric acid, serum creatinine, in selected cases HbA1c and oral glucose tolerance test (OGTT). Albuminuria was diagnosed from morning spot urine, based on albumin to creatinine ratio (ACR>30mg/g). The laboratory tests were performed in conformity with the standardized procedures by the Synevo Laboratories. The diagnosis of dyslipidaemia was based on the following profile (or on treatment): total cholesterol >200 mg/dL or LDL-cholesterol >115 mg/dL or HDL-cholesterol <40 mg/dL for men, <46 mg/dL for women and triglycerides >150 mg/dL. Hypertriglyceridemia was considered when TG levels were >150 mg/dL or participants were receiving drug treatment for hypertriglyceridemia. Hyper-LDL cholesterolemia was diagnosed when >115 mg/dL and/or participants were receiving statin therapy. Glucose metabolism impairment phenotypes (diabetes mellitus or prediabetes) were defined according to the American Diabetes Association (ADA) 2012 Guidelines. The diagnosis of DM was made on the basis of following elements: symptoms of hyperglycaemia, fasting plasma glucose (FPG) 126 mg/dL, HbA1c > 6.5%, oral glucose tolerance test with 2-h blood glucose > 200 mg/dL or on self-reported diagnosis of DM. The BP of the hypertensive patients was evaluated in the office with OMRON HEM 7251G devices and for ABPM with BTL 08 monitors.

Echocardiography was done by cardiologists with an ultrasound device Sonoscape SS 8000 and a transducer of 2.5 MHz. The diagnosis criteria that confirmed left ventricular hypertrophy (LVH) was the LV mass index >110 g/m^2 in men and >95 g/m^2 in women, calculated with the modified formula of Devereux (American Society of Echocardiography Convention). The relative wall thickness (RWT)

was determined with the formula RWT= (IVSD+PWTD/LVIDD. Other assessed echographic parameters were LV systolic and diastolic function, atrial enlargement and the dimensions of the aorta.

Carotid walls were evaluated by cardiologists with an ultrasound device Sonoscape SS 8000 with a transducer of 7.5 MHz, equipped with software that automatically identified the borders of the carotid arteries. The hypertrophy of the carotid walls was confirmed by intima-media thickness (IMT) ≥0.9 mm, while the presence of carotid plaques reflected especially atherosclerosis. IMT was measured at the level of the common carotid artery (CCA), 5 mm below the carotid bulb, in the far wall, from the leading edge of the first echogenic line (lumen-intima interface) to the leading edge of the second echogenic line (media-adventitia interface). Atherosclerotic plaques were defined as focal wall thickening with a diameter more than 50% of the surrounding normal wall or by a focal thickening ≥1.5 mm. The evaluation of the ankle brachial index was made with a continuous Doppler device and a Boso tonometer.

The statistical analyses were performed using SPSS version 12.0. Data were presented as frequencies and percentages for qualitative variables and as mean ± SD for quantitative variables. Differences between groups were assessed with the Pearson χ^2 for percentages and the Student t test for mean values. To determine the correlations between IMT and LVH and other risk factors, the logistic regression analysis was used. The independent variables with $p < 0.05$ were considered as having statistical significance. Odds ratios with 95% confidence interval (CI) were calculated for markers of hypertension mediated organ damage. Logistic regression analysis determined the independent predictors of elevated IMT and LVH.

3.Results and discussions

The study group with hypertension and CKD consisted of 131 patients. Their clinical, biochemical and paraclinical data were compared with a hypertension group without CKD, consisting of 142 patients, in order to establish the role of risk factors for the development of HMOD. The majority of patients with CKD belonged to stage 3 CKD (72.3%), followed stage 2 (13.72%), stage 1 (12.9%) and stage 4 (0.78%).

There were no statistic significant differences between the groups concerning the number of patients (131 vs.142), gender, educational level or living areas. The age of the subjects ranged from 18 to 80 years, the most frequent ages in the hypertension with CKD group were over 60 years and between 51-60 years in hypertension group without CKD. The mean age was 62.1 ± 12.5 years in the CKD group and 57.28 ± 13 years in the hypertension group without CKD. Mean values of main biochemical parameters of the study groups are presented in Table 1.

