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MICROALBUMINURIA - MORE THAN A RENAL FUNCTION INDICATOR FOR HYPERTENSIVE PATIENTS WITH ASSOCIATED CHRONIC DISEASES

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ABSTRACT The main objective of our research was to determine if microalbuminuria can be alone a cardiovascular predictor and if it influenced by the treatment changes. It is known that microalbuminuria is specific for patients with diabetes mellitus and hypertension and it is measured to monitor the progression of kidney disease. Many scientists demonstrated that microalbuminuria levels indicates the age of the hypertensive disease and the effectiveness of treatment, and it can be reversible when it has low levels. When it is compared with a cardiovascular risk calculator based on the Framingham risk score chart, microalbuminuria indicates almost the same results.

Keywords: microalbuminuria, proteinuria, cardiovascular risk.

Introduction

Recently many studies indicate a high mortality and morbidity risk in the hypertensive population with additional risk factors. Many government programs in different developing countries are spending high finances for hospital programs that include treatments for these patients, but preventing these maladies is not an easy objective taking in consideration human habits, life style and genetic heritage. Solutions are often simple and with the association of some proven markers for organ damage such as microalbuminuria, cardiovascular scores and others, it can be made a functional prevention protocol. [1-3]

When small amounts of albumin leaks off into the urine, that means there is an abnormally high permeability for albumin in the kidney's glomerulus. That is microalbuminuria, a well-known predictor of poor renal outcomes. It is known that microalbuminuria is specific for patients with diabetes mellitus and hypertension and it is measured to monitor the progression of kidney disease. [4]

Material and method

For our research we included 90 patients (43 males, females 47) suffering from hypertension with multiple cardiovascular risk factors (obesity, diabetes mellitus and renal disease). They have been grouped as follows: first group (A1) was formed by 30 patients (19 male, 11 females), with metabolic syndrome (hypertension grade I/II, obesity, decreased glucose tolerance, sedentary); the second group (A2) also with 30 patients (11 males, 19 females)with hypertension and diabetes mellitus type 2 under treatment; the third group (A3) includes 30 patients (13 males, 17 females) with grade 2 hypertensive concomitant with type 2 diabetes and chronic kidney disease. The control group had 20 healthy individuals (10 males, 10 females).

Inclusion criteria for the study was patients over 40 years of age and under 65 years of age (the average age for female patients was 52.5±2.3 and for male patients was 59.3±1.8) without cardiovascular disease history, without alcohol or tobacco intake.

Clinical data for hypertensive patients and control group were selected from anamnesis, clinical and para clinical examinations made to each patient at the moment of inclusion in our study. Blood pressure was measured taking in consideration the guideline of the ESH (European Society of Hypertension) [5].

Consecutively the anamnesis and clinical examination, the laboratory examination included determination from venous blood of the lipid profile (total cholesterol, triglycerides, LDL, HDL), glucose levels, and serum creatinine (specifically for the estimated calculation of glomerular filtration rate - eGFR). It was investigated the albumin/creatinine ratio, using the urinary dipsticks (for the evaluation of albuminuria) [6].

For the quantification the cardiovascular risk of our patients we used the Framingham risk score for male and female which predicts the risk of cardiac events for the next 10 years using a system of points based on anamnestic and para clinic data. The boundaries of risk score are: low risk (below 10% of the cardiovascular risk); intermediate risk (10-20%) and high risk (over 20%). [7, 8]

The obtained results were expressed as mean and standard deviation (SD) and all the data was analysed for statistical significance using the computer software Statistica 7. For the p values under 0.05 it was considered significant, for values under 0.01 it was distinctive statistically significant and for values of p under 0.001 it was considered very significant statistically. Values of *p* over 0.05 were considered non-significant.

Results

From anamnestic, clinical and para clinical exam we obtain the following results exposed in Table I. It can be seen that the age of the subjects in the study groups is significant close, also the BMI (body mass index) is modified in all the study groups.

Regarding the distribution by gender, the female patients had lower values in almost all measured parameters compared to those of the male. (Table I and Table II).

