Prevalence, Characteristics and Predictive Factors of Microalbuminuria in Resistant Systemic Arterial Hypertension

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The present cross-sectional observational study was made in family medicine offices of Timi' County, Romania. The aim of the study was to investigate the prevalence of urinary microalbumin excretion (MAU) in resistant systemic arterial hypertension (RH), to analyze patients' biochemical and clinical characteristics, and the predictive factors for MAU. From a total number of 347 patients, MAU was detected in 76 cases (21.9%). The microalbuminuria positive patients were older, with significant higher office systolic blood pressure (BP) (155 ± 13.50 vs 148 ± 12.40 mmHg, p < 0.0001) and diastolic blood pressure (94 ± 12.20 vs 88 ± 14.6 mmHg, p = 0.0013), higher prevalence of left ventricular hypertrophy, diabetes mellitus, obesity, ischemic and peripheral arterial disease. MAU positive patients presented statistical significant differences in biochemical data concerning: fasting plasma glucose (FPG) (118.80 ± 32.02 vs 108.01 ± 26.01 mg/dL, p = 0.003), impaired glucose tolerance (IGT) (10.52 % vs 4.94 %), glycated hemoglobin (HbA1c) (6.56 ± 0.98% vs 5.96 ± 0.91%, p < 0.001), reduced estimated glomerular filtration rate (eGFR) (56.10 ± 15.4 vs 69.30 ± 17.5 ml/min/1.73m^2, p < 0.001) and higher potassium levels (4.71 ± 0.43 vs 4.59 ± 0.44 mg/dL, p = 0.0378). No significant differences were noticed regarding LDL- and HDL-cholesterol, triglycerides, uric acid and serum creatinine. In a logistic multivariate analysis independent predictors for MAU were: systolic BP (odds ratio, OR = 1.024, 95% confidence interval, CI:1.011-1.039, p < 0.001), HbA1c (OR = 1.324, 95% CI: 1.078-1.724, p = 0.008) and eGFR (OR = 0.989, 95% CI: 0.977-0.999, p = 0.01). Our findings suggest that an important part of RH patients have microalbuminuria and highlight the importance of controlling its predictors, in order to improve patients' outcome.

Keywords: microalbuminuria, resistant systemic arterial hypertension-evaluation

The European Hypertension/Cardiology Society Guidelines [1] highlight the necessity to investigate target organ damage secondary to systemic arterial hypertension (HT) as left ventricular hypertrophy (LVH), reduced glomerular filtration rate (GFR), microalbuminuria (MAU) and macro-albuminuria, factors that are related to a greater cardiovascular (CV) morbidity and mortality. Epidemiological studies [2, 3] have demonstrated that chronic kidney disease (CKD) is an independent risk factor for HT and that even very low levels of microalbuminuria strongly correlate toCV risk, independent of the presence of other risk factors [4]. It was demonstrated that MAU is a marker of endothelial dysfunction that predicts a greater incidence of target organ damage, cardio- and cerebrovascular events and that its reduction lowers these comorbidities [5]. The reported prevalence of MAU is highly variable among studied populations, ranging from 7% to 58.4% [6, 7]. This variation can be explained by differences in population characteristics, investigation methods and prescribed drugs [8 - 10]. Early identification of high-risk patients through detection of MAU allows selection of treatment regimens based on angiotensin II blockade in order to assure its regression and prevent progression [11].

The aim of the study was to evaluate the prevalence of MAU in RH patients in primary care setting and to establish the biochemical and clinical profile of these patients and the predictors for MAU.

Experimental part

Material and methods

This is an observational cross-sectional study, done between 2011 and 2017, involving 19 general practitioners (GPs) from Timis County, Romania and affiliated university hospitals. From a number of 5146 hypertensive patients who were evaluated during the medical visits at the GPs offices and treated for at least three months, a number of 347 adult patients fulfilled the criteria of RH (treated with three or more antihypertensive agents, in optimal doses or maximal tolerated, including a diuretic, not reaching target blood pressure (BP) < 140/90 mmHg). RH included also controlled hypertension patients, treated with four or more antihypertensive drugs [1]. Exclusion criteria were secondary HT, acute myocardial infarction, instable angina and stage 5 of CKD. At the beginning of the study all participants signed a written informed consent. The study was approved by the Ethics Committee of the University of Medicine and Pharmacy Victor Babes Timisoara and acoordind to some published models and guidelines [12, 13].

