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Waist Circumference Is Strongly Associated with Renal Resistive Index in Normoalbuminuric Patients with Type 2 Diabetes

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Key Words

Albuminuria · Chronic kidney disease · Type 2 diabetes · Resistive index · Metabolic syndrome

Abstract

Objective: Anthropometric parameters may play a role in modulating the risk of kidney dysfunction. The aim of this study was to evaluate whether anthropometric indices and the metabolic syndrome are associated with alterations of the renal resistive index (RI) in normoalbuminuric type 2 diabetic (T2DM) patients. ***Methods:*** A sample of 99 consecutively recruited patients with T2DM (76 male and 23 female) was examined. The RI was assessed by duplex Doppler sonography. ***Results:*** In univariate analysis, a significant association between the RI values and age (r = 0.507, p < 0.0001), gender (being higher in women, p = 0.002), systolic blood pressure (r = 0.285, p = 0.011), smoking habit (being lower in current smokers, p = 0.047), estimated glomerular filtration rate (r = –0.435, p < 0.0001), and intima-media thickness of the carotid arteries (r = 0.271, p = 0.020) was observed. As far as anthropometric parameters are concerned, a strong correlation between waist circumference (WC; r = 0.401, p < 0.0001), BMI (r = 0.337, p = 0.003) and RI values was found but only WC maintained a significant correlation after adjusting for several confounders (p = 0.001). ***Conclusions:*** In normoalbuminuric T2DM patients, the intrarenal hemodynamic abnormalities seem primarily associated with WC.

O.L. and V.N. contributed equally to this work.

Introduction

Type 2 diabetes mellitus (T2DM) is the leading cause of end-stage renal disease in the Western world [1]. Thus, identifying and treating risk factors for early chronic kidney disease (CKD) may be the best approach to prevent and delay cardiorenal adverse outcomes [2].

The presence of intrarenal hemodynamic abnormalities, as reflected by changes in the resistive index (RI), has been demonstrated in T2DM patients with kidney dysfunction [3]. Glomerulosclerosis and increased interstitial fibrosis are likely responsible for the high RI values commonly observed in advanced diabetic nephropathy (DN), markedly elevated RI values being reported in tubulointerstitial diseases [4, 5].

Even microalbuminuria and macroalbuminuria, known to be risk factors for widespread vascular damage [6], are characterized by a significant increase in RI val-

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ues in diabetic patients, likely as a consequence of associated accelerated arteriosclerosis.

However, it is important to consider that the UK Prospective Diabetes Study demonstrated that 51% of patients progress to chronic renal failure while remaining normoalbuminuric, suggesting that different mechanisms may induce CKD in diabetic subjects [7].

Additionally, there are several indications that anthropometric parameters such as waist circumference (WC) [8], body mass index (BMI) [9] and waist-to-hip ratio [10], either singly or in concert with the other important components of metabolic syndrome (MS) [11], may also play a role in modulating the risk of arteriosclerosis as well as of kidney dysfunction in either diabetic or in nondiabetic subjects.

Thus, we evaluated in T2DM patients whether anthropometric indices and the MS are associated with alterations of renal RI in the range of normoalbuminuria.

Research Design and Methods

This study was conducted in Caucasian patients with T2DM who were residents in Apulia, south-eastern Italy. A total of 99 consecutive patients (76 male and 23 female) were recruited at the Unit of Endocrinology and Diabetology of the University of Foggia, Foggia, Italy. All patients were interviewed regarding age at T2DM onset, diagnosis and ongoing antidiabetic, hypolipidemic, antiplatelet and antihypertensive treatments. Duration of diabetes was calculated from the calendar year of data collection minus the calendar year of diabetes diagnosis.

As a control group, a total of 52 consecutive age- and sex-matched, normal-weight and nondiabetic subjects were examined.

All subjects enrolled in the study underwent physical examination, including measurements of height (measured with the altimeter), weight (measured with the body composition analyzer, type TBF-300 M; Wunder Tanita), WC (measured in full expiration at the level of the narrowest part between the lower border of rib cage and iliac crest) and blood pressure (i.e. two measurements rounded to the nearest 2 mm Hg in the sitting position after at least 5 min of rest, using an appropriate-sized cuff; diastolic blood pressure was recorded at the disappearance of the Korotkoff sound, phase V). Fasting venous blood was sampled from an antecubital vein from all patients in order to measure serum creatinine (standardized serum creatinine was measured by the modified kinetic Jaffe reaction), serum total cholesterol, high-density lipoprotein cholesterol, triglycerides, and glycated hemoglobin (HbA_{1c}). Urinary albumin and creatinine concentrations were determined on the morning of the clinical examination using an early-morning first-void sterile urine sample with the immunoturbidimetric and Jaffe reaction rate methods, respectively. The urinary albumin-to-creatinine ratio (ACR) was then calculated. Normoalbuminuria was diagnosed if the ACR was <2.5 mg/mmol in men and <3.5 mg/mmol in women. The estimated glomerular filtration rate (eGFR) was calculated with the abbreviated modification of diet in renal disease formula [12].

