MICROALBUMINURIA IN ESSENTIAL HYPERTENSION AT PATIENTS WITH OR WITHOUT TYPE 2 DIABETES

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Received October 6, 2011

The aim of the study was initiated to investigate the prevalence of microalbuminuria and its relationship with several clinical and biochemical variables in a population of patients with mild or moderate essential hypertension at patients with or without type 2 diabetes. The study population consisted of 85 patients with hypertension without DM (group A) 162 patients with type 2 DM without or with high blood pressure (group B and C) and 50 control subjects (control group). The patients in groups A, B and C were admitted in hospitals consecutively for one month. For every patient we determined clinical and biochemical variables, plasma insulinemia, HOMA-IR and renal function (albumin to creatinine ratio and GFR). We found the highest prevalence of microalbuminuria (29 %) in the group C (DM with high blood pressure). In groups B (DM without high BP) and A (hypertension without DM) the prevalence of microalbuminuria was 20% and respectively 15% respectively. Moreover, in group A there was a strong positive correlation with diastolic BP ($r=0.696$; $p<0.001$) and negative correlation with cholesterol HDL($r=-0.366$; $p<0.05$). Albumin excretion rate was increased in all groups with high risk for vascular damage. The decreasing order of the frequency of renal dysfunction was: group C, group B and group A. These data show that the most important factor of increased AER is related to the presence of diabetes and high blood pressure. This shows that an increased albumin excretion rate could be a valuable marker of vascular damage.

Key words: hypertension; microalbuminuria; prevalence; clinical and biochemical variables.

INTRODUCTION

Hypertension is a common comorbidity in diabetes, affecting the majority of patients, with a prevalence depending on the type of diabetes, age, obesity, and ethnicity. Hypertension is an independent and major risk factor for both CVD (Cardiovasular Disease) and chronic kidney disease (CKD). In type 1 diabetes mellitus hypertension is more often the result of underlying nephropathy, while in type 2 diabetes it usually coexists with other cardiometabolic risk factors[1].

The aggravating role of hypertension associated with diabetes is supported by numerous studies, especially by the results of United Kingdom Prospective Diabetes Study (UKPDS), which showed that BP reduction has a favorable impact on the evolution and complications of diabetes, equivalent to that of an optimal glycemic control[2].

These are only two arguments that support the need for serious addressing, assessing and treatment of the two pathological conditions (diabetes and hypertension) whose association concerns approximately 50% of the patients with type 2 diabetes.

Hypertension is the most important co-existing risk factor for death at a young age in patients with type 2 diabetes. Almost 75% of the cardiovascular complications in patients with diabetes can also be attributed to hypertension[3].

UKPDS showed that the presence of hypertension is a risk factor for microalbuminuria and retinopathy and that reducing the incidence of chronic complications was significantly associated with the amplitude of systolic BP (Blood Presure) decrease, the lowest risk corresponding to a systolic BP below 120 mmHg[1].

Hypertension is commonly found in patients with DKD (Diabetic Kidey Disease). Its prevalence

is estimated to range between 30 to 96% with a higher prevalence in patients with one increased albumin excretion rate. Uncontrolled hypertension induces a higher risk of cardiovascular events, including death, increasing proteinuria and progression to kidney disease.

An increased albumin excretion rate is a well-known predictor of poor renal outcomes in patients with type 2 diabetes and in essential hypertension[4,5]. More recently, albuminuria has also been shown more recently to be a predictor of cardiovascular out-comes in these populations[6–9]. There is emerging data that reduction of albumin excretion rate leads to reduced risk of adverse renal and cardiovascular events[10–13]. It has become increasingly clear that albumin excretion rate should not only be measured in all patients with type 2 diabetes and hypertension, but also steps should be taken to suppress albuminuria to prevent future renal and cardiovascular adverse events.

Increased urinary excretion of albumin ranging between 30 and 300 mg/d (*i.e.*, microalbuminuria) has been found in a relatively large number of patients with essential hypertension[14–19]. Variations in the prevalence of microalbuminuria between 10% and 40% that have been reported in other studies are likely due to differences in the selection criteria, to the techniques used for the detection of microalbuminuria, and, in some cases, to the small number of patients studied. Recently, a large clinical trial that enroled patients with mild and moderate essential hypertension showed a 6.1% prevalence of microalbuminuria, which is a considerably lower value than previously reported[19].