Table 1. Values of main biochemical parameters in the hypertension study groups

Biochemical variables ± SD	Grup1. Hypertension without CKD (nr=142)	Group2. Hypertension with CKD (nr=131)	p
LDL cholesterolemia mean ± SD, mg/dL	124±33	127±35	0.06
HDL cholesterolemia mean ± SD, mg/dL	46±17	40±18 mg/dL	0.04
Triglycerides, mean ± SD mg/dL	129±95	141±98.8	0.03
Creatinine, mg/dL	0.8±0.4 mg/dL	1.05±0.8 mg/dL	0.01
Estimated glomerular filtration rate, ml/min/1.73 m^2	70±8	58±12	0.001
Albumin to creatinine ratio, ACR mg/g	14±6	138±24	0.001
Glycaemia, mean ± SD mg/dL	104±28	110±38.5	0.01
Glycated haemoglobin, HbA1c, %	5.6%±0.9	5.8%±1.8	0.04
Hb, mg/dL	14.1±1.43	13.7±1.29	0.06
Uric acid, mg/dL	4.3±1.8 mg/dL	5.5±1.9 mg/dl	0.03

Abbreviations: HbA1c, glycosylated haemoglobin; Hb, haemoglobin; eGFR, estimated glomerular filtration rate; ACR, albumin to creatinine ratio; Hb, haemoglobin.

The CV risk factors, more frequent met in hypertension with CKD, were: male gender (51.56% vs 40.5%), age >55 years in men (57% vs 45.5%), premature family history of CV disease (31% vs 19.55), hyper LDL-cholesterolemia (52% vs 45.5%), hypertriglyceridemia (50.3% vs 31.6%), low

HDL-cholesterolemia (35% vs. 30%), hyperglycaemia (110±38.5 vs 104.2±25.2) and diabetes mellitus (p <0.05) for all comparisons.

The patients with hypertension and CKD demonstrated a very high cardiovascular risk, as they presented an association of multiple risk factors, multiple hypertension mediated organ damages and clinical overt cardiovascular diseases and diabetes. Prevalence of asymptomatic hypertension mediated organ damages in hypertension with and without CKD is presented in Table 2 and Figures 1 and 2.

Table 2. Asymptomatic hypertension mediated organ damage in the study groups with and without CKD

Asymptomatic hypertension mediated organ damage	Study group HTA with CKD, nr=131	Control gr. HTA without CKD, nr=142	P value
Left ventricular hypertrophy on ECG – nr (%)	7 (5.3%)	5 (4.03 %)	0.8311
Left ventricular hypertrophy on echocardiography-nr (%)	51 (39.9%)	44 (31%)	0.0461
Albuminuria ACR > 30 mg/g	54 (41.2%)	-	-
Microalbuminuria, nr (%) ACR 30-300 mg/g	49 (37.4%)	-	-
Macroalbuminuria ACR > 300 mg/g	5 (3.82%)	-	-
Reduced eGFR under 89 ml/min/1.73 m^2, nr (%)	114 (87%)	-	-
Reduced eGFR between 30-59 ml/min/1.73 m^2, n (%)	95 (72.5%)	-	-
Intima-media thickness ≥0.9 mm	41 (31.5%)	15 (10.5%)	p<0.05
Ankle brachial index < 0.9	8 (6.1%)	5 (3.5%)	p<0.05

Abbreviations: LVH, left ventricular hypertrophy; eGFR, estimated glomerular filtration rate; IMT, intima-media thickness; ABI, ankle brahial index.

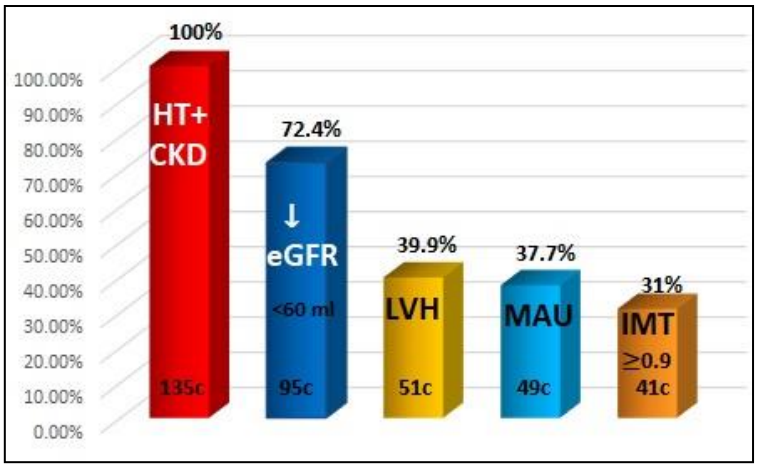

Figure 1. Asymptomatic hypertension mediated renal and cardiovascular organ damage