The diagnosis of MS was made using modified criteria proposed by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III), and in detail patients were considered to have arterial hypertension if systolic blood pressure was >130 mm Hg and diastolic blood pressure >85 mm Hg, or if they were currently receiving antihypertensive treatment. Patients were considered to have dyslipidemia if they were currently receiving lipid-lowering treatment or had total cholesterol >200 mg/dl, high-density lipoprotein cholesterol <40 mg/dl in men and 50 mg/dl in women, and triglycerides >150 mg/dl [13].

Ultrasound examinations by a duplex Doppler apparatus were performed with subjects in a supine position after they had rested for 15 min, as previously reported by others [14].

Images were obtained with a duplex Doppler apparatus (Model SSA-550A; Toshiba) with a 3.75-MHz convex array probe in both real-time/color-coded Doppler and pulsed Doppler modes. The ultrasound probe was positioned gently on the flank in an oblique projection, and the kidney was visualized as a longitudinal image. Sample volumes were obtained to position the cursor of the pulsed Doppler mode at the mid-portion of the interlobar arteries which flow along the renal pyramid. The pulsed Doppler mode was used to obtain quantitative measurements of velocity, by placing a cursor along the course of the interlobar arteries. The sample volume was adjusted to a pulse length of 1.0 mm, and was estimated using the angle correction menu of the apparatus. The examination was completed in 15 min. The peak systolic flow velocity (PSV) and the end-diastolic flow velocity (EDV) were automatically calculated by the ultrasound apparatus. Flow velocities were determined from signals that were stable for at least 5 pulse beats, and measurements represented the average of 5 complete waveforms. The RI was determined as follows: RI = (PSV – EDV)/PSV. All measurements were performed by the same examiner (V.N.), who was unaware of each subject's characteristics. Three different interlobar arteries from each kidney were randomly selected and examined, and a mean value from the two kidneys was calculated. The intraoperator coefficient of variance was small, less than 4%.

Measurements of the intima-media thickness of the common carotid artery (IMT-CCA) were obtained from the far wall of the distal CCAs (immediately proximal to the carotid bulb) and reported as mean value for the bilateral measurement. This location was chosen a priori because of its demonstrated reproducibility, compared with measurements of the IMT-CCA at other sites [15]. All studies were performed on a single ultrasound machine (Model SSA-550A; Toshiba) using a linear-array 8-MHz scan head. Ultrasound study was performed in a standard fashion by an examiner (V.N.) who was specifically trained to perform the prescribed study examination. All sonograms were obtained with the patient in supine position and the head turned slightly to the contralateral side.

All patients were also interviewed regarding smoking habits as previously described [16].

The study was performed according to the Helsinki Declaration, and the protocol was approved by the local ethics committee. All subjects provided written informed consent.

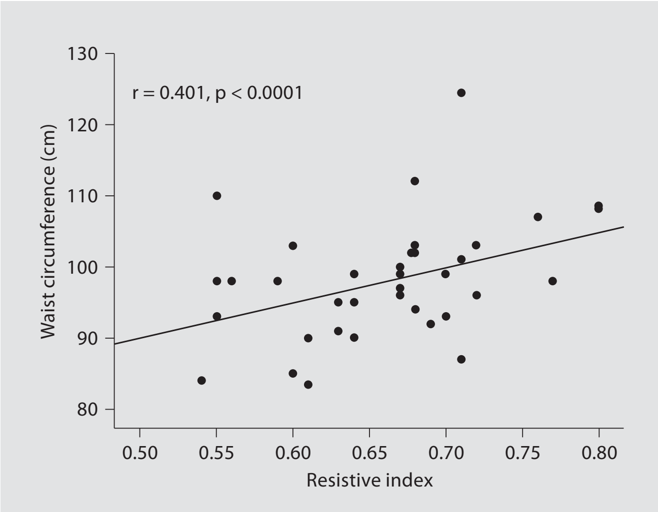

Fig. 1. The association between the RI values and WC.

