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ScienceDirect
Metabolism Clinical and Experimental 59 (2010) 279–284
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Insulin resistance is associated with increased renal resistive index independent of other factors in newly diagnosed type 2 diabetes mellitus and hypertensive patients

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Received 12 May 2009; accepted 27 July 2009

Abstract

Renal resistive index (RRI) is increased in subjects with diabetes. We analyzed whether insulin resistance is independently related with RRI. Medical history, physical examination, laboratory analysis, Doppler ultrasonography, and 24-hour urinary albumin excretion were analyzed. The threshold for an increased RRI was at least 0.70, which has been previously shown to be discriminatory of increased RRI level. Eighty newly diagnosed essential hypertensive and type 2 diabetes mellitus patients were included. Sixty-one patients had low RRI (<0.70). When compared with low-RRI patients, those with high RRI were older and had higher pulse pressure, serum creatinine, and homeostasis model assessment (HOMA) index. The HOMA index and RRI were positively correlated (r = +0.371, P = .001). In multivariate logistic regression analysis, age (odds ratio [OR] = 1.164, 95% confidence interval [CI] = 1.040-1.303, P = .008), pulse pressure (OR = 1.188, 95% CI = 1.020-1.384, P = .027), and HOMA index (OR = 1.422, 95% CI = 1.085-1.862, P = .011) were independently associated with high RRI. Increased insulin resistance is independently related with increased RRI.

1. Introduction

Duplex Doppler ultrasonography is used to assess intrarenal hemodynamics. The renal resistive index (RRI) calculated from blood flow velocities in vessels reflects renovascular resistance and is known to increase in various disorders [1]. Several studies have demonstrated that, in patients with diabetes, RRI is higher compared with that in subjects without diabetes and that RRI in association with diabetic nephropathy is higher than that in association with other specific causes of renal diseases (ie, chronic glomerulonephritis and nephrosclerosis) [2-8]. Regarding mechanisms by which RIs of intrarenal arterioles increase, it was previously reported that arteriolosclerosis rather than interstitial fibrosis could play an important role [9]. Moreover, histopathologic examination of renal biopsies in patients with diabetes showed not only typical diffuse or nodular lesions but also arteriosclerotic glomerulosclerosis [10]. It was also pointed out that macroangiopathy, not microangiopathy, is likely to affect glomerular filtration rate (GFR) regardless of the status of microalbuminuria, which has been considered to be a risk factor for diabetic nephropathy and progression of renal insufficiency, because systemic atherosclerotic vascular disease adversely affects renal blood perfusion, resulting in a decrease of GFR [1,11]. Indeed, there are several reports showing a correlation between RI and renal function [5,9,11]. Ohta et al [8] reported that increased RI of the main renal arteries is significantly correlated with the severity of systemic atherosclerosis. On the other hand, it is well demonstrated that increased RRI is related with atherosclerotic renal artery damage [12,13].

Insulin resistance (IR) is defined as a reduced responsiveness of peripheral tissues to the effects of the hormone, referring to abated ability of insulin in stimulating glucose uptake in peripheral tissues (mainly skeletal muscle and adipose tissue) and in inhibiting hepatic glucose output in an effort to maintain glucose homeostasis. Therefore, *insulin resistance* is a term, more often than

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0026-0495/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2009.07.025

not, relating to the metabolic effects of the hormone [14]. Insulin resistance is associated with several metabolic abnormalities, namely, obesity, essential hypertension, dyslipidemia, inflammation, and impaired glucose metabolism [15]. Insulin resistance is found frequently both in hypertensive [16] and in type 2 diabetes mellitus patients [17]. Because IR is closely related with systemic atherosclerosis [18,19] and RRI, which is a sensitive marker of atherosclerosis, we hypothesized that, in newly diagnosed hypertensive and diabetic patients, increased IR could be associated with RRI. To test our hypothesis, we investigated whether IR, as measured by homeostasis model assessment (HOMA) index, is independently related with RRI (a reliable marker for renal atherosclerosis) in patients with both newly diagnosed essential hypertension and type 2 diabetes mellitus.