Established cardiovascular diseases were more frequent met in hypertension with CKD. Coronary artery disease (CAD) was present in 32.07% vs. 16.9%, atrial fibrillation (AF) in 9.9% vs. 7.9%, carotid artery plaques in 28.25% vs 12.68%, heart failure (HF) in 13.7% vs 12%, peripheral arterial disease (PAD) in 11,4% vs 7.05%, diabetes mellitus (DM) in 38% vs 16% and cerebrovascular diseases were present in 9.16% vs. 4.90%, p<0.05 for all comparisons, as presented in Figure 3. Ankle brachial index <0.9, confirming a vascular peripheral arterial disease was present in 6.1% in hypertension with CKD and in 3.5% in hypertension without CKD. These results confirm the high cardiovascular morbidity and mortality of CKD hypertensive patients.

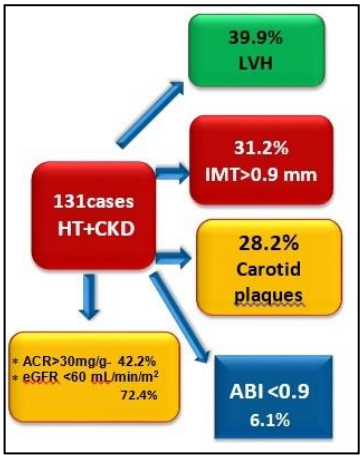

Figure 2. Organ damage and atherosclerotic vascular diseases in hypertension with CKD

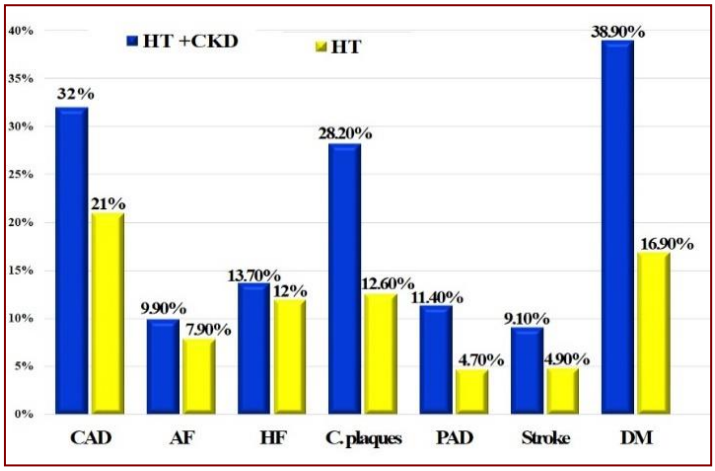

Figure 3. Established cardiovascular diseases in hypertension with and without CKD

Increased IMT was more often found in the hypertension study group with CKD than in the hypertension group without CKD. Patients with hypertension and CKD presented a higher mean IMT (0.98±0.35 mm versus 0.85± 0.22 mm, p=0.05) and higher prevalence of IMT ≥0.9 mm and of carotid plaques, with p <0.05 for all comparisons, as presented in Figure 4. Elevated CIMT and carotid plaques on ultrasound images are presented in Figures 5 and 6.

