

Microalbuminuria in non diabetic population as an marker of nephropathy

Microalbuminúria em população não diabética como marcador precoce de nefropatia

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ABSTRACT

Introduction: Years before the progression to *diabetes mellitus* type II patients can get by with a pre-diabetes called period. The pathogenesis involved pre-diabetes is insulin resistance **Objective:** This paper discusses the frequency of microalbuminuria in non-diabetic population, but with increased metabolic risk, and attempts to assess whether there is any correlation of microalbuminuria with data from glucose metabolism. **Methods:** A total of 132 nondiabetic patients who presented one or more risk factors for changes in glucose metabolism were included in the study: arterial hypertension; obesity; first-degree relatives with diabetes; individuals of Hispanic-American, Asian and African-American ethnicities; mothers of newborns who are large for gestational age (LGA) or who had gestational diabetes; serum measurements in fasting HDL cholesterol 250 mg/dL. **Results:** The results showed a frequency of abnormal microalbuminuria for the method in 16% of this population, and the presence of lower levels of HDL-cholesterol and creatinine clearance in this population. There was a positive correlation between microalbuminuria and serum creatinine and uric acid. **Conclusion:** Our study suggests that microalbuminuria be evaluated as a marker of incipient nephropathy in non-diabetic population with increased metabolic risk.

Keywords: *diabetes mellitus*; prediabetic state; chronic kidney disease; albuminuria.

INTRODUCTION

Years before the progression to type II *diabetes mellitus* (DM2), the patient can live in a period called pre-diabetes. The

RESUMO

Introdução: Anos antes da evolução para *diabetes mellitus* tipo II, o paciente pode conviver com um período chamado pré-diabetes. A patogênese envolvida no pré-diabetes é a resistência à insulina. **Objetivo:** Discutir a frequência de microalbuminúria em população não diabética, porém com risco metabólico aumentado, e avaliar a existência de correlação da microalbuminúria com dados do metabolismo glicídico. **Métodos:** Foram incluídos no estudo 132 pacientes não diabéticos que apresentassem um ou mais fatores de risco para alteração do metabolismo glicídico: hipertensão arterial; obesidade; parentes em primeiro grau com diabetes; indivíduos das etnias hispano-americanas, asiáticas e afro-americanas; mães de recém-nascidos grandes para a idade gestacional (GIG) ou que apresentaram diabetes gestacional; dosagens séricas em jejum de HDL colesterol 250 mg/dL. **Resultados:** A frequência de microalbuminúria anormal para o método ocorreu em 16%, havendo presença de menores valores de HDL-colesterol e clearance de creatinina nessa mesma população. Considerando a amostra como um todo houve correlação positiva da microalbuminúria com a creatinina sérica e com o ácido úrico. **Conclusão:** Nosso estudo sugere que a microalbuminúria seja avaliada como marcador de nefropatia incipiente em população não diabética com risco metabólico aumentado.

Palavras-chave: albuminúria; *diabetes mellitus*; estado pré-diabético; insuficiência renal crônica.

pathogenesis involved in pre-diabetes is insulin resistance.¹⁻³ It is characterized by subnormal glucose uptake by cells in response to insulin, requiring high

production of this hormone by the pancreas to maintain normal glucose levels, which generates the state of hiperinsulinemia.¹⁻³ One of the tests used to assess insulin resistance is the homeostasis model assessment of insulin resistance index (HOMA-IR), which evaluates endogenous insulin and glucose, and it is considered an accurate method for such evaluation.³⁻⁶

The pre-diabetes status may be associated with an increased risk of complications even before the progression to type 2 diabetes. In a study by Rosenbaum *et al.*,⁷ they found microalbuminuria in pre-diabetic patients, and that microalbuminuria was considered a marker of endothelial dysfunction and not only nephropathy. Another study showed that microalbuminuria was significantly higher in individuals with pre-diabetes compared to a group with normal glucose levels.⁸ The association of microalbuminuria with insulin resistance in non-diabetic patients has also been demonstrated.^{9,10}