Demographic informations were obtained from written questionnaires. The GPs performed history, physical examination and measured height, weight, blood pressure (BP), the body mass index (BMI) being calculated. The laboratory analyses included total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), triglycerides (TG), uric acid, creatinine, eGFR, urine analysis, fasting plasma glucose

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(FPG), HbA1c, oral glucose tolerance test (OGTT), tests performed in conformity with the standardized procedures. All pacients underwent a screening for urmary albumin excretion baseded on a dip stick test, the readings being based on urinary chemistry reflectance photometry. Urinary albumin excretion was expressed as the urinary albumin to creatinine ratio (UACR). The cutoff values for the presence of MAU were 30 mg-300 mg/g, < 30 mg/g defined normalbuminuria and over 300 mg/g macroalbuminuria. The GFR was estimated (eGFR) based on the serum creatinine level using the a simplified equation developed from the Modification of Diet in Renal Disease (MDRD). CKD stages were classified as following: stage 1 with eGFR > 90 mL/min/1.73 m^2, stage 2 with eGFR 90-60 mL/min/1.73 m^2, stage 3 with eGFR 59-30 mL/min/1.73 m^2 and stage 4 with eGFR < 30-15 mL/min/ 1.73 m^2. Stage 5 CKD was excluded from the study, being followed up in nephrology centres. LVH was detected on echocardiography with a Sonoscape 8000 echo-Doppler system, based on calculation of left ventricular mass (LVM) with the formula : 0.6 + 0.832 x $((LVID + PW + IVS)^3 - LVID^3)$ g. ABPM BTL 04 monitors were used for ABPM (ambulatory blood pressure monitoring). Average 24 h, day-time and night-time systolic and diastolic BP were obtained. Only patients with complete data were included in the study.

Statistical analysis

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 qualitative variables and the Student t test for quantitative data. The independent variables with $p < 0.05$ were considered as having statistical significance. Multivariate logistic regression analysis determined the independent predictors for MAU in RH patients.

Results and discussions

From a number of 5146 hypertensive patients from 19 family medicine offices, a number of 347 (6,74%) cases met the criteria for resistant hypertension. The evaluation of urinary albumin excretion detected microalbuminuria present (MAU+) in 76 cases (21.9%) and MAU absent (MAU-) in 243 (70.02%) cases, the 28 patients with macro-

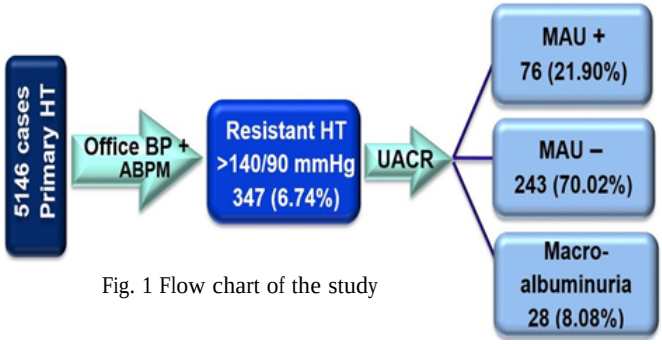

Fig. 1 Flow chart of the study

albuminuria (8.08%) being excluded from the evaluation (fig.1).

The comparison of the study groups with MAU+ and MAU- outlined differences regarding biochemical and clinical data. RH patients with MAU+ were older, having a significant greater mean age (66.10 ± 11.20 vs 62.30 ± 10.20 years, p = 0.0060), age ranged from 31 to 76 years. Male gender was present in 43 (56.58%) cases with MAU+ vs 124 (51.03%) in the MAU- group. Higher office systolic BP (155 ± 13.50 vs 148 ± 12.40 mmHg, $p < 0.0001$) and diastolic BP (94 ± 12.20 vs 88 ± 14.6 mmHg, p = 0.0013)