2. Methods

This study was undertaken between May 2004 and April 2006 in the outpatient hypertension clinic of Baskent University Ankara Hospital Nephrology Department. The study population was composed of newly diagnosed essential hypertensive and type 2 diabetes mellitus patients who have not been hitherto treated with antihypertensive agents, oral hypoglycemic agents, lipid-lowering agents, and insulin. Patients with serum creatinine greater than 1.4 mg/dL and with secondary hypertension, type 1 diabetes mellitus, *coronary artery disease* (defined as history of acute coronary syndrome, myocardial infarction, angina pectoris, or coronary revascularization procedure), *cerebrovascular disease* (defined as history of stroke, transient ischemic attack, or carotid revascularization procedure), or *peripheral vascular disease* (defined as history of intermittent claudication, ischemic leg ulcer, peripheral revascularization, or amputation for critical limb ischemia) were excluded. None of the patients had any significant pulmonary, hepatic, autoimmune, endocrine, or malignant disease. On 12-lead electrocardiogram, all patients had normal sinus rhythm, without any conduction disturbances and ST-T changes. After receiving local ethical approval, written informed consent was obtained from all patients before enrollment. After the evaluation of medical history and physical examination (including blood pressure [BP] measurement as detailed below); diagnosis of type 2 diabetes mellitus was based on 2 fasting plasma glucose levels (after at least 8 hours of fasting) using a cutoff point of 7.0 mmol/L, regardless of postload plasma glucose concentrations, according to the American Diabetes Association criteria [20]. These newly diagnosed patients with type 2 diabetes mellitus and hypertension were recruited; and after an overnight fasting, each patient underwent the additional procedures: (*a*) determination of full blood count, clinical chemistry profile, lipid profile, serum creatinine, and insulin; (*b*) electrocardiographic evaluation; (*c*) renal Doppler ultrasonography; and (*d*) determination of 24-hour urinary albumin excretion. Biochemical, electrocardiographic, and Doppler evaluation was performed on the same day.

The calculation of GFR was based on the Modification of Diet in Renal Disease formulation, as follows:

$$\mathrm{GFR} = 170 \times \mathrm{SCr} - 0.999 \times \mathrm{age} - 0.176 \times \mathrm{SUN} - 0.170 \times \mathrm{SAlb} + 0.318(0.762\mathrm{female}),$$

where SCr is serum creatinine (in milligrams per deciliter), SUN is serum urea nitrogen (in milligrams per deciliter), SAlb is serum albumin (in grams per deciliter) [21].

Insulin resistance was calculated using the HOMA index, as follows: HOMA index = [fasting plasma glucose (in millimoles per liter) × fasting serum insulin (in microunits per milliliter)]/22.5 [22].

2.1. Clinic BP measurement

Clinic BP measurements were performed with a mercury sphygmomanometer with a standard cuff (23 × 12 cm) and a large cuff (34 × 15 cm) applied around each patient's nondominant arm. The first and fifth phases of Korotkoff sounds were taken as the systolic and diastolic BPs, respectively. Blood pressure measurements were obtained after the patients had rested for 15 minutes in a sitting position with their arm comfortably placed at the level of the heart. Two consecutive BP measurements were taken at 5-minute intervals and were averaged to provide clinic systolic and diastolic BP measurements. *Hypertension* was defined as systolic BP greater than 140 mm Hg and/or diastolic BP greater than 90 mm Hg. Pulse pressure was calculated according to the following formula:

$$\text{Pulse pressure} = \text{systolic pressure} - \text{diastolic pressure}.$$

