

Visceral Obesity is Associated with Higher Urinary Albumin Excretion Levels in Normoalbuminuric Type 2 Diabetic Patients

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ABSTRACT

Aim: To analyze the relationship between visceral obesity and urinary albumin excretion rate (UAER). **Methods:** A cross-sectional study of 73 normoalbuminuric (urinary albumin excretion rate < 20 µg/min) type 2 patients was performed. Patients were divided into two groups according to the median of UAER (7.5 µg/min). Office auscultatory blood pressure was measured in sitting position after a 10-min rest. **Results:** Waist to hip ratio was higher in the group with UAER > 7.0 µg/min (0.98 ± 0.08), when compared to the other group (0.93 ± 0.08 , $p = 0.01$). Waist to hip ratio significantly correlated with UAER ($r = 0.28$; $p = 0.018$). In multiple linear regression analysis, only waist to hip ratio was associated with UAER ($r = 0.29$; $p = 0.04$). A1c, DM duration and systolic BP levels were excluded from the model. **Conclusions:** Type 2 normoalbuminuric diabetic patients with higher levels of UAER could represent a group with an elevated risk for the development of cardiovascular diseases. (Arq Bras Endocrinol Metab 2006;50/3:466-471)

Keywords: Diabetes; Visceral obesity; Albuminuria; Waist-hip ratio

RESUMO

A Obesidade Visceral Está Associada com Níveis Elevados da Excreção Urinária de Albumina em Pacientes com Diabetes Tipo 2 Normoalbuminúricos.

Objetivo: Analisar a relação entre obesidade e taxa de excreção urinária de albumina (TEUA). **Métodos:** Este é um estudo de corte de 73 pacientes com diabetes tipo 2 (DM) normoalbuminúricos (TEUA < 20 µg/min), que foram divididos em dois grupos de acordo com a mediana da TEUA (7,5 µg/min). A pressão sanguínea auscultatória foi medida em consultório com o paciente sentado, após repouso de 10min. **Resultados:** A relação cintura:quadril (RCQ) foi maior no grupo com TEUA > 7,0 µg/min ($0,98 \pm 0,08$), em comparação com o outro grupo ($0,93 \pm 0,08$, $p = 0,01$). A RCQ correlacionou-se significativamente com a TEUA ($r = 0,28$; $p = 0,018$). Na análise de regressão linear múltipla, somente a RCQ associou-se com a TEUA ($r = 0,29$; $p = 0,04$). A HbA1c, a duração do DM e os níveis da PA sistólica foram excluídos do modelo. **Conclusões:** Pacientes com DM2 normoalbuminúricos com níveis mais elevados de TEUA podem representar um grupo com risco mais elevado para o desenvolvimento de doenças cardiovasculares. (Arq Bras Endocrinol Metab 2006;50/3:466-471)

Descritores: Diabetes; Obesidade visceral; Albuminúria; Relação cintura-quadril

DIABETES MELLITUS (DM) is a chronic degenerative disease characterized by micro- and macrovascular complications. It is also associated with a higher prevalence of systemic arterial hypertension, dyslipidaemia and, consequently, cardiovascular diseases.

A great proportion of type 2 DM patients presents features of metabolic syndrome which was described by Reaven in 1988 (1), defined as glucose intolerance, insulin resistance or hyperinsulinemia, hypertension, dyslipidaemia and atherosclerotic macrovascular disease. Posteriorly, microalbuminuria, hyperuricemia, hyperandrogenism, coagulability abnormalities and visceral obesity were aggregated to this group of metabolic disturbances (2-7). This hyperinsulinemic state leads to an abnormal sodium retention, greater sympathetic activity and disturbances of lipid profile and fibrinolysis leading to an increased risk for cardiovascular events (8-10).

Among the methods available to access the degree of visceral abdominal fat, computed tomography and magnetic resonance are the most accurate, but they are very expensive (11,12). Waist to-hip ratio (WHR) has the advantage over simple waist circumference measurement, since that method reveals the real fat distribution avoiding misclassification when analyzing obese patients without androgenic fat distribution (13).