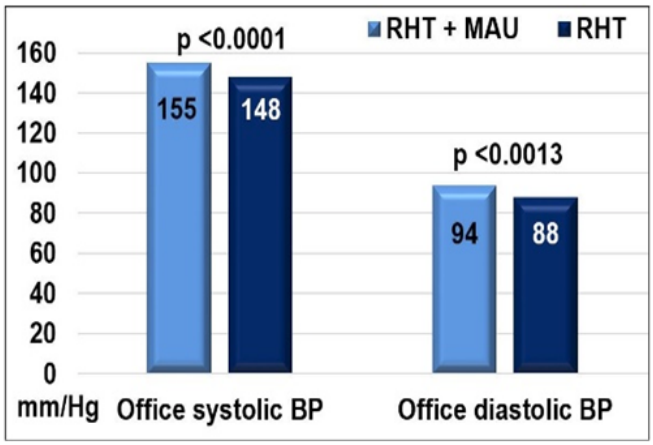

Fig. 2 Office BP in RH with MAU+ compared with RH

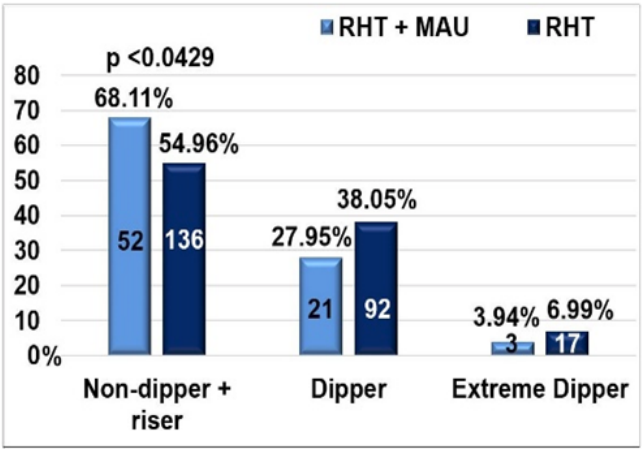

Fig.3. Blood pressure profile in RH with MAU+ compared to RH

were measured in the MAU+ group (fig. 2), who also presented an unfavorable 24 h (h) BP profile (68.11% nondippers and risers vs 54.96%) as seen in figure 3.

There was a tendency to greater duration of HT in the MAU+ group, but without statistical significance (15.20 ± 9.90 vs 13.10 ± 9.80, p = 0.1048).

Statistical significant differences between the MAU+ and MAU- groups were observed in connection with the presence of obesity (64.47% vs 48.97%, p = 0.0184), diabetes mellitus (DM) (36.84% vs 18.10%, p = 0.0007), impaired glucose tolerance (10.52% vs 4.94%, p = 0.0803), LVH (18.42% vs 6.99%, p = 0.0034), ischemic heart disease (42.10% vs 23.87%, p = 0.0021), peripheral arterial disease (30.26% vs 18.10%, p = 0.0233) and number of administrated medication (3.72 ± 0.78 vs 3.44 ± 0.46, p = 0.001). No significant differences between the studied groups were noticed regarding gender (p = 0.3986), the living area (urban living 57.89% vs 55.97%, p = 0.7686), family history of CV disease (39.47% vs 37.04%, p = 0.7031), sedentary lifestyle (59.21% vs 53.91%, p = 0.4182), smoking (14.47% vs 16.05%, p = 0.7413) and incidence of cerebrovascular disease (25.00% vs 23.04%, p = 0.7255).

The prevalence of MAU was influenced by age, being smallest in the 30-40 years age group and increasing in association toolder age, being the greatest in the 60-70 years (35.52%) and 70-80 years (30.26%) groups as presented in figure 4.

MAU was present across all CKD stages, increasing with the severity of CKD. In stage 1 of CKD, stage 2 of CKD, stage 3 of CKD and stage 4 of CKD prevalence was, respectively: 3.95%, 18.43%, 38.15%, and 39.47% (fig. 5).

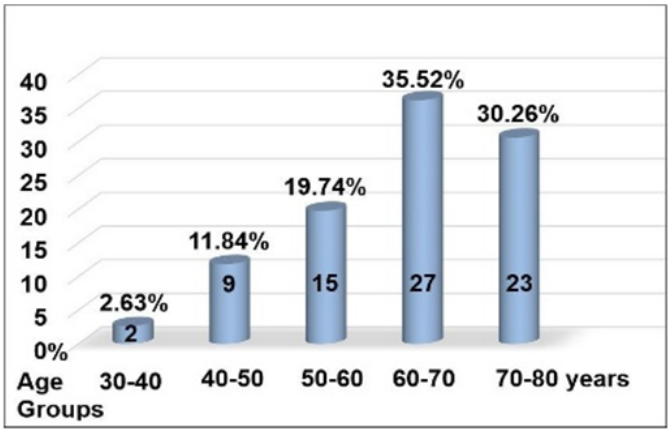

Fig. 4 Prevalence of microalbuminuria depending on age groups

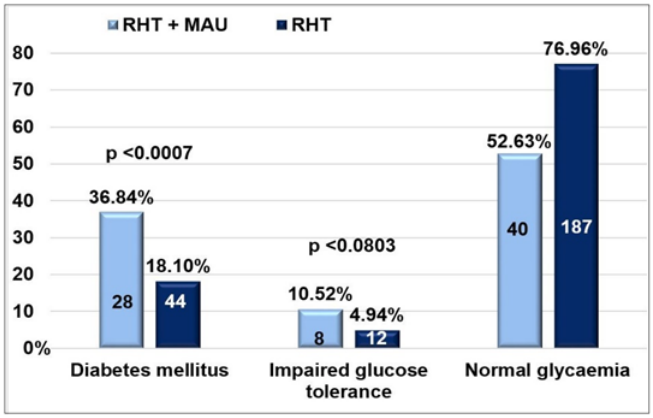

Fig. 6 Prevalence of microalbuminuria in resistant hypertension depending on the presence of glucose metabolism disorders