Table I. Biochemical data for male patients in all study groups compared with the control

Legend:

***** mean values; **SD**- standard deviation; the value of $p<0.05$ considered significant, $p>0.05$ considered non-significant; **BMI** –body mass index; **DBP** – diastolic blood pressure; **SBP** – systolic blood pressure; **TC** – total cholesterol; **HDL** – high- density lipoprotein; **LDL** – low-density lipoprotein; **TG** – triglycerides; **eGFR** – estimated glomerular filtration rate (calculated with MDRD formula); **Albumin-creatinine ratio**: **N** – normal values, **M** – presence of miroalbuminuria, **P**- clinical proteinuria; **Framingham risk score** - expressed in points and percentages [9].

For patients in study group A1 (hypertensive patients with metabolic syndrome) it can be noticed that there are a significant modification of the lipid profile and a slightly deviated value of the albumin/creatinine ratio towards microalbuminuria in male patients (Table I) more than female patients (Table II), which indicates a glomerular damage due to hypertension and blood glucose increased levels. This group has obese patients with highly modified lipid profile, hypertension for more than 1 year, with a vicious and sedentary life style, with low glucose tolerance, microalbuminuria and high values of eGFR indicating impairment of renal function, and p values (bellow 0.05) are significant compared with the control group (C).

The Framingham risk score was statistically significant higher in the A3 group study compared with the control group and with the other study groups taking in consideration that this group has a higher age value and with associated chronic diseases (diabetes and renal disease), over 30% risk of developing heart diseases in the next 10 years for male hypertensive patients and over 27% risk for female hypertensive patients. The albumin/creatinine ratio and the serum creatinine values confirm the renal disease by indicating the presence of clinical albuminuria notated with P in the table I and II.

Correlated with the hypertension values and blood sugar values, we discovered mild microalbuminuria in A1 group with higher values for male patients (mean value 75 mg/g). In the A2 group, we had elevated microalbuminuria values (mean value 180 mg/g) and in the A4 group we had clinical proteinuria (mean value >420 mg/g).

Parameters	**Male patients**						
	C	**A1**	***p***	**A2**	***p***	**A3**	***p***
Age, years (SD)*	36 (3.1)	46 (4.8)	0.00036	47 (5.1)	0.00007	61 (2.3)	0.0013
BMI, kg (SD)*	24 (2.7)	31 (4.6)	0.25144	26 (1.7)	0.01158	26 (3.8)	0.0345
DBP, mmHg (SD)*	78 (1.7)	92 (2.4)	0.00039	106 (2.4)	0.00023	108 (4.1)	0.008
SBP, mmHg (SD)*	123 (1.9)	150 (3.2)	0.00058	168 (2.1)	0.00017	176 (2.8)	0.007
TC, mg/dl (SD)*	188 (7.2)	289 (10.2)	0.00075	235 (21.5)	0.00092	252 (30.2)	0.0136
HDL, mg/dl (SD)*	54 (3.7)	34 (7.1)	0.00218	38 (27.4)	0.01125	36 (8.6)	0.0159
LDL, mg/dl (SD)*	129 (5.6)	201 (7.9)	0.01555	168 (213.7)	0.01142	174 (11.8)	0.0247
TG, mg/dl (SD)*	138 (4.3)	387 (5.2)	0.00078	260 (13.8)	0.01139	281 (42.5)	0.0234
Glucose, mg/dl (SD)*	93 (2.4)	110 (21.7)	0.00398	324 (14.7)	0.00027	298 (10.1)	0.0156
Serum creatinine, mg/dl (SD)*	0.92 (0.12)	1.4 (0.46)	0.01554	1.6 (0.26)	0.00054	2.2 (0.26)	0.092
eGFR, ml/min/1.73 m^2 (SD)*	105 (3.4)	69 (2.5)	0.01999	58 (4.8)	0.02268	31 (4.8)	0.0148
Albumin/creatinine ratio (mg/g) (SD)*	27 (1.2) **N**	75 (8.9) **M**	0.00072	180 (12.5) **M**	0.00017	420 (10.2) **P**	0.0162
Framingham score Points;%*	1; 1 %	15; >20 %		17; >25 %		21; >30 %	