Statistical Analysis

Data are reported as mean ± SD or median (range). Mean differences of normal-distributed variables were compared by the unpaired Student's *t* test. Univariate and multivariate analyses were performed to correlate independent variables with the dependent variable such as RI. For these analyses, skewed distributed variables (i.e. ACR, triglycerides) were logarithmically transformed. SPSS statistical package version 11.5 (SPSS Inc., Chicago, Ill., USA) was used. A p value <0.05 was considered to be significant.

Results

Clinical features of the diabetic subjects and control subjects are reported in table 1. Compared to the 52 control subjects, a significant increase in the RI value was found in the 99 T2DM patients ($p < 0.0001$).

A significant association was observed between RI and age ($r = 0.507$, $p < 0.0001$), gender (higher in women, $p = 0.002$), systolic blood pressure ($r = 0.285$, $p = 0.011$), and smoking habit (lower in current smokers, $p = 0.047$), while a strong negative association was observed between RI values and eGFR ($r = -0.435$, $p < 0.0001$). Current smokers showed lower WC values than never smokers (94.9 ± 5.2 vs. 100.2 ± 9.1 cm, $p = 0.001$). We did not find any significant association between ACR and RI ($r = 0.095$, $p = 0.407$). As far as anthropometric parameters are concerned, RI values strongly correlated with WC ($r = 0.401$, $p < 0.0001$; fig. 1) and BMI ($r = 0.337$, $p = 0.003$), but not with MS ($p = 0.533$). However, only WC maintained a significant correlation after adjusting for gender, duration of disease, HbA_{1c}, systolic and diastolic blood pressure, treatment with angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, low-density lipoprotein cholesterol, triglycerides, smoking habit, BMI, GFR and ACR ($p = 0.002$).

We then stratified the whole sample according to the diagnostic value of WC for MS (men = 102 cm; women = 88 cm; table 2).

Moreover, to examine the relationship between RI and arteriosclerosis, we correlated RI values with the carotid IMT, and a significant, positive association was found ($r = 0.271$, $p = 0.020$).

Table 1. Clinical features of diabetic and control patients

	Diabetic patients (n = 99)	Control group (n = 52)
Male/female	76/23	37/15
Age, years	57.2 ± 10.5	55.0 ± 5.7
Duration of diabetes, years	9.7 ± 8.3	–
BMI	27.8 ± 4.0	22.3 ± 3.7*
Weight, kg	75.9 ± 10.3	62.8 ± 13.0*
WC, cm	99.0 ± 8.5	82.4 ± 7.8*
SBP, mm Hg	125.6 ± 14.5	121.6 ± 5.8
DBP, mm Hg	75.1 ± 9.1	76.5 ± 4.4
Glycated hemoglobin, %	8.4 ± 2.0	–
Total cholesterol, mg/dl	186.9 ± 45.8	163.6 ± 9.2*
HDL cholesterol, mg/dl	51.2 ± 19.1	49.0 ± 12.1
LDL cholesterol, mg/dl	112.0 ± 36.1	91.0 ± 7.0*
Triglyceride, mg/dl	134.0 (59–545)	100 (89–130)*
ACR, mg/mmol	0.62 (0.16–3.25)	0.60 (0.14–3.20)
eGFR, ml/min/1.73 m^2	98.1 ± 29.4	122.2 ± 3.7*
RI	0.65 ± 0.06	0.56 ± 0.04*
IMT, mm	0.89 ± 0.2	0.6 ± 0.1*
Current smokers	26 (26.3)	14 (26.9)
Hypoglycemic therapy		–
Diet alone	2 (2.0)	
OHA	51 (51.5)	
Insulin ± OHA	22 (22.2)	
Arterial hypertension	61 (61.6)	–
Treatment with ACE inhibitors/ARBs	40 (40.4)	–
Dyslipidemia	61 (61.6)	–
Hypolipidemic therapy	56 (56.6)	–
MS	65 (65.7)	–
WC >102/88 cm	37 (37.4)	–

Figures either indicate numbers with percentages in parentheses, means ± SD, or median values with ranges in parentheses. SBP = Systolic blood pressure; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OHA = oral hypoglycemic agent; ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers. * p < 0.0001.