2.2. Biochemical analysis

Serum hemoglobin was measured in a Coulter STKS machine (Coulter Electronics, Miami, FL). Plasma glucose concentration was determined by glucose oxidase method (Boehringer-Mannheim, Mannheim, Germany). Serum insulin was measured in an AXSYM autoanalyzer (Abbott Laboratories, Abbott Park, IL) using the microparticle enzyme immunoassay method. Serum uric acid was measured by colorimetric method (Roche/Hitachi Modular Analytics; Roche Diagnostics, Mannheim, Germany), and serum albumin was measured by bromocresol green method. The turbidimetric latex agglutination method (Biosystems, Barcelona, Spain) was used to determine serum C-reactive protein concentrations. Serum concentrations of total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and triglyceride were measured by direct quantitative colorimetric method (Human Gesellchaft für Biochemica und Diagnostica, Wiesbaden, Germany). Twenty-four–hour urinary albumin excretion was measured by radioimmunoassay method (Diagnostic Products Corp,

Los Angeles, CA). Other biochemical parameters were measured using standard laboratory methods.

2.3. Renal Doppler ultrasonography

All patients were examined in the morning after an overnight fasting. Ultrasound examinations by a duplex Doppler apparatus were performed on all patients. Two investigators who were blinded to the medical status of the patient performed all Doppler measurements. All examinations were carried out by the same ultrasound device with 7.5-MHz linear phased array transducer (Sonoline Elegra; Siemens, Erlangen, Germany). Doppler signals were obtained from the interlobar arteries. The mean RI was calculated by using 6 measurements (3 from the each of the 2 kidneys) taken for each patient. Resistive index at the level of the interlobar arteries was measured in particular because RI measured at interlobar arteries was shown to be associated with the severity and duration of essential hypertension [23]. It was also shown that, in particular, calculating the RI at the level of the interlobar arteries was a very accurate and reproducible indicator of vascular impedance to downstream blood flow [24]. The RRI was calculated as follows: RRI = peak systolic velocity − end-diastolic velocity/peak systolic velocity. The threshold for an increased RRI was at least 0.70 because this value has been shown to be a discriminatory RI level [2]. Before the beginning of the study, 2 investigators sequentially measured the RI of 20 healthy control subjects to calculate interobserver variability. The interobserver variability was 4.48%, which meant a good degree of reproducibility between investigators.

2.4. Statistics

Statistical analysis was performed with SPSS software (Statistical Package for the Social Sciences, version 10.0; SPSS, Chicago, IL). Results were considered statistically significant if the 2-tailed P value was < .05. Normality of the data was evaluated by the Kolmogorov-Smirnov test with Lilliefors correction. Data are shown as mean ± standard deviation or median (range [minimum-maximum]) where appropriate. Comparisons of the groups were assessed by means of the t test for normally distributed continuous variables and by the Mann-Whitney U test for nonnormally distributed continuous variables. For the analysis of categorical variables, we used the χ^2 test and Fisher exact test, where available. We used Spearman analysis for the correlations between HOMA index and other variables. Univariate and multivariate backward logistic regression analyses were performed to assess the independent effects of several variables, including IR, on increased RRI. These effects were measured by odds ratios (ORs), and their 95% confidence intervals (CIs) were based on logistic regression models. We also performed multiple stepwise regression analysis to analyze the independent relationship between the same independent variables and RRI treated as a continuous dependent variable. The data were checked for collinearity, and variation inflation factors were shown when appropriate. Logarithmic conversion was performed for albumin excretion rate before statistical analysis.