Parameters	Female patients						
	C	A1	p	A2	p	A3	p
Age, years (SD)*	35 (2.3)	44 (3.6)	0.0026	49 (7.2)	0.00001	58 (1.7)	0.0010
BMI, kg (SD)	20 (2.1)	29 (5.3)	0.26005	25 (1.4)	0.0108	27 (4.7)	0.0392
DBP, mmHg (SD)	74 (1.5)	98 (2.3)	0.0035	104 (2.8)	0.00008	104 (2.9)	0.002
SBP, mmHg (SD)	118 (1.2)	148 (2.8)	0.0028	156 (2.6)	0.0010	172 (3.5)	0.001
Total cholesterol, mg/dl (SD)	186 (4.7)	275 (9.7)	0.0036	212 (14.5)	0.00098	244 (25.7)	0.0125
HDL, mg/dl (SD)	58 (4.5)	38 (5.9)	0.0224	46 (18.1)	0.01115	42 (5.9)	0.0169
LDL, mg/dl (SD)	127 (7.5)	192 (8.7)	0.0145	166 (17.3)	0.01159	172 (28.5)	0.0258
Triglycerides, mg/dl (SD)	122 (9.8)	368 (4.9)	0.0068	256 (14.8)	0.01144	262 (30.7)	0.0264
Serum glucose, mg/dl (SD)	88 (1.6)	102 (23.6)	0.03888	262 (13.8)	0.00025	286 (18.4)	0.0158
Serum creatinine, mg/dl (SD)	0.84 (0.18)	1.3 (0.51)	0.01488	1.45 (0.25)	0.00059	1.9 (0.73)	0.0098
eGFR, ml/min/1.73 m^2 (SD)	110 (2.2)	78 (4.8)	0.01888	61 (4.8)	0.0278	38 (3.9)	0.0194
Albumin/creatinine ratio (mg/g) (SD)	18 (1.5) **N**	68 (12.5) **M**	0.0065	162 (11.5) **M**	0.0012	380 (10.2) **P**	0.0185
Framingham score Points;%*	< 1 %	22; >17 %		23; >22%		24; >27%	

Table II. Biochemical data for female patients in all study groups compared with the control group

Legend:

***** mean values; **SD**- standard deviation; the value of $p<0.05$ considered significant, $p>0.05$ considered non-significant; **BMI** –body mass index; **DBP** – diastolic blood pressure; **SBP** – systolic blood pressure; **TC** – total cholesterol; **HDL** – high- density lipoprotein; **LDL** – low-density lipoprotein; **TG** – triglycerides; **eGFR** – estimated glomerular filtration rate (calculated with MDRD formula); **Albumin-creatinine ratio**: **N** – normal values, **M** – presence of miroalbuminuria, **P**- clinical proteinuria; **Framingham risk score** - expressed in points and percentages.

For the estimative calculation of glomerular filtration rate (eGFR) we used an online free calculator based on MDRD formula (Modification of Diet in Renal Disease) developed by the International Society of Nephrology (ISN). Whit anamnesis data and serum creatinine level we managed to determine the estimated value of the GFR (ml/min/1,73m2) and to classify the functional state of the kidneys' function for all the study groups (Table III). A1 and A2 groups were in the stage II chronic kidney disease (microalbuminuria on set), and A3 group was in stage IIIb chronic kidney disease (albumin/creatinine ratio indicating clinical proteinuria) with the presence of renal dysfunction.

Table III. Classification of renal disease by ISN

I	**90+**	*Normal renal function (urine analysis, structural malformations or genetic*
II	**60-89**	*Mild renal dysfunction (eGFR correlate with urine analysis, structural*
III a	**45-59**	*Moderate kidney dysfunction (with or without other evidence of kidney damage).*
III b	**30-44**	*Moderate kidney dysfunction.*
IV	**15-29**	*Severe renal dysfunction.*
V	**<15**	*Severe renal insufficiency.*

Legend:

*e**GFR** glomerular filtration rate (ml/min/1.73 m^2), estimated values were obtained with the MDRD formula; ** **ISN** (International Society of Nephrology) classification of kidney disorders. [10]