Microalbuminuria pathogenesis in cases of pre-diabetes is not yet established. Hyperglycemia is suspected of causing renal injury, or there is a direct effect of insulin resistance in various organs triggering endothelial injury.¹¹ A microalbuminuria study in the general population was related to deaths from cardiovascular and non-cardiovascular causes, reinforcing again that microalbuminuria could be a marker of endothelial injury.¹²

In a study performed in our clinic, we found pre-diabetes in 68% of a population at increased metabolic risk.¹³ Thus, in addition to the concern for the prevention of T2DM, there is the need to assess the possible existence of endothelial injury in this population.

Thus, we carried out this study with the aim of showing the frequency of microalbuminuria in a non-diabetic population, of high metabolic risk, and to evaluate a possible correlation of microalbuminuria with glucose metabolism data.

MATERIALS AND METHODS

PATIENT SELECTION

A cross-sectional study was carried out from January to December 2010, involving patients consecutively seen at the outpatient clinic of the Clinical Service of the State Public Servant Hospital of São Paulo - Francisco Morato de Oliveira, who met the inclusion criteria and agreed to participate in study.

INCLUSION CRITERIA

The study included 132 patients who had one or more risk factors for changes in glucose metabolism, namely: high blood pressure (hypertension); body mass index (BMI) ≥ 25 kg/m²; first degree next-of-kin with diabetes; individuals of Hispanic-American ethnic groups, Asians and African-Americans; mothers of babies large for their gestational age (LGA) or with gestational DM; fasting HDL cholesterol serum levels < 35 mg/dL and triglycerides > 250 mg/dL.

EXCLUSION CRITERIA

The exclusion criteria were: previous diagnosis of DM or use of oral hypoglycemic agents or insulin. Hematuria or urinary tract infection at the time of inclusion.

PARAMETERS ANALYZED

We evaluated the following anthropometric and clinical data: weight, height, waist circumference (WC), hip circumference (HC), blood pressure (BP) and body mass index (BMI) calculated by the ratio of weight in kg by height in squared meters (kg/m²). WC was assessed with the patient standing, placing an inelastic tape at the midpoint between the lowest rib and the anterior superior iliac crest and at the end of expiration, and HC at the height of the trochanter major.¹⁴ High Blood Pressure was considered at pressure $\geq 140/90$ mmHg on two different occasions or use of antihypertensive medications, regardless of blood pressure levels.¹⁵

From laboratory parameters, patients were subjected to the oral glucose tolerance testing (GTT) 2 hours after ingestion of 75 g glucose, and serum levels of glucose and insulin levels after 8 h of fasting, to be used for calculating the HOMA-IR (fasting blood glucose (mmol/L) x fasting insulin (one/L)/22.5; reference values ≤ 3.4) index.⁴ The serum levels of total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and creatinine were evaluated after 12 hours of fasting by standard methods, and to calculate the creatinine clearance we used the simplified MDRD formula.¹⁶ Microalbuminuria analysis was carried out in a 24-hour urine sample by the chemiluminescence method (normal value ≤ 20 µg/minute).

DIAGNOSTIC CRITERIA FOR PRE-DIABETES

We considered a single fasting plasma glucose between 100 to 125 mg/dL or GTT ≥ 140 and ≤ 199 mg/dL values as criteria for the diagnosis of pre-diabetes.¹⁷

STATISTICAL ANALYSIS

The numerical variables data was expressed as mean \pm standard deviation or median with quartiles variation for samples without normal distribution, and percentage for categorical variables. The differences of numerical variables between the two groups were evaluated using the Student *t*-test or Mann-Whitney test when appropriate. For analysis of categorical variables, we used the chi-square test. Correlations were obtained by Pearson's or Spearman's correlation analysis where appropriate. The values were considered significant when $p < 0.05$.