3. Results

Eighty patients with newly diagnosed type 2 diabetes mellitus and essential hypertension (male-female ratio, 25/55; mean age, 55.5 ± 12.6 years) were included in the study. Sixty-one patients (76.2%) had low RRI and 19 patients (23.8%) had high RRI according to the accepted RRI cutoff of 0.70. When compared with those with low RRI, patients with high RRI were older, had higher pulse pressure and serum creatinine, and were insulin resistant as detected by higher HOMA index. Insulin levels tended to be higher in patients with high RRI than in patients with low RRI. On the other hand, patients with low RRI had higher diastolic BP and GFR than patients with high RRI. Other parameters were not different between patient groups (Tables 1 and 2). There were positive correlations between the HOMA index and the demographic and laboratory parameters including body mass index (r = +0.282, P = .01), serum uric acid (r = +0.300, P = .009), and albumin excretion rate (r = +0.399, P = .001), whereas there was a negative correlation between HOMA index and HDL-C (r = −0.259, P = .0022).

Renal resistive index was positively correlated with HOMA index (Fig. 1). There were no significant correlations between HOMA index and other parameters. In the whole group, estimated GFR was inversely correlated with RRI (r = −0.256, P = .038).

In stepwise multivariate linear regression analysis, RRI (treated as continuous variable) was found to be independently correlated with age (β = +0.504, P = .003, variance inflation factor = 2.063) and HOMA index (β = +0.298, P = .032, variance inflation factor =1.419). Univariate logistic regression analysis of factors that might be predictive of an increased RRI (age, sex, smoking, body mass index, pulse pressure, sodium, uric acid, C-reactive protein, total cholesterol, triglyceride, albumin excretion rate, GFR, and HOMA index) demonstrated that age (OR = 1.093, 95% CI = 1.031-1.158, P = .003), pulse pressure (OR = 1.065, 95%

Table 1
Comparison of demographic characteristics and BP measurements of patients with low and high RRIs

	Low RRI (<0.70) (n = 61)	High RRI (≥0.70) (n = 19)	P
Age (y)	53.0 ± 12.3	63.7 ± 10.0	.001
Sex (male/female)	22/39	3/16	.096
Smoker/nonsmoker	17/44	3/16	.373
Body mass index (kg/m^2)	28.4 ± 5.1	28.8 ± 4.5	.767
Clinic systolic BP (mm Hg)	157.4 ± 14.7	161.1 ± 18.2	.398
Clinic diastolic BP (mm Hg)	97.6 ± 12.8	88.3 ± 10.9	.007
Pulse pressure (mm Hg)	59.8 ± 11.7	72.7 ± 19.2	.001

Table 2
Comparison of laboratory parameters of patients with low and high RRIs

	Low RRI (<0.70) (n = 61)	High RRI (≥0.70) (n = 19)	P
Hemoglobin (g/L)	139 ± 12	136 ± 11	.318
Blood urea nitrogen (mmol/L)	5.53 ± 1.61	6.21 ± 2.21	.146
Creatinine (μmol/L)	72.5 ± 15.9	88.4 ± 28.3	.026
Uric acid (μmol/L)	315.2 ± 95.0	309.3 ± 95.2	.975
Albumin (g/L)	44.6 ± 3.6	44.7 ± 3.8	.902
CRP (mg/L)	3.0 (0.26-21)	2.8 (1.2-17)	.551
Sodium (mmol/L)	140.0 ± 3.4	139.8 ± 2.0	.766
Potassium (mmol/L)	4.3 ± 0.4	4.4 ± 0.5	.156
Calcium (mmol/L)	2.35 ± 0.01	2.35 ± 0.12	.852
Total cholesterol (mmol/L)	5.33 ± 1.15	5.38 ± 1.23	.873
HDL-C (mmol/L)	1.34 ± 0.32	1.35 ± 0.35	.903
LDL-C (mmol/L)	3.15 ± 0.87	3.22 ± 1.24	.946
Triglyceride (mmol/L)	1.58 (0.52-5.01)	1.68 (0.45-2.42)	.861
TSH (μIU/mL)	1.4 (0.2-7)	1.1 (0.3-4.6)	.099
Fasting plasma glucose (mmol/L)	9.0 (7.1-11.8)	9.0 (7.1-17.2)	.631
Insulin (μU/mL)	10.4 (2-60.6)	14.1 (2-61)	.05
HOMA index	4.1 (0.7-24.2)	5.9 (0.7-33.6)	.026
Albumin excretion rate (mg/d)	13.8 (1.3-357)	24.0 (1.1-475)	.687
GFR (mL/min)	98.4 ± 35.5	74.3 ± 31.4	.018

CRP indicates C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TSH, thyroid-stimulating hormone.