Visceral obesity defined by the WHR > 0.85 for women and > 0.90 for men (14) and is associated with insulin resistance and hyperglycemia. It was already demonstrated that visceral fat accumulation is a major contributor for multiple risk factor clustering in patients with different degrees of glucose intolerance (15).

Visceral obesity could be related to renal damage and higher urinary albumin excretion rate (UAER) both in type 2 DM patients and also in non diabetic subjects (16-18). However, other authors failed to demonstrate such associations (19-21).

Since microalbuminuria and central obesity are strongly associated with cardiovascular diseases, the aim of this study was to analyze the relationship between visceral obesity and UAER in normoalbuminuric type 2 diabetic patients.

PATIENTS AND METHODS

Subjects and methods

This study followed a cross-sectional design. All type 2 DM patients attending the endocrinology out-patient clinic of the Hospital Independência – Universidade Luterana do Brasil (a tertiary public care center) from

March 2003 to December 2003 were evaluated. Patients with BMI > 40 kg/m², diabetic (micro- or macroalbuminuria) or nondiabetic renal disease, cancer, AIDS or heart failure class IV were excluded. Seventy-three normoalbuminuric patients with type 2 DM were included. They were classified as having type 2 DM using World Health Organization (WHO) diagnostic criteria (22). They were divided in two groups according to the median of UAER – 7.5 µg/min. Ethnicity was self-reported. Informed consent was obtained from each patient, and the protocol was approved by the Research Ethics Committee of the hospital.

Anthropometric measurements were taken in a standing position after subjects removed their heavy clothes. WHR was measured by the author twice and the mean value was used for analysis. Waist and hip circumferences were measured on bare skin at the level of the umbilicus and iliac crest during mid-respiration to the nearest 0.5 cm. The WHR was defined according to the average of two duplicate measurements. Office auscultatory blood pressure (BP) was measured twice in sitting position after a 10-min rest, with a standard 12.5 cm cuff mercury sphygmomanometer (phases I-V), and the mean BP value was used. The presence of diabetic retinopathy was assessed by an ophthalmologist using fundoscopic examination after mydriasis.

Laboratory methods

UAER was determined by radioimmunoassay (DPC, Los Angeles, CA) in 24-h sterile specimens. Patients were classified as normoalbuminuric if at least two measurements at 6-months interval were < 20 mg/min in the absence of angiotensin converting enzyme (ACE) inhibitors for at least two weeks. Glucose was measured by the glucose-oxidase method, A_{1c} by chromatography method (HPLC, L9100-Hitachi; normal range: 4.3–6.0%), serum creatinine, total and HDL cholesterol and triglycerides by an enzymatic colorimetric method.

Statistical analysis

Clinical and laboratory characteristics of the two groups of patients who were divided according to the UAER median (7.5 µg/min) were compared by the Student's *t* test or Mann-Whitney's rank-sum test as indicated. Pearson's correlation test was used for the correlation between UAER and WHR. A multiple linear regression analysis was carried out to determine the effects of different variables on UAER using the forward conditional method. UAER was entered as the dependent variable and WHR, A_{1c}, DM duration and

systolic BP as independent variables. Data were expressed as means \pm SD, except for the UAER and triglycerides that were log transformed for analysis and were expressed as median and range. $P < 0.05$ was considered significant.

RESULTS

Clinical characteristics of the two groups of type 2 DM patients are shown in table 1. The WHR was higher in the group of patients with UAER ≥ 7.5 $\mu\text{g}/\text{min}$ ($p = 0.01$). No difference was observed when comparing age, sex, ethnicity, DM duration, BMI, prevalence of retinopathy and BP ($P > 0.05$). Thirty-two patients (89%) were in use of ACE inhibitors in the group of patients with UAER < 7.5 $\mu\text{g}/\text{min}$. In the other group, 11 patients (46%) were in use of ACE inhibitors. Patients with higher levels of UAER were in use of higher insulin dose, although the difference did not reach statistical level of significance ($p = 0.07$). Laboratory features (table 2) were comparable between the two groups of patients ($p > 0.05$).