The study was approved by the Research Ethics Committee of the same hospital under # 0112/11 and the research subjects signed the informed consent form.

RESULTS

We evaluated 132 patients, 78 (59.0%) were female and 54 (40.9%) were males, with a mean age of 62.5 ± 12.5 years, whom the main metabolic risk factors were: hypertension in 70%, hypertriglyceridemia in 38.7% and obesity in 39.6%, mean waist circumference of 100.5 ± 12.8 cm and median BMI of 29.0 (26.0 to 33.3) kg/m^2 . We also point out that these patients had a fasting glucose of 100.0 (93.0 to 108.0) mg/dL , GTT of 138.0 (105.0 to 161.5) mg/dL , total cholesterol 201.8 ± 40.5 mg/dL , triglycerides 136.0 (85.0 to 186.5) mg/dL , uric acid 6.2 ± 1.6 mg/dL and microalbuminuria of 6.9 (4.1 - 13.6) g/min .

Of the patients studied, 21 (16%) had microalbuminuria ≥ 20 $\mu\text{g}/\text{min}$, considered abnormal for the method. Comparing the group with normal microalbuminuria ($n = 111$) to that with abnormal microalbuminuria ($n = 21$), we found that the analyzed groups were similar with respect to age (62.2 ± 11.9 vs. 64.2 ± 15 , 6 years old, respectively), BMI (29.0 (26.2 to 34.3) versus 29.4 (25.7 to 33.0) kg/m^2 , respectively), hypertension and dyslipidemia (71.4% vs. 66.6 vs. 66.6, respectively), fasting glucose of 100.0 (93.0- 108.0) vs. 104.5 (99.5 to 112.5) mg/dL respectively), and GTT (134.0 (105.0 to 160.0) vs. 143.0 (116.0 to 190.0) mg/dL , respectively), but patients with normal microalbuminuria had higher serum levels of HDL cholesterol (50.9 ± 13.0 vs. 44.2 ± 10.8 mg/dl , $p = 0.03$, respectively), minor amounts of serum creatinine (0.9 (0.8-1.0) versus 1.0 (0.9-1.4) mg/dl , $p = 0.01$, respectively) and higher creatinine clearance ($72, 7 \pm 18.1$ vs. 62.8 ± 24.1 $\text{ml}/\text{min}/1.73\text{m}^2$, $p = 0.03$, respectively) (Table 1).

We calculated the HOMA-IR index of 76 patients with a median of 2.1 (1.0-3.8). Comparing this index in patients with normal microalbuminuria ($n = 65$ who underwent the index) with patients with abnormal microalbuminuria ($n = 11$ who underwent the index), no statistical difference was found (2.0 (0.9 to 4.5) vs 2.7 (2.1 to 3.2), respectively (Table 1).

Separating patients based on glucose metabolism, we found 58 (44%) patients with normal fasting blood glucose and GTT levels and 74 (56%) with pre-diabetes. The microalbuminuria comparison between these patients showed higher microalbuminuria values in the pre-diabetic group compared to the euglycemic patients, 7.5 (4.6 to 15.6) vs. 5.6 (3.4 to 9.2) $p = 0.03$, respectively.

There was no statistically significant correlation between microalbuminuria with glucose or GTT or HOMA-IR or between these anthropometric data; as there was also no correlation with cholesterol and triglycerides data; however, there was a positive correlation between microalbuminuria and serum creatinine ($r = 0.6$, $p < 0.0001$), Figure 1; and positive correlation with serum uric acid levels ($r = 0.3$, $p < 0.001$), Figure 2.