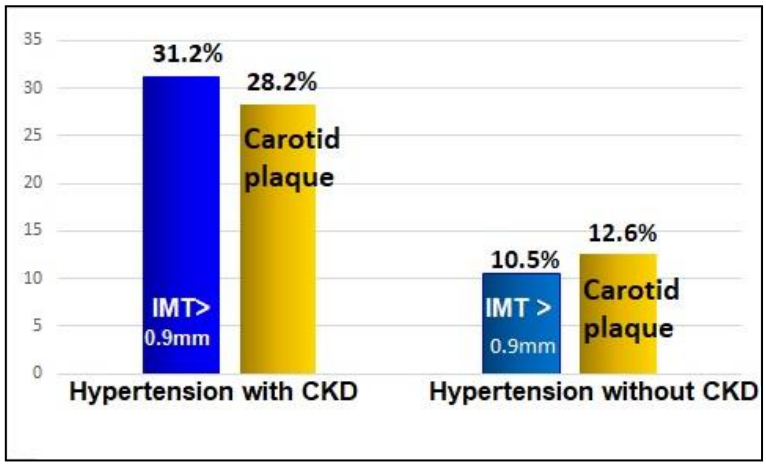

Figure 4. IMT and carotid plaques in hypertension with and without CKD

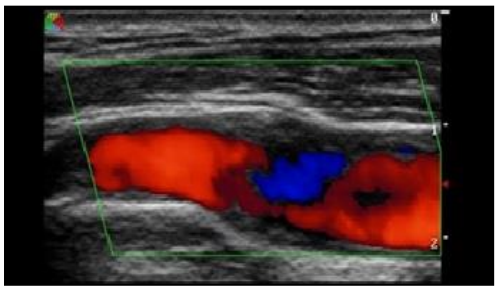

Figure 5. Elevated carotid IMT and carotid plaques

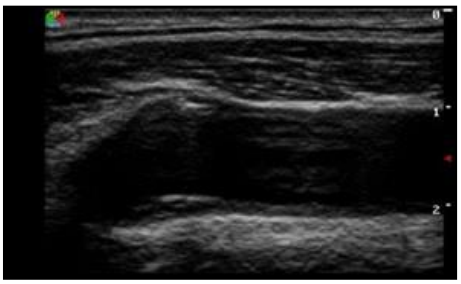

Figure 6. Atherosclerotic carotid plaques

The analysis of the severity degree of hypertension in patients with IMT≥ 0.9 mm outlined the parallel relationship of the thickening of the carotid artery with the severity of hypertension, presence of higher BP values and longer duration of hypertension. The most important part of patients with IMT

≥0.9 mm, respectively 48.7% (20 cases) belonged to severe grade 3 hypertension group, 41% (17 cases) belonged to moderate grade hypertension and 9.75% (4 cases) had mild hypertension.

The comparison of the hypertensive with CKD having IMT ≥0.9 mm with those with IMT <0.9 mm revealed important clinical and biochemical differences.

In the IMT ≥0.9 mm the mean age was 65.1 ± 8.9 years vs 57± 8.1 years, male gender was present in 56% vs 51.2%, current smokers were 24.3% vs 21.9%, body mass index was 31 kg/m^2 vs 30 kg/m^2, hypertriglyceridemia was present in 48.6% vs 43.9%, hypercholesterolemia was present in 63.4% vs 58.5% and diabetes mellitus was present in 31.7% vs. 21.9%. These characteristics are largely presented in table 3.

Table 3. Characteristics of the study groups with IMT < 0.9 MM and ≥0.9 MM

Variable	CIMT < 0.9 mm	CIMT≥ 0.9 mm	p
Age - years	57± 8.1	65 ± 8.9	<0.01
Male gender %	51.2 % (21)	56%(23)	0.7
Current smoker %	21.9% (9)	24.3 (10)	0.8
Office SBP mm Hg	145 ± 17.9	154 ± 22.4	<0.01
Office DBP mm Hg	86.7 ± 9.9	87.2 ± 10.3	0.8
BMI kg/m^2	30.4 ± 2.5	31 ± 4.7	0.8
Diabetes mellitus %	21.9% (9)	31.7% (13)	<0.01
Hypercholesterolemia	58.5% (24)	63.4% (26)	<0.01
Hypertriglyceridemia	43.9% (18)	48.6% (20)	0.7
eGFR ml/min	70.5 ± 8.8 ml/min	57±8.2 ml/min/m^2	<0.01
Albuminuria	39% (16)	53.6% (22)	<0.01
Mean IMT mm	0.85 ± 28	0.98 ± 0.35	<0.01

Abbreviations: IMT, intima media thickness; SPB, systolic blood pressure;
DBP, diastolic blood pressure; eGFR, estimated glomerular filtration

IMT and plaques in CKD patients presented important differences according to age groups. In the age group ≤ 50 years, mean IMT was 0.72±0.15 mm, in the 50-64 years group mean IMT was 0.82±0.35 mm, in the 65-74 years group mean IMT was 0.92±0.34 mm and in the over 75 years group mean IMT was 0.96±0.26 mm. In the logistic multiple regression analysis, albuminuria and reduced eGFR were associated with IMT, after adjustment for age, SBP, FPG, hypercholesterolemia, hypertriglyceridemia and smoking. CKD was also significantly associated with the presence of carotid plaques.