CI = 1.022-1.111, P = .003), GFR (OR = 0.973, 95% CI = 0.951-0.996, P = .021), and HOMA index (OR = 1.132, 95% CI = 1.027-1.249, P = .013) were associated with increased RRI. In multivariate logistic regression analysis using backward model, the same covariates as independent variables, age (OR = 1.164, 95% CI = 1.040-1.303, P = .008), pulse pressure (OR = 1.188, 95% CI = 1.020-1.384, P = .027), and HOMA index (OR = 1.422, 95% CI = 1.085-1.862, P = .011), were independently associated with high RRI. The relationship between estimated GFR and RRI was no longer significant in a multivariate regression analysis after accounting for the same variables (OR = 1.015, CI = 0.963-1.070, P = .577).

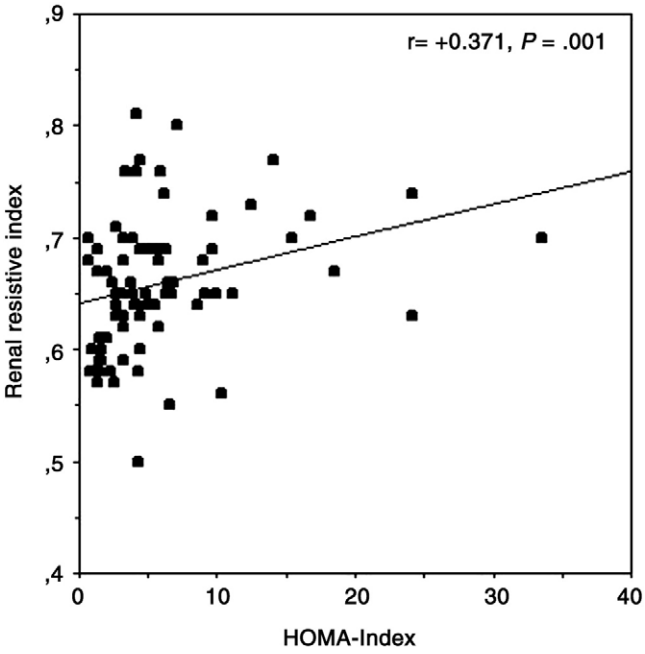

Fig. 1. The regression graphic between RRI and HOMA index.

4. Discussion

In this study, we found that newly diagnosed essential hypertensive and type 2 diabetes mellitus patients with high RRI were more insulin resistant, as defined by higher HOMA index, when compared with patients with low RRI. Age and pulse pressure were independently and positively related with RRI. As a novel finding, we found that RRI was independently and positively related with IR.

Insulin resistance has been assumed to be the primary factor in the pathophysiology of type 2 diabetes mellitus and is observed years before the precipitation of overt disease. Almost half of the type 2 diabetes mellitus patients already have macroangiopathy at the time of diagnosis. Therefore, it is thought that the atherosclerotic process has developed already in the "prediabetic" stage, which is often characterized by IR [25,26].