Epidemiological data show that the prevalence of microalbuminuria is 30% in diabetic adults and 10–15% in non-diabetic adults[20]. Microalbuminuria, a result of increased renal endothelium permeability, is a marker of systemic endothelial dysfunction as well[20].

Increased urine albumin excretion is associated with most cardiovascular risk factors, hyperglycemia, hypertension, renal dysfunction, dyslipidemia, hyperhomocysteinemia, increased protein intake, smoking, and presence of acute phase inflammation markers. Among these, diabetes and hypertension are the major risk factors for development of microalbuminuria[21].

Microalbuminuria is a indicator of endothelial dysfunction and an independent marker for cardiovascular morbidity and mortality in individuals with and without DM (Diabetes Mellitus)[22].

The present study was initiated to investigate the prevalence of albumin excretion rate and its relationship with several clinical and biochemical variables in a population of patients with mild or moderate essential hypertension in patients with or without type 2 diabetes.

PATIENTS AND METHODS

The present study took place at the „N. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases (164 patients with type 2 DM with/or without hypertension) in collaboration with Cantacuzino Hospital – Internal Medicine (85 patients with hypertension, without diabetes mellitus) Bucharest Romania. The patients we selected and analyzed were admitted in these hospitals consecutively for one month.

For a better assessment of its relationship with several clinical and biochemical variables, the patients in this study were divided in one control group and three study groups:

– *control group*: 50 subjects (26 men and 24 female) non diabetic, non hypertensive;

– *group A*: 85 patients (43 men and 22 female) with high blood pressure, without DM;

– *group B*: 82 patients (42 men and 40 female) with DM and normal blood pressure;

– *group C*: 82 patients (40 men and 42 female) with DM and high blood pressure.

Type 2 diabetes was defined according to American Diabetes Association[1] criteria.

The inclusion criteria for patients with high blood pressure (group A) were: age 25–60 years, BMI $\leq$ 35 kg/m², level of blood pressure $\geq$ 140/90 mmHg (According to JNC – VII) in least three different occasions or by the presence of antihypertensive treatment, fasting blood glucose level <110 mg/dl and HbA1c $\leq$ 6%. *The inclusion criteria* for patients with DM (group A and C) were: age 35–70 years, BMI $\leq$ 35 kg/m², level of blood pressure $\geq$ 130/80 mmHg, fasting blood glucose level > 126 mg/dl (> 7 mmol/l), HbA1c>6 %, duration of diabetes $\geq$ 3 years, previous oral antidiabetic therapy or nutrition therapy.

The exclusion criteria were: age <25 years, urinary infection, hepatic/or renal disease (defined as serum creatinine > 1,5 mg/dl in men and > 1,4 mg /dl in women min), chronic heart failure (New York Heart Associations classes III and IV) or advanced chronic obstructive pulmonary disease, severe obesity, severe hypertension disabling diseases such as dementia and the inability to cooperate.

All patients gave written informed consent to participate in the study, which was approved by the local ethical committees for human investigation.

Microalbuminuria was determined by measuring with the albumin excretion rate (AER) in three non consecutive first morning urine samples. Normal albumin excretion rate was < 30 mg/g creatinine and microalbuminuria was defined as AER in the range of 30 and 299 mg/g creatinine.[1] The ACR (albumin to creatinine ratio) was calculated as follows: urinary albumin concen-tration (mg/liter)/ urinary creatinine concentration (mg/dl). The mean value of each patient's three ACRs was used to indicate the level of albumin excretion[1]. In Table 1 are given reference values for albumin excretion rate (AER):

Table 1

	Normal AER	**Higher AER (Microalbuminuria)**
1. Microalbumin / creatinine excretion rate	M < 20 mg/g F < 30 mg/g	M ≥ 20m/g F ≥ 30mg/g
2. AER (Albumin Excretion Rate)	< 20 μg/min <30 mg/24h	20-200 μg/min 30-300 mg/24h
3. Albumin concentration (morning urine sample)	< 30 mg/l	30-300 mg/l

Factors that interfere with the determination of AER (exclusion criteria): old age, physical exercise, forced diuresis, nictemeral rhythm, masive obesity, urinary infections, vaginal secretions, chronic diseases or fever, heart failure, hepatic cirrhosis nephritic syndrome, hypercatabolism, hyperthy-roidism, poorly controlled diabetes, drugs (non steroidal anti-inflammatory drugs-NSAID).