Left ventricular hypertrophy

Left ventricular hypertrophy is an important component of the hypertensive heart disease, being frequently met in hypertension with CKD. Diagnosis is based on investigations as electrocardiography and echocardiography, the last examination being the best for supporting the diagnosis. Echocardiography is an efficient and accurate investigation for the evaluation of LVH, left atrial measurement and systolic and diastolic left ventricular function. LVH in CKD was present in 5.3% on ECG and in 39.9% on echocardiography, which is known to be the most sensible diagnosis method. On echocardiography the LV geometry was represented by four structure patterns, calculated with LVM and RWT.

1 Normal geometry (normal mass and normal RWT)
2 Concentric remodelling (normal mass and increased RWT)
3 Concentric left ventricular hypertrophy (increased mass and increased RWT)
4 Eccentric left ventricular hypertrophy (increased mass and normal RWT).

There were statistical significant differences between the study groups regarding the lower prevalence of normal LV structure in the CKD group (37.5% vs 48.5%) and the higher prevalence of LV hypertrophy in the CKD study group (39.9% vs 31%), p< 0.05. In both hypertension study groups the eccentric hypertrophy was predominant. The comparison of LV geometry pattern of the

hypertension groups with and without CKD is presented in Figure 7. Echocardiography images of M mode and 2D mode of LVH are presented in Figure 8 and 9.

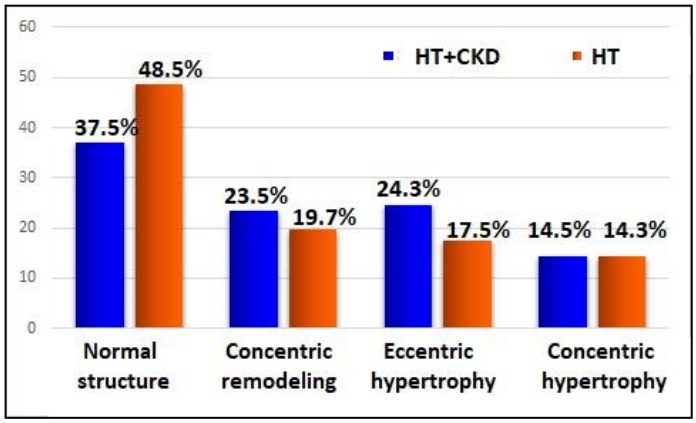

Figure 7. Left ventricular geometry in hypertension with and without CKD

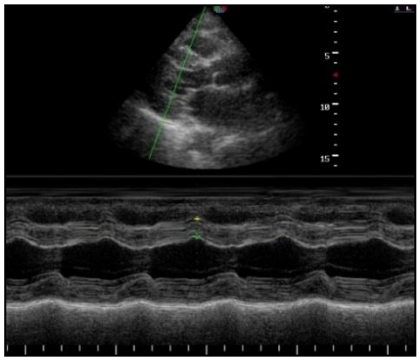

Figure 8. M mode echocardiography of LVH

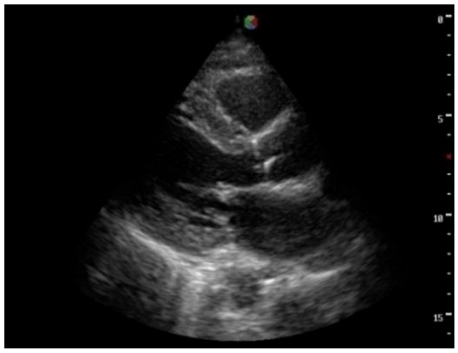

Figure 9. 2D mode echocardiography of LVH

Differences were noticed between the two study groups regarding the following echographic parameters: the dimension of the left atrium (LA), left ventricular end-systolic diameter (LVSD), left ventricular end-diastolic diameter (LVDD), the thickness of the interventricular septum (IVST), the dimensions of the posterior wall (LVPW), the left ventricular mass index (LVMI) and the relative LV wall thickness (RWT), data which are presented in Table 4. The measurements of these parameters revealed statistical significant higher values in the hypertension group with CKD, compared with the hypertension group without CKD.

