

RENAL RESISTANCE INDEX IN TYPE 2 DIABETES

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SUMMARY

Diabetic nephropathy is a common microvascular complication in diabetic patients. Alterations in vascular compartments result in the increase of renal vascular resistance, manifested by the elevation of Doppler sonographic renal resistance index (RI). The aim of the study was to investigate the predictive variables for RI elevation in patients with type 2 diabetes. Forty-three patients (21 male and 22 female, age range 39-71 years, diabetes duration 0-25 years) were included in the study. The stepwise regression method was used to analyze the influence of predictor variables: patient age, diabetes duration, systolic and diastolic blood pressure, albumin excretion rate (AER), lipid values, glycated hemoglobin and creatinine clearance on RI elevation. A statistically significant correlation was found between RI and diabetes duration, systolic blood pressure and AER. In the group of normoalbuminuric patients (24 of 43), RI elevation was observed in 8 patients. A statistically significant difference was found in diabetes duration between normoalbuminuric patients with $RI < 0.70$ and $RI \geq 0.70$ ($p < 0.05$), but not in systolic blood pressure ($p = 1.000$). RI elevation can be observed prior to the

occurrence of microalbuminuria. The values of diabetes duration, systolic blood pressure and albumin excretion rate can explain the high percentage (53%) of RI variance.

INTRODUCTION

Diabetic nephropathy is a relatively common form of chronic renal disease. It is the most frequent microvascular complication in diabetic patients (1,2). Diabetic nephropathy has become the leading cause of chronic renal failure in developing countries (3). It is estimated that death due to renal disease is 17 times more common in diabetic than in non-diabetic patients (4-7).

Microalbuminuria, as one of the first signs of diabetic nephropathy, has recently been brought into focus also as a predictor of cardiovascular disease and early mortality in diabetic patients (1,8-10). Clinical manifestations of nephropathy are similar in type 1 and type 2 diabetic patients. However, some differences in the clinical course of nephropathy are evident (3). Abnormal albumin excretion rate (AER) is rarely observed at the onset of type 1 diabetes, whereas a substantial proportion of patients have microalbuminuria or overt proteinuria at the time of diagnosis of type 2 diabetes. The early stage of diabetic nephropathy is characterized by hypertrophy of glomerular and tubular cells (11,12). Histopathologic changes can be found primarily in the vascular

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compartments of the glomeruli. In the first stage of nephropathy, microalbuminuria need not be present (13). These changes are followed by basement membrane thickening, mesangial expansion and elevation of intraglomerular blood pressure (14-16). Finally, glomerular and interstitial sclerosis develops, with a resultant markedly impaired glomerular function (17,18). Elevated blood pressure, microalbuminuria and proteinuria can be considered as important signs of the progression of glomerular abnormalities (18-20).

Alterations in vascular compartments of the kidney result in the elevation of renal vascular resistance (RVR), manifested by increased values of the Doppler sonographic renal resistance indexes (RI) in intrarenal arteries (21-23). The aim of this study was to determine the variables predictive of RI elevation in patients with type 2 diabetes.

STUDY DESIGN AND METHODS

Subjects

During a two-year period, 43 patients with type 2 diabetes were examined. There were 21 male and 22 female patients, age range 39-71 years and disease duration 0-25 years. In all patients RI, systolic blood pressure, diastolic blood pressure, AER, creatinine clearance, glycated hemoglobin (HbA_{1c}), total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides were measured. Patients with AER <30 mg/24 h were considered normoalbuminuric and those with AER 30-300 mg/24 h microalbuminuric. All study patients were in good clinical condition, with no clinical signs of macrovascular complications, such as diabetic foot or ischemia and its major symptoms of angina and claudication. All patients were on a diabetic diet, with special attention paid to adequate protein, salt, fat, and other nutrient consumption. Body activity was standardized. Patients with a history of glomerular or tubulointerstitial disease other than diabetic renal disease were excluded from the study. Also, patients with B-mode ultrasonography (US) findings of renal calculi, collecting system dilatation, or suspected renal masses were excluded from the study. An informed consent was obtained from all patients.

Assays and measurements

Urine albumin levels were measured by double antibody radioimmunoassay (RIA) (Pharmacia AB, Uppsala, Sweden). The intra- and inter-assay coefficients of variation were 3.3% and 7.1%, respectively. The sensitivity of the assay was 0.3 mg/L. Urinary levels of Tamm-Horsfall protein were measured by an enzyme linked immunoassay (ELISA) (Dialab Co., Vienna, Austria). The intra- and inter-assay coefficients of variation were 6.2% and 8.1%, respectively. The sensitivity of the assay was 1.0 mg/L. Urine from each individual was collected three times over a 24-hour period after excluding urinary tract infection. Urine samples were stored in polystyrene plastic tubes and kept at -20 °C until analysis. Normal AER values were below 30 mg/24 h. HbA_{1c} was measured by ion-exchange chromatography using the HPLC system (Pharmacia, Uppsala, Sweden). Serum cholesterol, triglycerides and creatinine were determined using commercially available reagents (Olympus Scientific, Tokyo, Japan). Systolic and diastolic blood pressures were measured in supine position after a 5-min rest, using an appropriately sized cuff, and systematically controlled by random zero sphygmomanometer. The mean of two readings was used for analysis.