Patients with high pathological level of AER (>20 μg/min or >30 mg/24h) or with a urinary albumin to creatinine ratio ≥20 mg/g in males and ≥ 30mg/g in females, were identified, analysed and followed-up during their hospitali-sation, checking for at least 2 pathologically high AER values in three consecutive measurements**.**

Blood pressure measurements: using standards procedures (with the patients in seated position and after 5- minute of rest) BP was measured on the right arm and left arm with a mercury sphygmomanometer (cuff size 12,5/40 cm) by a physician or trained nurse. The higher value was selected.

LABORATORY ASSAY

The blood samples were obtained after 12 hours of overnight fasting. Morning urine sample was collected in a container for analysis of creatinine and albuminexcretion rate. Fasting blood glucose, glicosylated hemoglobin (reference range 4.0–6.0%), total cholesterol, high density lipoprotein, trigly-ceridemia, serum creatinine, urea and uric acid were measured using standard techniques. To estimate low-density lipoprotein (LDL) cholesterol we used Fridewald formula as follows:

LDL-cholesterol=Total cholesterol-HDL cho-lesterol- triglycerides/5.

Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as the product of fasting plasma insulin value (micro units per ml) and fasting plasma glucose value (mg per deciliter) divided by 405. We performed anthropometric measurements: weight, height, BMI (Body Mass Index) kg/m^2. The body mass index (BMI) was calculated as weight in kilograms divided by height in square meter[23].Creatinine clereance was estimated by calculating GFR (Glomerular Filtration Rate) using MDRD formula[24].

STATISTICAL ANALYSIS

Data were analyzed using the SPSS package for Windows version 16 and Excels 2003. Patient's characteristics are presented as mean values ± SD and data skewed distributed were expressed as median (interquartile range). Pearson's correlation was calculated to measure the relationship between variable. All p-values < 0.05 were considered statistically significant.

RESULTS

Clinical and biochemical data recorded in the four study groups are given in Table 2.

Table 2

Clinical and biochemical characteristics of the population

Caracteristica	Control group	HBP without DM- Group A	p value Gr A/Ctrl_	DM without HBP – Group B	p value GrB/Ctrl	DM with HBP Group C	p value Gr C/Ctrl
	N=50	N=83		N=82		N=82	
Sex	M/F=26/24	M/F=43/42		M/F=42/40		M/F=40/42	
Age	52.28+/-1.69	53.2+/-1.19	0.671	52.82+/-1.11	0.792	57.12+/-1,23	0.03
Duration of DM (years)	-	-	-	4.04±1.61		6.21±3.16	-
Duration of HBP(years)	-	6.8+/-0.41	-	-	-	8.15+/-1.06	,
Blood glucose	84.39+/-2.03	95.03+/-1.61	0.001	163.53+/-3.21	0.001	152.39+/-4.04	0.001
HbA1c	3.92+/-0.15	5.8+/-0.06	0.001	7.73+/-0.11	0.001	7.78+/-0.14	0.001
Insulinemie	7.19+/-0.7	10.35+/-0.52	0.002	18.02+/-0.62	0.001	12.25+/-1.04	0.004
BMI	23.12+/-0.53	28.73+/-0.14	0.001	30.52+/-0.39	0.001	31.36+/-0.37	0.001
Cholesterol	179.17+/-4.95	202.67+/-2.97	0.001	214.44+/-3.67	0.001	203.15+/-4.78	0.005
Triglyceride	129.12+/-3.21	143.14+/-5.4	0.117	181.87+/-9.57	0.001	175.43+/-12.54	0.020
HDL col	54.23+/-0.82	42.94+/-0.91	0.001	45.67+/-1.52	0.001	41.14±1.52	0.001
LDL col	99.13+/-4.44	131.11+/-2.98	0.001	136.93+/-4.61	0.001	122.4+/-4.98	0.006
SBP	118.39+/-1.23	151.83+/-1.23	0.001	120.87+/-0.72	0.076	136.89+/-1.2	0.001
DBP	70.17+/-1.13	93.89+/-0.44	0.001	69.66+/-0.66	0.685	82.67+/-0.79	0.001
Urea	30.89+/-1.27	37.8+/-0.46	0.001	36.78+/-0.61	0.001	35.54+/-1.34	0.040
Creatinine	0.6+/-0.02	0.75+/-0.02	0.001	0.67+/-0.02	0.009	0.78+/-0.03	0.001
HOMA-IR	1.27+/-0.08	2.41+/-0.13	0.001	7.28+/-0.29	0.001	4.69+/-0.45	0.001
ACR	5.37+/-0.42	17.37+/-1.55	0.001	19.23+/-1.7	0.001	23.53+/-2.34	0.001
Uric acid	4.19+/-0.15	4.71+/-0.11	0.010	4.45+/-0.1	0.150	5.65+/-0.22	0.001
GFR	135.73+/-6.42	105.6+/-4.57	0.001	114.19+/-4.34	0.009	97.29+/-3.99	0.001