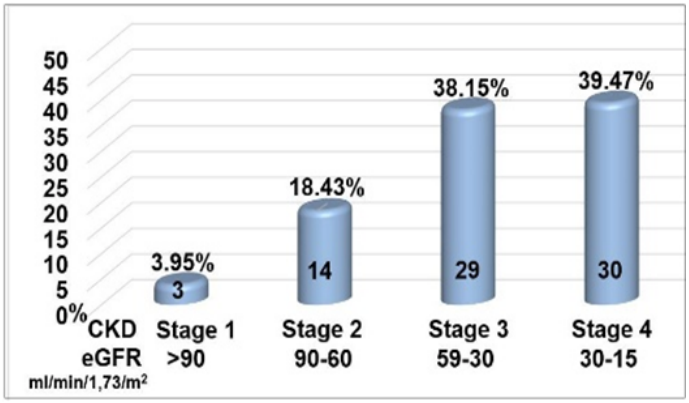

Fig. 5 Prevalence of microabuminuria depending on CKD stage

Table 1

BIOCHEMICAL CHARACTERISTICS OF RESISTANT HYPERTENSION WITH MICROALBUMINURIA ABSENT AND PRESENT

Biochemical parameters	RHT MAU- n = 243 cases	RHT MAU+ n = 76 cases	p
Dyslipidemia, n (%)	112 (46.09%)	41(53.95%)	0.2320
Hyperuricemia, n (%)	34 (13.99%)	12 (15.79%)	0.6971
Glycemia, mg/dL	108.01±26.01	118.80±32.02	0.0031
HbA1c %	5.96±0.91	6.56±0.98	< 0.0001
Creatinine, mg/dL	1.04±0.22	1.09±0.27	0.1032
Uric acid, mg/dL	5.31±1.7	5.56±1.6	0.2575
Potassium, mg/dL	4.59±0.44	4.71±0.43	0.0378
eGFR, mL/min/1.73 m^2	69.30±17.5	56.10±15.4	< 0.0001
LDL-c, mg/dL	136.40±46.7	139.80±46.9	0.5804
HDL-c, mg/dL	44.70±10.2	46.80±10.5	0.1208
TG, mg/dL	172.01±74.32	179.80±73.16	0.4240

The incidence of MAU was greater in RH patients presenting glucose metabolism disorders as seen in figure 6.

Regarding the relationship between MAU+ and CV events, MAU was present in 42.10% patients with ischemic heart disease, in 30.26% of those with peripherial artery disease and in 25% of those with cerebrovascular disease (fig. 7). The comparison between the MAU+ and MAU- groups was statistical significant for ischemic heart disease (p = 0.0021) and peripherial artery disease (p = 0.0233).

The analysis of biochemical data in patients with RH revealed important differences between the MAU+ and MAU- group. Significant statistical differences were noticed regarding FPG (118.80 ± 32.02 vs 108.01 ± 26.01 mg/dL), HbA1c (6.56 ± 0.98 vs 5.96 ± 0.91 %), eGFR (56.10 ± 15.4 vs 69.30 ± 17.5 mL/min/1.73 m^2) and potassium (4.59 ± 0.44 vs 4.71 ± 0.43 mg/dL). No semnificatve differences were noted referring to serum creatinine, uric acid, LDL-c, HDL-c, TG and impaired glucose tolerance (table 1).

An univariate logistic regression analysis revealed the following related factors to MAU: age (OR 1.028, 95% CI 1.018-1044, p < 0.001), BMI (0.987, 95% CI 0.977-0.998, p = 0.01), 24 h systolic BP (OR 1.023, 95% CI 1.014-1.032, p < 0.001), eGFR (OR 0.99, 95% CI 0.982-0.997, p < 0.001), glycaemia (1.003, 95% CI 1.002-1.008, p = 0.01), HbA1c (OR 1.384, 95% CI 1.231-1.692, p < 0.001), ischemic heart disease (OR 1.018, 95% CI 1.003-1.032, p = 0.04), peripheral arterial disease (OD 1.520, 95% CI 1.150-2.015, p = 0.010) and DM (OR 1.560, 95% CI 1.256-1.904, p < 0.001).