DISCUSSION

Microalbuminuria can be considered an independent cardiovascular risk factor from conventional atherogenic factors such as blood pressure, glucose metabolism, dyslipidemia and smoking, increasing by 2.3 times the risk of cardiovascular events.¹⁸ Its definition of normality is based on patients with DM with microalbuminuria levels able to predict their progression to diabetic nephropathy. In the said healthy population, 3 to 15% have microalbuminuria ≥ 15 $\mu\text{g}/\text{min}$, leaving questions about the pathological values of microalbuminuria for the non-diabetic population.^{18,19}

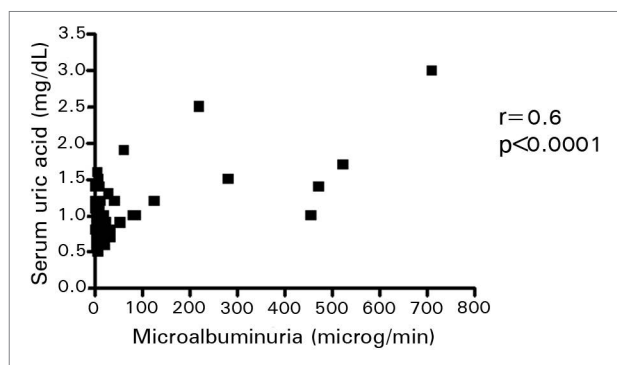
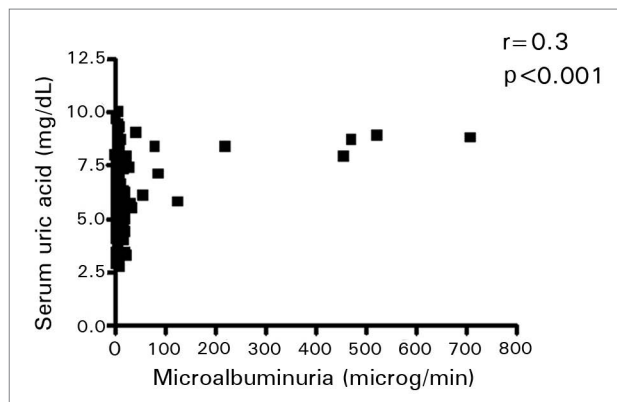
In our study with diabetes-free patients, but with increased metabolic risk, it was shown that abnormal microalbuminuria occurred in 16% of cases. These patients had higher serum creatinine levels and lower HDL-cholesterol levels. In addition, there was a positive correlation between microalbuminuria and serum creatinine and with uric acid levels.

Our findings of low HDL-cholesterol in patients with abnormal microalbuminuria and who, at the same time, had higher serum creatinine, could be related to the pathogenesis of an incipient nephropathy. High

TABLE 1 DATA COMPARISON BETWEEN PATIENTS WITH NORMAL AND ABNORMAL MICROALBUMINURIA

	Patients with normal microalbuminuria (n = 111)	Patients with abnormal microalbuminuria (n = 21)	<i>P</i>
Age (years)	62.2 ± 11.9	64.2 ± 15.6	ns
BMI (kg/m ²)	29.0 (26.2-34.3)	29.4 (25.7-33.0)	ns
WC (cm)	100.6 ± 13.2	100.2 ± 10.9	ns
HC (cm)	104.0 (99.0-115.0)	104.0 (98.5-110.0)	ns
Risk Factors (n)	4.0 (3.0-5.0)	4.0 (3.0-5.0)	ns
Hypertension (%)	69.3	71.4	ns
Dyslipidemia (%)	66.6	66.6	ns
Fasting glucose (mg/dL)	100.0 (93.0-108.0)	104.5 (99.5-112.5)	ns
GTT (mg/dL)	134.0 (105.0-160.0)	143.0 (116.0-190.0)	ns
Total cholesterol (mg/dL)	202.0 ± 40.9	201.1 ± 39.2	ns
HDL-cholesterol (mg/dL)	50.9 ± 13.0	44.2 ± 10.8	0.03
LDL-cholesterol (mg/dL)	124.3 ± 36.6	122.9 ± 36.6	ns
Triglycerides (mg/dL)	135.0 (81.5-186.5)	136.0 (102.0-192.5)	ns
Creatinine (mg/dL)	0.9 (0.8-1.0)	1.0 (0.9-1.4)	0.01
Creatinine clearance by MDRD (mL/min/1.73m ²)	72.7 ± 18.1	62.8 ± 24.1	0.03
HOMA-IR	2.0 (0.9-4.5) [#]	2.7 (2.1-3.2) [*]	ns
Uric acid (mg/dL)	6.1 ± 1.5	6.8 ± 1.7	ns
Microalbuminuria (µg/min)	5.8 (3.8-9.0)	55.0 (26.5-250.1)	< 0.001