Data in table are presented as mean ± SD;N= number; HBP=high blood presure; SBP and DBP=sistolic and siastolic presure; BMI=body mass index; HbA1c=glycated hemoglobin; ACR=urinary albumin to creatinine ratio; GFR= glomerular filtrate rate.

Patients with hypertension without DM (group A) had a mean age of 53.2±1.19 years, a mean systolic blood pressure of 151.83±1.83 mmHg and a mean diastolic blood pressure was 93.89±0.44 mmHg. Patients with DM (from group B and C) had a mean age of 52.82±1.11 and 57.12±1.23 years and mean value of HbA1c was 7.73 ±0.11 and 7.78±0.14% respectively.

The prevalence of microalbuminuria and the distribution of ACR (mean value in mg/g) in the entire population are shown in the Figure 1. The prevalence of microalbuminuria was: 15.56% in group A; 20% in group B and 29% in group C. Mean value of albumin to creatinine ratio (ACR-mg/g) was: 17.37±1.55 for group A, 19.23±1.7 for group B and 23.53±2.34 for group C vs. 5.37±0.42 for control group (Figure 1).

The Figure 2 shows the mean value of ACR in quartiles of HOMA-IR for patients included in group A (hypertension without DM). We found not a direct proportional distribution of ACR per HOMA-IR quartiles, the highest value of ACR were in Q2 and Q3 quartiles intervals.

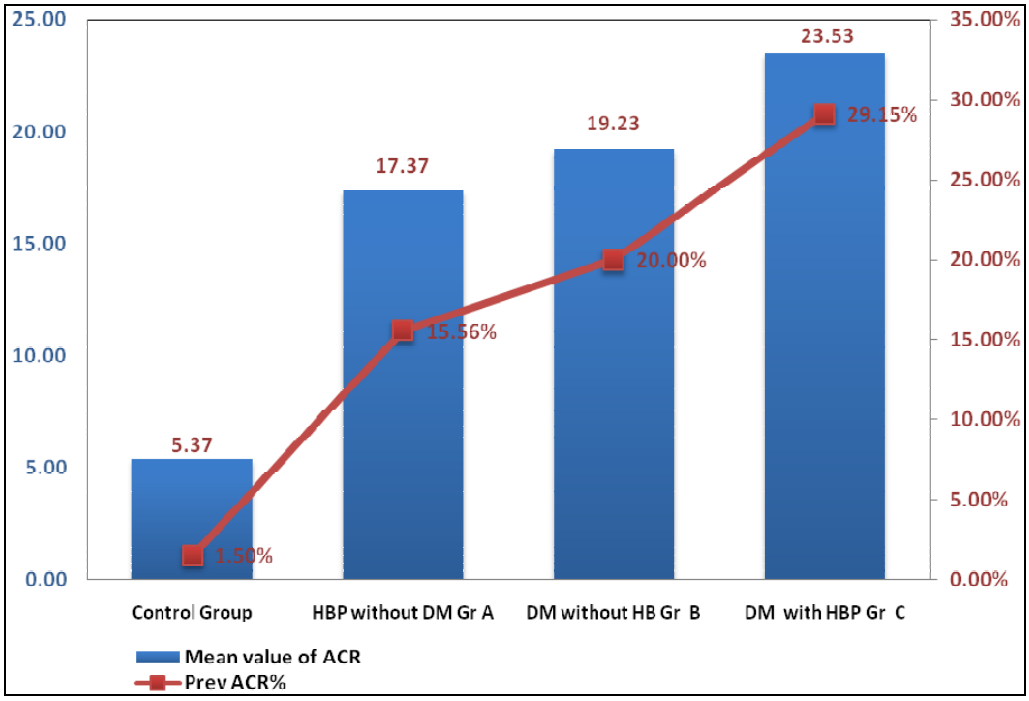

Fig. 1. The prevalence of microalbuminuria and comparative situation of ACR (mean value) in study groups.