Table 4. Echocardiographic data of hypertension study groups with and without CKD

Echographic Parameters	Hypertension without CKD (n = 142)	Hypertension with CKD (n = 131)	p
LVDD (mm)	48 ± 4	55 ±6	0.05
LVSD (mm)	35 ± 5	39 ± 5	0.05
IVST (mm)	11 ± 4	12 ± 7	0.04
PWT (mm)	9 ± 4	10 ± 6	0.05
EF (%)	60 ± 7	58 ±6	0.46
LA (mm)	34 ± 3	39 ±4	0.02
LVMI (g/m^2)	126 ± 28	153 ± 58	0.01
RWT	0.44 ± 0.02	0.47 ± 0.07	0.03

LVDD, left ventricular diastolic diameter; LVSD, left ventricular systolic diameter; IVST, interventricular septum thickness; PWT, posterior wall thickness; EF, ejection fraction; LA, left atrial dimension; LVMI, left ventricular mass index; RWT, relative wall thickness.

Our study is in agreement with literature data regarding the prevalence and the positive correlation between CKD and the more accentuated development of subclinical organ damage, confirming the strong link between the cardiovascular system and the kidney [16].

IMT and plaques correlated with age, duration of hypertension, the presence of albuminuria, diabetes mellitus and the presence of cardiovascular diseases ($p<0.05$). Other factors associated with increased IMT were male gender, low HDL cholesterol, high LDL cholesterol levels, coronary heart disease or cerebrovascular disease. Starting from our data, which indicate that a relevant percentage of patients with arterial hypertension and CKD have a great incidence of carotid plaques and of increased IMT, we recommend to search for carotid damage in all hypertensive subjects with CKD.

Similar data regarding carotid artery damage were reported in other trials. In many other studies [17-18] carotid IMT was greater in CKD patients, aspects also noticed in the study of Matsushita et al. [19]. The cross-sectional studies of Geraci et al. [20] demonstrated that MAU was associated with the growth of IMT of the carotid arteries, when compared with normalbuminuric patients [21-24]. It was also demonstrated that microalbuminuria predicts the development and progression of atherosclerosis, correlates with vascular functional abnormalities, impaired elastic properties and the growing stiffness of the large arteries [23].

LVH is reported in studies to be present in hypertension with CKD up to 70%. In the present research prevalence of LVH was 39.9% in CKD and 31% in the total hypertensive population. In the SEPHAR III Survey, LVH was present in 31% of the adult hypertensive patients. LVH is an important risk factor for atrial fibrillation, diastolic and systolic heart failure, arrhythmias and sudden death [24-27]. Studies have demonstrated that concentric left ventricular hypertrophy implies the highest CV risk and that angiotensin converting enzyme inhibitors favour regression of both LVH and albuminuria [25-28]. In some studies patients with MAU showed a higher prevalence of concentric than eccentric LVH [26]. Prevalence of CKD (13.32%) of albuminuria and reduced eGFR in hypertensive patients was similar to other studies [27-31]. To reduce the burden of CKD and HMOD by hypertension screening programmes and by development of public primary care health strategies, lower blood pressure and risk factors, represented a priority of the present research.

Limitations of the study result from the cross-sectional design, the selection of the study population based on visits to the GPs office and the relative limited number of patients with HMOD. Other limitations result from a single estimation of the eGFR and of ACR, which could introduce bias. Non-traditional CV risk factors were not explored. Follow up data were registered only from few participants, so that information regarding the prognosis and evolution were not available.

4.Conclusions

Detection of hypertension mediated organ damage in asymptomatic stages, when prevention and treatment strategies addressed to their reversal are efficient and cost-effective, imposes early diagnosis especially in primary care, where most of these hypertensive patients are followed up. The prevalence of hypertension mediated organ damage was greater in hypertension with CKD. Prevalence of elevated carotid IMT $\geq$ 0.9 mm was three times greater, of carotid plaques two times greater, LVH was present in 39.9% vs 31%, and ABI <0.9 in 6.1% vs. 3.5%. The high prevalence of HMOD in CKD was associated with cardiovascular risk factors as albuminuria, reduced eGFR <60 mL/min/m^2, hyper-LDL cholesterolemia, hypertriglyceridemia, low HDL-cholesterolemia and hyperglycaemia. As a consequence of these findings, the search for HMOD and associated risk factors appears to be useful in hypertensive with CKD, improving risk class classification and updating the prevention and treatment strategies.

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