In a multivariate analysis the related factors to the presence of MAU were systolic BP (OR 1.024, 95% CI 1.011-1.039, p < 0.001), HbA1c (OR 1.324, 95% CI 1.078-1.724, p = 0.008) and eGFR (OR 0.989, 95% CI 0.977-0.999, p = 0.01).

MAU is an early marker of progressive CV and renal disease. As MAU is more sensitive than proteinuria in detecting CKD, its identification with screening programs, before the clinical phase, is meaningful in all hypertensive patients, expecially in severe hypertension as RH [14 - 16]. The biochemical and clinical characteristics of MAU+ patients were analysed in comparison with a goup of RH

with MAU-. Evaluation of MAU was based in most cases on one dip stick tests, aspect that represent a limit of our study as it has been showed that confirmation of MAU needs two or three repeated tests [17, 18].

The prevalence of MAU in RH patients was 21.99%. Literature data regarding prevalence of MAU in RH are scarce. The reported prevalence of MAU in hypertensive patients is highly variable among studies, ranging from 15% to 58.4% [19, 20]. In Romanian SEPHAR II survey 27.68% of hypertensive patients were considered with RH based on office BP [20]. As ABPM was not applied, RH was overestimated by including "white coat HT". MAU was recorded in SEPHAR II survey only in a minority of the hypertension (7.1%), but mild reduction of the eGFR (60 and 90 mL/min/1.73m^2) had an incidence of 41% in the total evaluated hypertensive population. As noticed in our study, several factors can affect the prevalence of MAU: older age, DM, CKD, obesity, and inefficient BP control. In the present study prevalence of MAU increased in concordance with the level of systolic BP, age, LVH, CKD stage, obesity and DM. The greater incidence of LVH, observed also in many trials, is considered to contribute to the increase of CV disease observed in these patients [21 - 24].

MAU is appreciated in all trials to be as a marker of generalized endothelial dysfunction and atherosclerosis, data consistent with the findings of the present study as it was more frequently diagnosed in RH patients with atherosclerotic disease as ischemic heart disease and peripheral vascular disease [25-30]. The relationship between CV comorbidities and the presence of MAU was investigated in the i-SEARCH study on 21,867 patients with high-risk hypertension. The prevalence of MAU increased to 74% in the presence of more than 3 comorbidities [31-33]. The present study confirms previous trials that have demonstrated a strong relationship between MAU and the level of systolic BP [5, 6]. Most of our RH patients had severe, second and third degree hypertension, with high CV risk. Mean systolic BP was greater in the MAU+ group, the difference between groups being 7 mmHg for systolic BP and 6 mmHg for diastolic BP. Control of BP to targets has been demonstrated to reduce MAU and prevent the progression of CKD [34-36].

Diabetes is a well-known predictor of proteinuria and studies have demonstrated that controlling strictly glycaemia wouldresult in preventing and reducing this complication [37]. MAU was significantly associated in our study with glycaemia level and DM. As MAU is an independent risk factor for atherosclerotic disease, clinicans must achieve a better control of both BP and glycemia to prevent the apearance of CV disease [38 - 42]. A relationship between MAU and obesity was reported in large studies, as obesity affects renal blood flow, GFR and determines renal hypertrophy [43 - 45]. This relationship was also observed in the present study, as obesity was present in neary two third of RH patients with MAU. It has been demontrated in large trials that some classes of antihypertensive drugs as ACEIs and ARBs reduce albuminura. In our study informations regarding the prescribed drugs were partially missing, so we could not assess differences in the class effects of these medications [46 - 49].

Limitations of our obsevational study can result from selection bias of the study population, diagnosis of MAU based in the majority of the cases on a single dip stick test and the absence of follow up data.

Conclusions

The prevalence of microalbuminuria in RH patients evaluated in primary care setting in Timis County Romania was 21.99%. Several factors affected the prevalence of MAU as older age, obesity, inefficient blood pressure control, diabetes mellitus and the presence of moderate–severe CKD. Biochemical characteristics of RH associating MAU were higher HbA1c levels, higher fasting plasma glucose, potassium and reduced eGFR. Predictors for the presence of MAU in a multivariate logistic regression analysis were high systolic blood pressure, high HbA1c levels and reduced eGFR. As MAU is an independent risk factor for cardio-vascular morbidity and mortality, its early detection is important for proper management, primary and secondary prevention and to achieve a better outcome of resistant hypertension patients.

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