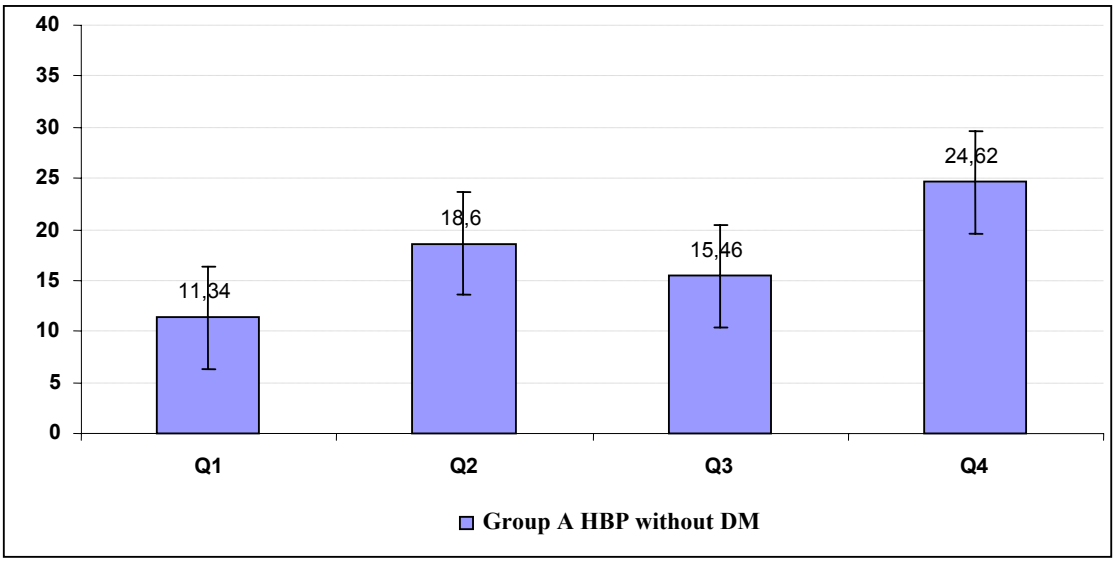

Fig. 2. Repartition ACR in quartiles of HOMA-IR in Group A.

Univariate correlation between ACR and selected clinical and biochemical variables for group A, B and C are presented in Table 3, Table 4 and Table 5 respectively. In patients from group A Table 3 shows a strong positive correlation between ACR and both diastolic BP (r=0.696; p<0.001) and systolic BP (r=0.622; p<0.001) and moderate positive correlation with plasma trygliceride (r=0.418; p<0.05) and uric acid (r=0.310; p<0.005). In group A mean value of ACR was unrelated to BMI and duration of hypertension.

Table 4 shows Pearson's correlation between ACR and selected variables from group B. In this group ACR was positively correlated with blood glucose (r=0.490; p=0.001), HbA1c (r=0.494; p=0.001), level cholesterol (r=0.683; p=0.001) and cholesterol LDL (r=0.642, p<0.001).

Univariate correlations between ACR and selected clinical and biochemical variables for groups C were as follow: with diastolic BP(r=0.364; p<0.005), blood glucose(r=0.526; p< 0.001), HbA1c (r=0.615; p<0.001) and HOMA-IR (r=0.395; p=0.01) (Table 5).

Table 3

Pearson's correlation between ACR and selected variables.
Group A: HBP without DM

	ACR	
	Pearson Correlation	**Sig. (2-tailed)**
Col	***0.003***	***0.983***
Trygliceride	***0.418(**)***	***0.004***
HDLcol	***-0.366(*)***	***0.013***
LDL	***-0.037***	***0.807***
SBP	***0.622(**)***	***<0.001***
DBP	***0.696(**)***	***<0.001***
Uree	***0.522(**)***	***<0.001***
Creat	***0.154***	***0.311***
Uric acid	***0. 310***	***0.04***

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

Table 4

Pearson's correlation between ACR and selected variables.
Group B: DM without HBP