BMI: Body Mass Index; WC: Waist circumference; HC: Hip circumference, GTT: oral glucose tolerance test, Ns: not significant. [#] n = 65, ^{*} n = 1

Figure 1. Correlation between microalbuminuria and serum creatinine**Figure 2.** Correlation of microalbuminuria with serum uric acid

HDL-cholesterol level has proven protective for coronary artery disease in several studies,^{20,21} without an assessment of it being a protective factor against the development of nephropathy, although studies have shown that individuals without nephropathy have higher levels of HDL cholesterol than those with nephropathy.²²⁻²⁷

Histopathology, epidemiological and experimental evidence data suggest that dyslipidemia may start glomerular injury and contribute to the renal disease progression.²⁸ Several studies have shown the relationship between plasma lipoproteins and renal dysfunction in type 2 diabetic patients with microalbuminuria, in which there was a positive association between microalbuminuria and plasma concentrations of lipoproteins containing apolipoprotein E.²⁹ Another analysis performed on a subset of the ARIC (Atherosclerosis Risk in Communities) study, in order to establish the association between plasma lipids and loss of renal function, concluded that triglycerides and HDL-cholesterol levels, but not LDL-cholesterol, were predictive of increased risk of kidney dysfunction.³⁰ The mechanisms that involve dyslipidemia in the

glomerular disease progression would be similar to those involved in atherosclerosis.

In the last decade, uric acid has been reintroduced as a potential mediator of endothelial dysfunction and kidney disease. Serum uric acid levels are correlated with adverse cardiovascular outcomes in the general population.³¹ Animal studies blame uric acid as a cause of dysfunction and endothelial inflammation, and as a player in the progression of kidney disease.³² A prospective study involving 1.743 Korean men over five years showed through multivariate analysis that high serum uric acid would be an independent risk factor for the development of microalbuminuria.³³ There is no pathophysiological explanation for the correlation of microalbuminuria and serum uric acid levels for now, unless the very loss of creatinine clearance that leads to lower renal clearance of this substance.

Our study showed no correlation of microalbuminuria with fasting glucose, GTT or HOMA-IR; however, pre-diabetic patients had higher microalbuminuria values when compared to their euglycemic counterparts. Data on insulin resistance and microalbuminuria is still scarce and unreliable. In a subgroup of nondiabetic patients with hypertriglyceridemia we found an excellent correlation between HOMA-IR and microalbuminuria.³⁴ Our study may have failed to show HOMA-IR relations because of the small number of patients studied.

In conclusion, this study of non-diabetic patients showed that those with normal microalbuminuria had higher serum levels of HDL-cholesterol, lower serum creatinine levels and higher creatinine clearance, compared to those with abnormal microalbuminuria. Patients with pre-diabetes had higher microalbuminuria values than euglycemic patients. Microalbuminuria is still the best marker of diabetic nephropathy, and can be associated with the development of cardiovascular events; however, these are controversial for a non-diabetic population. We can also discuss normal albuminuria values for different populations. From this study, we suggest that microalbuminuria in pre-diabetic patients or patients with metabolic risk be assessed as an incipient nephropathy marker. However, this information should be analyzed taking into consideration that our study had a limited number of patients.

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