There was a significant correlation (Pearson's test) of WHR and UAER levels ($r = 0.28$; $p = 0.01$, figure 1). A multiple linear regression analysis was performed with UAER as the dependent variable and WHR, A_{1c} , DM duration and systolic BP as independent variables. Only WHR was associated with UAER variation ($r = 0.29$; $p = 0.04$). A_{1c} , DM duration and systolic BP were excluded from the model.

DISCUSSION

In this study, type 2 normoalbuminuric diabetic patients with UAER levels greater than the median (7.5

$\mu\text{g}/\text{min}$) presented higher WHR when compared to the patients of the other group. WHR was responsible for approximately 30% of UAER variation. As far as we know, this is the first time that levels of UAER under the conventional limit for microalbuminuria were associated with visceral obesity, an important feature of insulin resistance.

The association of WHR and UAER levels was already expected. However, the relationship of these two measurements in patients with normal levels of UAER is not yet clear. The World Health Organization included microalbuminuria and visceral obesity in the definition of metabolic syndrome (7), and these components showed 99% specificity and 93% sensitivity, respectively for the diagnosis of this syndrome (23). In fact, there is a possible link between elevated visceral fat and glomerular vascular lesion. Adipose tissue is an endocrine organ, which secretes cytokines implicated in the vascular and systemic inflammatory process. These adipokines are elevated in obese subjects and lead to a lower insulin receptor phosphorylation leading to insulin resistance and vascular inflammatory abnormalities with elevation of vasoconstrictor substances (24-27).

Centrally obese non-diabetic patients presented a relative risk of abnormal UAER of 18 times greater than controls (17), and this association was also demonstrated in diabetic patients with metabolic syndrome, who presented a relative risk of 3.99 for the development of albuminuria (16). Even in lean patients with a central body fat distribution, renal impairment was already demonstrated (18), reinforcing the importance of visceral obesity and not obesity *per se* in the genesis and maintenance of this metabolic disturbance.

Other authors (19) did not observe any difference in insulin-stimulated glucose uptake when normo- and microalbuminuric type 2 DM patients

Table 1. Clinical characteristics of type 2 DM patients.

	UAER < 7.5 $\mu\text{g}/\text{min}$ (n= 38)	UAER ≥ 7.5 $\mu\text{g}/\text{min}$ (n= 36)	p
Age (years)	57.2 \pm 11.4	58.4 \pm 12.0	0.66
Male n (%)	13 (34)	12 (33)	0.93
White n (%)	16 (42)	14 (39)	0.78
DM duration (years)	10.2 \pm 7.0	11.0 \pm 9.4	0.68
Insulin dose (U/Kg)*	0.7 \pm 0.6 (0.4-1.0)	1.0 \pm 0.8 (0.3-2.4)	0.07
WHR	0.93 \pm 0.08	0.98 \pm 0.08	0.01
BMI (Kg/m ²)	29.4 \pm 5.1	28.4 \pm 4.0	0.38
Retinopathy (%)	14 (36)	9 (25)	0.35
Systolic BP (mmHg)	139 \pm 21	139 \pm 15	0.99
Diastolic BP (mmHg)	85 \pm 10	82 \pm 10	0.21

* Data are percent or means \pm SD (range). DM: diabetes mellitus; WHR: waist-hip ratio; BP: blood pressure.

Table 2. Laboratory features of type 2 DM patients.

	UAER < 7.5 µg/min (n= 36)	UAER ≥ 7.5 µg/min (n= 37)	P
Fasting Plasma Glucose (mmol/L)	8.96 ± 3.47	9.67 ± 3.8	0.41
A ¹ c (%)	7.9 ± 6.5 (3.8–12.2)	7.7 ± 2.0 (4.8–12.4)	0.86
Total Cholesterol (mmol/L)	5.59 ± 1.12	5.19 ± 1.14	0.14
HDL Cholesterol (mmol/L)	1.26 ± 0.35	1.27 ± 0.34	0.90
Triglycerides (mmol/l)*	3.5 (1.2–7.7)	4.1 (1.5–24.5)	0.10
Serum Creatinine (mmol/L)	75.14 ± 23.0	78.68 ± 20.33	0.49
UAER (µg/min)*	2.30 (0.23–3.95)	9.35 (4.66–16.93)	–

* Data are means ± SD or median (range). UAER= urinary albumin excretion rate.