	ACR	
	Pearson Correlation	**Sig. (2-tailed)**
Blood glucose	***0.490(**)***	***0.001***
HbA1c	***0.494(**)***	***0.001***
Insulinemie	***0.365(*)***	***0.015***
HOMA	***0.562(**)***	***<0.001***
BMI	***0.285***	***0.061***
Chol	***0.683(**)***	***<0.001***
Trygliceride	***-0.130***	***0.402***
HDLcol	***-0.166***	***0.281***
LDL	***0.642(**)***	***<0.001***
SBP	***0.03(**)***	***<0.001***
DBP	***0.409(**)***	***0.006***
Uree	***0.144***	***0.350***
Creat	***0.348(*)***	***0.040***
Uric acid	***0.248(*)***	***0.100***

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

Table 5

Pearson's correlation between ACR and selected variables.
Group C: DM with HBP

	ACR	
	Pearson Correlation	**Sig. (2-tailed)**
Blood glucose	***0.526(**)***	***<0.001***
HbA1c	***0.615(**)***	***<0.001,000***
Insulinemie	***0.287***	***0.065***
HOMA	***0.395(**)***	***0.010***
BMI	***0.009***	***0.953***
Chol	***0.240***	***0.126***
Trygliceride	***0.151***	***0.340***
HDLchol	***-0.011***	***0.947***
LDL	***0.158***	***0.319***
SBP	***0.222***	***0.158***
DBP	***0.364(*)***	***0.018***
Uree	***-0.054***	***0.734***
Creat	***-0.210***	***0.181***
Uric acid	***-0.006***	***0.969***

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

In group A, we found a linear positive relationship between diastolic BP and ACR (r=0.696; p<0.01), as shown in Figure 3.

In the same group we also found a negative correlation between cholesterol-HDL and ACR(r=0.366; p<0.05) (Figure 4).

Figure 5 illustrates a strong linear positive relationship between level cholesterol and mean value of ACR (r=0.683; p<0.001) in patients from group B (DM without high BP).

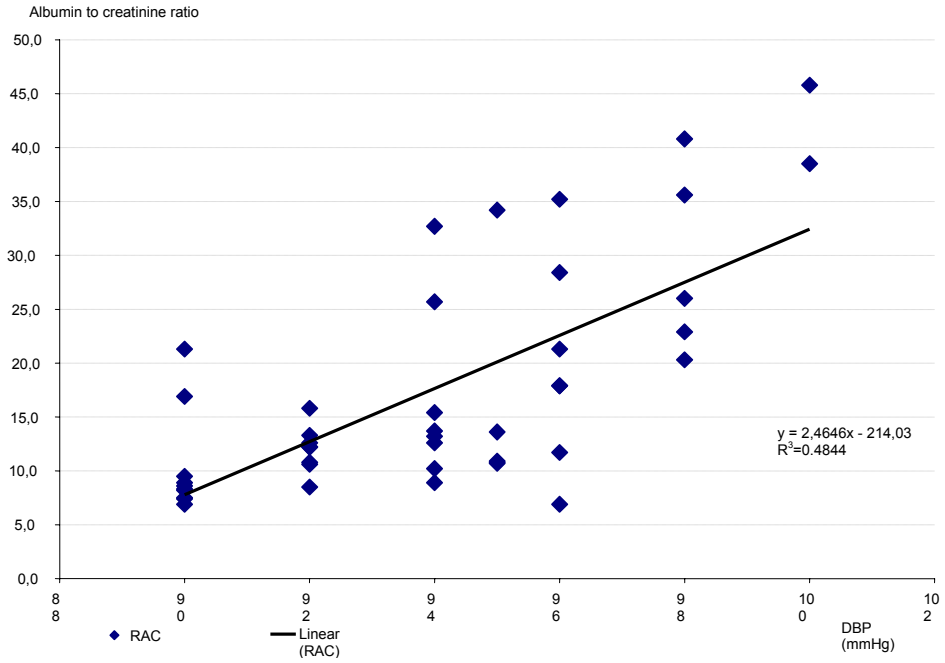

Fig. 3.Correlation between diastolic BP and ACR for group A(r=0.696, p<0.001).