Parameters	Female patients						
	C	A1	*p*	A2	*p*	A3	*p*
DBP, mmHg (SD)	70 (4.6)	82 (1.8)	0.0073	99 (2.4)	0.00012	108 (4.1)	0.0009
SBP, mmHg (SD)	117 (2.7)	132 (2.6)	0.0058	148 (2.1)	0.00018	162 (2.8)	0.0012
Total cholesterol, mg/dl (SD)	165 (3.5)	185 (7.5)	0.0047	201 (21.5)	0.00036	218 (30.2)	0.0113
HDL, mg/dl (SD)	60 (2.8)	41 (4.8)	0.0135	46 (27.4)	0.0129	44 (8.6)	0.0126
Serum glucose, mg/dl (SD)	86 (1.9)	98 (12.2)	0.02669	197 (14.7)	0.00014	211 (10.1)	0.0148
Serum creatinine, mg/dl (SD)	0.78 (0.21)	1.2 (0.236)	0.01511	1.8 (0.25)	0.00038	2.6 (0.19)	0.0091
eGFR, ml/min/1.73 m^2 (SD)	107 (1.4)	69 (1.7)	0.01125	43 (3.6)	0.01159	28 (3.9)	0.0148
Albumin/creatinine ratio (mg/g) (SD)	18 (3.1) **N**	72 (8.9) **N**	0.0087	103 (27.5) **M**	0.00011	322 (19.4) **P**	0.0123
Framingham score Points;%*	< 1 %	18; >6 %		15; >17 %		18; >23 %	

After six months of changed treatment (especially antihypertensive medication and life style changes), we intended to check the microalbuminuria levels if it's have any connection with the risk of cardiovascular diseases.

Table IV. Biochemical data for male patients after six months

Parameters	Male patients						
	C	A1	*p*	A2	*p*	A3	*p*
DBP, mmHg (SD)*	76 (1.4)	80 (1.8)	0.0048	98 (2.4)	0.00004	103 (4.1)	0.0001
SBP, mmHg (SD)*	122 (1.2)	134(2.6)	0.0013	148 (2.1)	0.00008	150 (2.8)	0.0002
TC, mg/dl (SD)*	184 (4.5)	195 (7.5) 48	0.0035	215 (21.5)	0.00041	225 (30.2)	0.0111
HDL, mg/dl (SD)*	52 (3.7)	48(4.8)	0.01158	42 (27.4)	0.01008	39(8.6)	0.0145
Serum glucose, mg/dl (SD)*	88 (2.8)	99(12.2)	0.02258	199 (14.7)	0.00021	178 (10.1)	0.0098
Serum creatinine, mg/dl (SD)*	0.89 (0.12)	1.2 (0.236)	0.01411	1.8 (0.25)	0.00054	2.6 (0.19)	0.0047
eGFR, ml/min/1.73 m^2 (SD)*	107 (2.2)	69 (1.7)	0.01149	43 (3.6)	0.02048	28 (3.9)	0.0122
Albumin/creatinine ratio (mg/g) (SD)*	22 (1.2) **N**	72 (8.9) **M**	0.0036	103 (27.5) **M**	0.00011	322 (19.4) **P**	0.0114
Framingham score, % *	< 1 %	11; >8 %		14; >16 %		16; >25 %	

Legend:

***** mean values; **SD**- standard deviation; the value of $p<0.05$ considered significant, $p>0.05$ considered non-significant; **BMI** –body mass index; **DBP** – diastolic blood pressure; **SBP** – systolic blood pressure; **TC** – total cholesterol; **HDL** – high- density lipoprotein; **eGFR** – estimated glomerular filtration rate (calculated with MDRD formula); **Albumin-creatinine ratio**: **N** – normal values, **M** – presence of miroalbuminuria, **P**- clinical proteinuria; **Framingham risk score** - expressed in points and percentages.

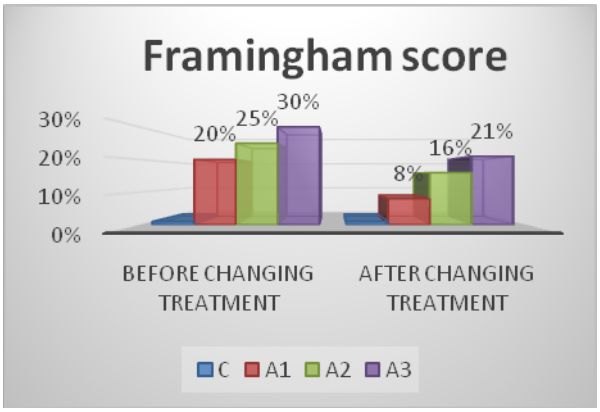
As it can be observed in Table IV and V, after changes in blood pressure treatment, microalbuminuria was reversible for the A1 group for both male and female patients. Also in the rest of the hypertensive groups A2 and A3 the levels of proteinuria were significant lower compared with its values before the changing of treatment and lifestyle.