Renal resistive index, a reliable marker for renal arteriosclerosis, was found to be higher in diabetic patients compared with control subjects [2-7,27]. The exact mechanism underlying the effect of diabetes on RRI elevations remains unknown. It was hypothesized that the increase in RRI values most likely reflected a generalized decreased compliance of the vasculature in patients with type 2 diabetes mellitus. Recently, it has been shown that the RRI is positively correlated with aortic stiffness and brachial ankle pulse wave velocity [1]. Another study by Ishimura et al [5] demonstrated that RRI values were significantly correlated with both femoral and carotid arterial intima media thickness in type 2 diabetes mellitus patients with nephropathy and that intrarenal hemodynamics were affected by decreased GFR, probably through advanced arteriosclerosis. Tedesco et al [28] demonstrated that hypertensive patients with higher RRI showed increased left ventricular mass index and carotid intima media thickness with a higher prevalence of microalbuminuria. There were differences in overall diastolic parameters, in particular when evaluated by Doppler tissue imaging. They concluded that RRI, especially the higher values, was positively correlated with target organ damage in hypertensive patients, indicating that renal vascular resistance was related to morphologic and hemodynamic alteration of the cardiovascular system [28].

Here, with the results of previous findings and this study, we present the hypothesis that IR as measured by the HOMA index may be an important factor that clusters with other risk factors that are associated with the preclinical manifestation of arteriosclerosis including renal vessels, thus leading to increased RRI.

Patients with high RRI had lower diastolic pressures in our study. Moreover, age and pulse pressure were found to be related to RRI. Our findings are neither novel nor surprising, with previous studies showing a relationship between RRI, diastolic BP, age, and pulse pressure [12,29]. In a recent study, Hamano et al [1] demonstrated that RI had significant associations with diastolic BP ($r = -0.398$, $P < .0001$). With increasing arteriolar rigidity, renal resistance also increases, resulting in alterations of renal flow patterns. When renal resistance is increased, renal blood flow declines for a given perfusion pressure. Because the decline is more prominent in diastole than in systole, it leads to an increase in RRI [27]. Pulse pressure is a known marker of increased rigidity of the arterial vascular bed [30] and increases during aging as a consequence of stiffening of the arterial wall [31]. Indeed, it was postulated that stiffening of the aorta and large conduit arteries increases systolic BP and decreases diastolic BP, thereby increasing pulse pressure, which is a significant predictor of cardiovascular risk [32,33]. Thus, the postulated factors above might explain the observed relationship between age, pulse pressure, diastolic BP, and RRI.

One might expect that smoking should affect RRI. However, although acute nicotine consumption induces renal vasoconstriction in healthy nonsmokers, tolerance to its renal hemodynamic effects has been reported in chronic smokers [34]. Accordingly, we could not demonstrate any association between smoking habit and RRI in our study population. We found no relationship between RRIs, blood urea nitrogen, and creatinine. This may seem surprising at first glance; however, it is known that blood urea nitrogen or creatinine levels do not very accurately reflect renal functions [35]. We found no correlation between albumin excretion rate and GFR. It is known that, in type 2 diabetes mellitus, albuminuria does not correlate with impairment of renal function and, in turn, end-stage renal failure is not associated with albuminuric nephropathy in up to 54% of patients [36,37]. We also found no relationship between RRI and albumin excretion rate. This might indicate that the intrarenal impedance is not influenced by glomerulopathy, which is the main mechanism responsible for albumin excretion rate in diabetic patients.

This study has limitations that deserve mention. Because our study had a cross-sectional design, it did not prove a cause and effect relationship between RRI and IR. Secondly, we were unable to examine the impact of IR and other variables on RRI over time. Thirdly, our study sample was relatively small; and currently, we do not know whether our findings are especially applicable to type 2 diabetes mellitus patients without hypertension because essential hypertensive patients also have increased RRI. Still, we believe that because our study group was composed of special patients that included both newly diagnosed hypertensive and type 2 diabetes mellitus patients without previous known cardiovascular diseases and who were not receiving any antihypertensive and oral hypoglycemic drugs; thus the effects of cardiovascular comorbidity and medication were potentially ruled out. Fourthly, GFR was not measured by criterion standard methods.

In conclusion, we think that increased IR, which is highly prevalent in type 2 diabetes mellitus and hypertension, is independently related with increased RRI. Yet, further studies should be performed to clarify a possible cause and effect relationship.

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