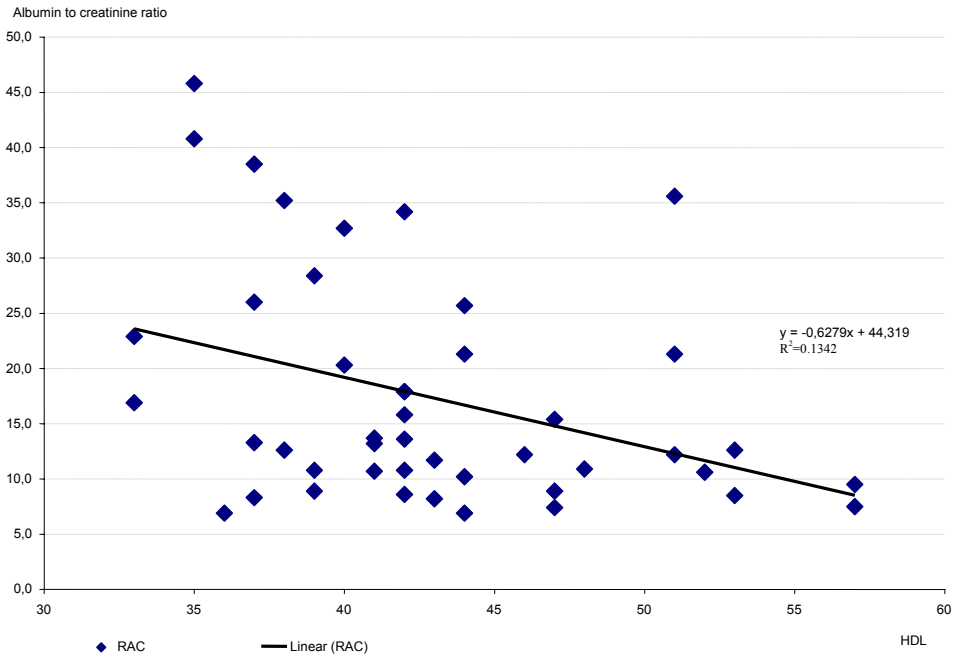

Fig. 4. Correlation between HDL cholesterol and ACR for group A(r=0.366, p<0.013).

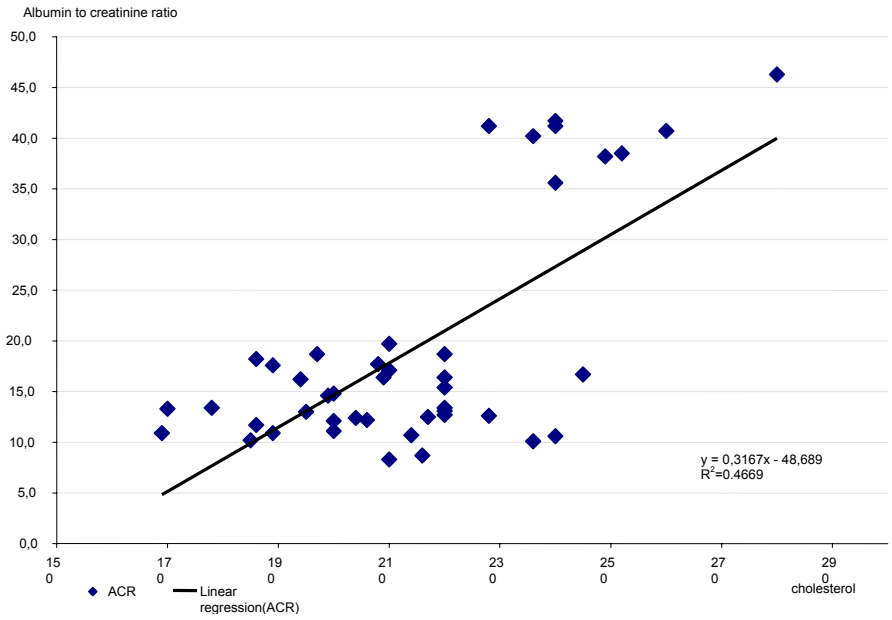

Fig. 5. Correlation between Cholesterol and ACR for group B: DM without HBP(r=0.683; p<0.001).

DISCUSSION

Increased urinary albumin excretion is a known risk factor for cardiovascular events and clinical nephropathy in patients with diabetes. Whether the presence of microalbuminuria predicts long-term development of chronic renal failure (CRF) in patiens without diabetes but with primary hypertension remains to be documented.