Table V. Biochemical data for female patients after six months

Legend:

***** mean values; **SD**- standard deviation; the value of $p<0.05$ considered significant, $p>0.05$ considered non-significant; **BMI** –body mass index; **DBP** – diastolic blood pressure; **SBP** – systolic blood pressure; **TC** – total cholesterol; **HDL** – high- density lipoprotein; **eGFR** – estimated glomerular filtration rate (calculated with MDRD formula); **Albumin-creatinine ratio**: **N** – normal values, **M** – presence of miroalbuminuria, **P**- clinical proteinuria; **Framingham risk score** - expressed in points and percentages.

The Framingham risk score was significant modified after the treatment. But in the A2 and A3 hypertensive group were high values of this risk score (16% and 25% for male patients and 17% and 23% for female patients) maybe because of the multiple risk factors associated with hypertension.

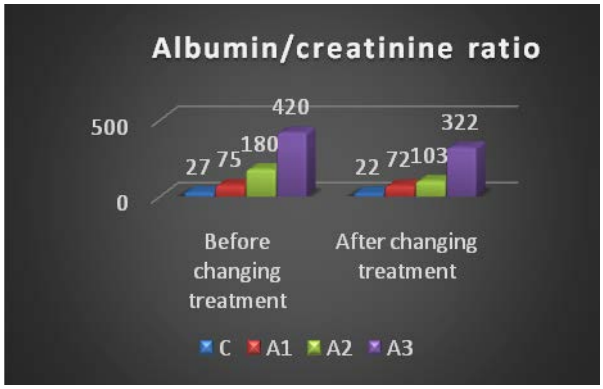


Picture 1 – Framingham risk score and albumin/creatinine ratio compared before and after the changing of antihypertensive medication

As it can be seen, these two important tools (Framingham risk score and albumin/creatinine ratio) have almost the same modifications, as the Framingham risk is high for the group A3 so is the albumin/creatinine ratio, so, by analogy, the last one can be associated with CV risk.

Discussions

The main objective of our research was to determine if microalbuminuria can be alone a cardiovascular predictor and if it is an influenced by the



treatment changes. Obtained data reveals that the hypertensive patients' groups' modifications were distinctive, taking in consideration the onset of the hypertension and the associated chronic illnesses. We know from anamnesis that all the patients'hypertenion was old and under treatment, and for having good results we stopped the treatment one week and after that we collected the blood samples and managed to obtain the biochemical data. These data were significant for associating the microalbuminuria levels with the cardiovascular risk for the next years.

The ratio of albumin/creatinine shown us the amount of microalbuminuria which, according to some researchers [11] can be directly correlated with high blood pressure and kidney function. Many scientists demonstrated that microalbuminuria levels indicates the age of the hypertensive disease and the effectiveness of treatment [12], and it can be reversible when it has low levels, which directs us that the glomerular apparatus is not yet damaged, so we can say it's not a kidney major problem for its function. In the other hand for the A_2 and A_3 groups the situation was different, we can observe high values for microalbuminuria even

proteinuria, very significant statistically compared to control group which indicates an obvious renal damage, confirmed also by the eGFR values for these groups, similar with literature data [13].

Based on these researches we changed the treatment of these patients and also included indication of changing their lifestyle for improving their condition. As PREVEND-IT trial shows, we included the ACE inhibitors as main choice for antihypertensive treatment [14]. After six months we obtained great results by having modified all biochemical parameters that were initial very high and with raised values of risk score for cardiovascular events for the next 10 years.

The utmost result was that for group A2 hypertensive patients with metabolic syndrome, after changing the treatment, we managed to reverse the microalbuminuria to normal values so by consequence to reduce the CV risk to low range area. Even though we decreased values for A2 and A3 groups, the microalbuminuria wasn't reversible because of the associated CV factors and the age of hypertension and its irreversible damaged to the glomerulus. But even so, microalbuminuria is indeed a barometer for antihypertensive treatment, if it decreases it is known that the treatments works [15].

In conclusion, by comparing each group from our study, we were able to highlight the importance of microalbuminuria in indexing the risk of kidney damage and also the cardiovascular risk in time by the simple presence of its positive values. For the physician in his medical act, it can be a useful instrument for diagnosis, treatment and prevention of chronic cardiovascular disease and renal outcomes.

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