Table 2. Clinical features of the diabetic patients stratified according to the diagnostic value of WC for the MS

	Patients with WC <102 or 88 cm (n = 62)	Patients with WC >102 or 88 cm (n = 37)
Male/female	58/4	18/19**
Age, years	55.5 ± 10.0	59.8 ± 11.0
Duration of diabetes, years	10.0 ± 9.1	9.1 ± 6.8
BMI	26.2 ± 2.9	30.6 ± 4.2**
Weight, kg	73.1 ± 9.2	80.5 ± 10.6*
WC, cm	94.6 ± 5.1	106.3 ± 8.1**
SBP, mm Hg	125.0 ± 14.5	126.7 ± 14.8
DBP, mm Hg	75.3 ± 7.7	74.8 ± 11.1
Glycated hemoglobin, %	8.4 ± 2.1	8.3 ± 2.0
Total cholesterol, mg/dl	195.3 ± 41.9	172.7 ± 49.2*
HDL cholesterol, mg/dl	52.9 ± 15.8	48.4 ± 23.5
LDL cholesterol, mg/dl	115.5 ± 38.6	105.8 ± 30.7
Triglyceride, mg/dl	134 (59–545)	144 (62–444)
ACR, mg/mmol	0.58 (0.18–2.45)	0.7 (0.16–3.25)
eGFR, ml/min/1.73 m^2	102.6 ± 28.3	90.6 ± 30.1
RI	0.64 ± 0.05	0.69 ± 0.07*
IMT, mm	0.84 ± 0.17	0.96 ± 0.23*
Current smokers	22 (35.5)	4 (10.8)*
Hypoglycemic therapy		
Diet alone	0 (0)	2 (5.4)*
OHA	38 (61.2)	13 (35.1)*
Insulin ± OHA	10 (16.1)	12 (32.4)*
Arterial hypertension	36 (58.1)	25 (67.6)
Treatment with ACE inhibitors/ARBs	24 (38.7)	16 (43.2)
Dyslipidemia	38 (61.3)	23 (62.2)
Hypolipidemic therapy	40 (64.5)	16 (43.2)*

Figures either indicate numbers with percentages in parentheses, means ± SD, or median values with ranges in parentheses. SBP = Systolic blood pressure; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OHA = oral hypoglycemic agent; ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers. * $p < 0.05$; ** $p < 0.0001$.

Discussion

The RI describes the percentage reduction of end-diastolic blood flow in a vessel in relation to maximal systolic blood flow. Several evidences suggest that increased RI values may be due to advanced arteriosclerosis. High renal RI values have indeed been found in patients with microalbuminuria and macroalbuminuria and have been attributed to the associated vascular damage (arteriosclerosis) [3]. In the present study, we described a strong positive correlation between renal RI and WC and BMI, and a negative one with GFR in a sample of 99 T2DM normoalbuminuric patients. However, after adjusting for several confounders, only WC maintained a significant correlation with RI values. Previous studies observed changes in the RI in diabetic patients, usually at an advanced stage of DN, and the RI changes were likely attributable to progressive glomerulosclerosis, tubular atrophy and interstitial fibrosis, while RI values do not appear to become significantly elevated in the early course of DN, likely because renal damage at an early stage is located primarily in the glomeruli, in which case a normal RI would be expected [17].

However, it is noteworthy that a large proportion of diabetic subjects progress toward CKD while remaining normoalbuminuric, and in these patients nonspecific vascular changes and tubulointerstitial fibrosis usually associated with pre- or coexisting hypertension and atherosclerosis are frequently observed [18]. These observations may also account for our findings showing the presence of an increase in RI values in diabetic patients, even if normoalbuminuric. Interestingly, by contrast with the other anthropometric parameters, only WC was associated with RI values independently of other confounders. This finding may likely be accounted for by the accelerated atherogenesis caused by the greater traffic of atherogenic lipoproteins, driven by the increased visceral fat mass, already many years before the diagnosis of T2DM [19]. Indeed, the results of our study are consistent with those reported by Ishimura et al. [3], who also found a significant association between RI values and IMT of the carotid and femoral arteries, but in addition, our study extends the above correlation to T2DM patients in the normal range of albuminuria. Furthermore, lipotoxicity, typically associated with visceral obesity, has also been shown to alter the renal redox state over time and eventually leads to organ remodelling and interstitial fibrosis [20], and this mechanism may likely account for the strong association between WC and the increase in RI value we found in our survey. Surprisingly, we found an inverse association between smoking habit and RI values that reached the limit of statistical significance ($p = 0.047$). However, smokers had significantly lower WC values and this may provide for their lower RI values. Another possible mechanism for the above association may be the increased heart rate commonly observed in smokers, being inversely associated with RI [21].

In summary, we demonstrated that intrarenal hemodynamic abnormalities are present in normoalbuminuric T2DM patients and seem primarily associated with WC.

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