Renal dysfunction is a common finding in patients with hypertension and is associated with an increased risk for cardiovascular events (CVEs)[25,26] as well as with progression to ESRD[27]. It has been pointed out that cardiovascular risk progressively increases as renal function declines and that it is already significantly elevated in the earliest stages of renal damage[28]. Identifying the precursors of overt kidney disease is therefore of utmost importance for limiting the burden of cardiovascular and renal morbidity. Increased albumin excretion rate (AER) has been related to unfavorable cardiovascular outcomes in the general population[29,30] and in patients with diabetes and in high-risk patients[31]. Furthermore, the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study[32] confirmed the predictive power of microalbuminuria and its changes over time[33] in a large cohort of carefully monitored patients during a 5-year follow-up; however, the renal predictive value of albuminuria is thus far limited to high-risk patients with or without diabetes[34,35] and to the general population[36]. Some studies have suggested that the presence of microalbuminuria increases the relative risk of an adverse cardiovascular event similarly to the presence of hypercholesterolemia[37]. The prence of micoalbuminuria may need to be viewed in the same light as other risk factors such as blood pressure, cholesterol and blood glucose.

To better understand the natural history of hypertensive renal disease, especially in the early stage when intervention may prevent or delay sequelae. In this study we examined the prevalence of microalbuminuria and its relationship with clinical and biochemical variables in essential hypertension in patients with or without type 2 DM.

In this study microalbuminuria was present in all groups and the highest prevalence was observed in group C (DM with high BP). Also, the prevalence of microalbuminuria was significantly higher in patients with hypertension without DM (group A) vs. control group.

Patients with hypertension without diabetes (group A) and microalbuminuria were more likely male and showed higher blood pressure and serum trygliceride, serum uric acid levels when compared with patients with normoalbuminuria despite similar renal function and lipid profile. We found no association between basal levels of albumin excretion rate and eGFR (r=0.222; p=0.158). The patients (bots male and female) in group C (hypertension and DM) with microalbuminuria had a higher diastolic blood pressure, blood glucose and HbA1c as compared with patients with

normoalbuminuria both in male and female. While in patients from group A the relationship between mean value of ACR and HOMA-IR quartiles was not directly proportional, in patients from group C mean value of ACR increased with quartiles intervals. These data show that insulin resistance, as refines today, has nothing to do with renal involvement in diabetes.

The presence of albuminuria is a powerful predictor of renal and cardiovascular risk in patients with type 2 diabetes and hypertension. In addition, multiple studies have shown that decreasing the level of albuminuria reduces the risk of adverse renal and cardiovascular outcomes. The pathophysiology is not completely known, but is hypothesized to be related to endothelial dysfunction, inflammation, or possibly abnormal-lities in the renin-angiotensinaldosterone system. Albuminuria is therefore an important risk factor in detecting the patients at risk. The American Diabetes Association recommends that patients with type 2 diabetes be tested for albuminuria at the time of initial diabetes diagnosis and yearly thereafter[1]. Initiation of ACE inhibitor or ARB (angiotensin receptor blockers) therapy should be considered in patients with microalbuminuria or overt proteinuria.

In summary, albuminuria is associated with adverse renal and cardiovascular outcomes, and decreasing albuminuria with ACE inhibitor or ARB therapy, blood pressure lowering, and/or other agents can lead to improved outcomes. Physicians should measure urinary albumin excretion in patients with type 2 diabetes and hypertension routinely and be as aggressive in treating this modifiable risk factor as they do blood pressure, cholesterol, or blood glucose.

This study confirms that increased urinary albumin excretion is associated with a worse pattern of cardiovascular risk factors and is a marker of concomitant cardiovascular damage in essential hypertension.

CONCLUSIONS

Albumin excretion rate was increased in all groups with high risk for vascular damage. The decreasing order of the frequency of renal dysfunction was: group C (diabetes with blood pressure), group B (normotensive diabetes), group A (hypertensive patients without diabetes). These data show that the most important factor of increased albumin excretion rate is related to the presence of diabetes and high blood pressure.

This shows that an increased albumin excretion rate could be a valuable marker of vascular damage. Pathologically high AER is both a marker for vascular damage and a risk indicator of premature cardiovascular morbidity and mortality. This risk did not correlation with insulin resistance assessed by HOMA-IR. Early detection and dosage of microalbuminuria is important, not only in diabetic patients, but also in non-diabetic patients.

***Abreviation**: ADA=American Diabetes Association; ACR=albumin-to-creatinine ratio; AER=albumin excretion rate; BMI=body mass index;DM=diabetes mellitus*; *GFR= glomerular filtration rate HOMA-IR=homeostasis model assessment of insulin resistance.ACE=angiotensin converting enzyme; ARB=angiotensin receptor blockers*

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