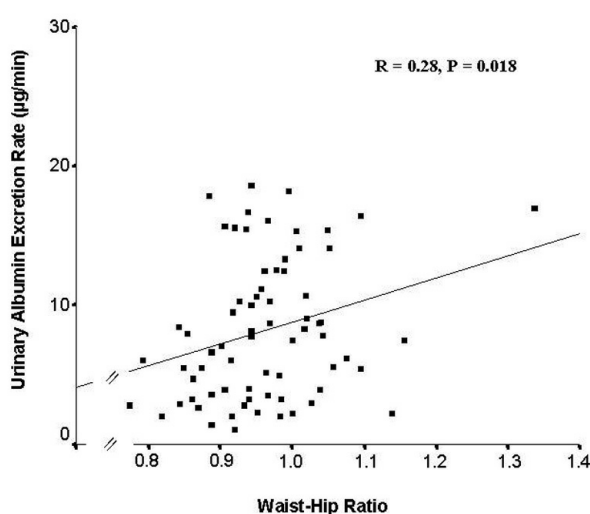


Figure 1. Correlation (Pearson's test) between WHR (waist-hip ratio) and UAER (urinary albumin excretion rate).

were compared. However, DM duration of the normoalbuminuric group (9.1 ± 4.6 years) was similar to the duration of the disease of the patients with higher levels of UAER in our study (9.1 ± 5.7 years). Furthermore, the levels of UAER of the normoalbuminuric patients of that study were higher than the levels of the patients with UAER lower than median (geometric mean= $4.8 \times / \div 1.6$ µg/min vs. $1.84 \times / \div 1.1$ mg/min, respectively). It can be hypothesized that the normoalbuminuric group of the study of Nielsen and cols. (19) presented clinical characteristics comparable to our patients with higher levels of UAER and possibly had a greater degree of insulin resistance. Another study (20) did not demonstrate any relationship between UAER and WHR. However the subjects analyzed were healthy individuals with normal glucose tolerance. Recently, other authors also did not observe a higher prevalence of microalbuminuria when glucose intolerant patients were compared to controls (21),

but a multivariate analysis was not performed in order to analyze the possible factors related to UAER variation, which could probably reveal this association.

We did not observe any difference in other conventional risk factors for cardiovascular disease such as BP and lipid values when the two groups of patients were compared. Also, these parameters were not associated with WHR. These findings could be explained by the number of patients analyzed. Another explanation is the fact that, unlike UAER, variables such BP and lipid profile are more exposed to different factors (i.e. diet), which could hide a possible difference between the two groups of patients.

Some authors suggest that waist circumference is strongly linked to cardiovascular disease risk factors and is more related with visceral obesity assessed by computed tomography and magnetic resonance (11,12), which are very expensive and could not be applied in routine clinical care. WHR has the advantage over simple waist circumference measurement, since that method reveals the real fat distribution avoiding misclassification when analyzing obese patients without androgenic fat distribution. A cross-sectional study involving nineteen populations observed that, when comparing WHR and abdominal circumference, the former is better to analyze visceral obesity. The measurement of abdominal circumference reflects mainly the degree of overweight (13).

Microalbuminuria is a risk factor for cardiovascular disease (28), which is the leading cause for mortality in type 2 diabetic patients (29). Higher levels of UAER, even within the normal range, were associated with diabetic nephropathy, diabetic retinopathy and hemodynamic abnormalities (30-34) and UAER levels greater than 10 µg/min were considered a risk factor for the development of diabetic nephropathy in type 2 diabetic patients (35). Recently, another study (36) observed that UAER values over 4.8 µg/min were strongly determinant of coronary heart disease and death in general population.

In conclusion, type 2 diabetic patients with higher levels of UAER even within the conventional normal range, present more visceral obesity than patients with lower levels. UAER values under the standard limit for microalbuminuria (20 µg/min) could be associated with insulin resistance and might be predictive for future development of diabetic nephropathy and cardiovascular disease.

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