Color Doppler ultrasonography

Doppler US RI values in intrarenal arteries reflect RVR. RI measurements were performed with a color Doppler scanner (Acuson 128 XP 10, Acuson Corp., Mountain View, CA, USA) with a curved-array 2.5-3.5 MHz transducer. Pulsed Doppler US studies of segmental, interlobar and arcuate arteries were performed in both kidneys in each patient. Recordings were obtained in at least three distinct vessels in each kidney, and measurements were obtained only when at least three consecutive waveforms with similar appearance were noted. From each recording, the RI was measured by the following formula: peak systolic frequency shift – minimum diastolic frequency shift/peak systolic frequency shift during the whole cardiac cycle. The wall filter was set at the low value of 50 Hz, and the Doppler sample volume was set at 2-3 mm. The minimal pulse repetition frequencies that did not produce aliasing were used. Only optimal

spectral waveforms for a particular vessel were used for measurement. Color and/or power Doppler identification of intrarenal arteries considerably facilitated the positioning of the Doppler sample volume, and the examinations were performed at the lowest possible angle between the ultrasonic beam and the insonated vessel. The duration of examination *per* patient was 30-40 minutes. All Doppler US examinations were performed by the second author (B.B.), who was blinded to clinical and laboratory data related to renal status of the study patients. Median kidney RIs were used for statistical analysis of differences between the groups of patients and normal controls. As proposed by Platt, diabetic patients were classified into two groups according to RI values: group 1 with RI <0.70 and group 2 with RI \geq 0.70 (24).

Statistical analysis

Descriptive statistics (mean, standard deviation, minimum, median, maximum, 25th(Q₁) and 75th(Q₃) percentile) was performed for all variables analyzed. Kolmogorov-Smirnov test was used to test normality of distribution of the variables (25). Multiple regression was applied to analyze the relationship between dependent variable RI and other analyzed variables (patient age, diabetes duration, systolic and diastolic blood pressure, AER, lipid values, HbA_{1c}, creatinine clearance) as independent variables. In order to select a model in which variables are significant and which appropriately describes changes in the response (RI), we used the stepwise regression method (26). Student's t-test was used to test differences in mean

values between the two patient groups (AER <30 mg/24 h and AER 30-300 mg/24 h). Analyses were performed using STATISTICA 5.0 and SAS 6.12.

RESULTS

Clinical and biochemical data of study patients are summarized in Table 1. Normality of AER distribution in the groups of normoalbuminuric and microalbuminuric patients was proved using Kolmogorov-Smirnov test. The study group consisted of 24 normoalbuminuric patients (9.06 \pm 4.69) and 19 microalbuminuric patients (76.28 \pm 45.84). A statistically significant difference in RI was found between the groups of normoalbuminuric patients and microalbuminuric patients (0.68 \pm 0.03 *vs.* 0.73 \pm 0.06; *p*<0.01) (Fig. 1). The influence of the analyzed variables of patient age, disease duration, systolic blood pressure, diastolic blood pressure, AER, HbA_{1c},

Figure 1. RI in the group of patients according to AER

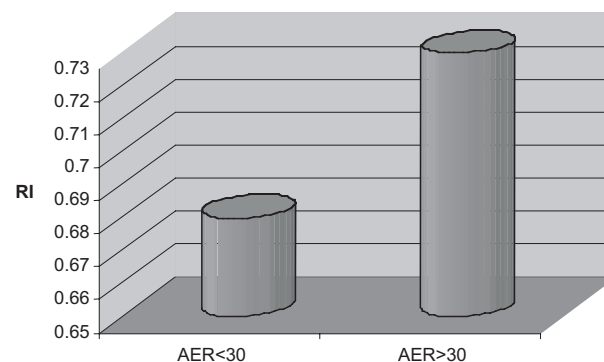


Table 1. Clinical and biochemical data of study patients (n=43)

Variable	Valid N	Mean	Std.Dev.	Minimum	Q1 25%	Median	Q1 75%	Maximum
Age (yrs)	43	59.2093	7.2327	39.0000	54.0000	61.0000	64.0000	71.0000
Diabetes duration (yrs)	43	11.0930	7.0129	0.0000	5.0000	11.0000	16.0000	25.0000
Resistance index	43	0.7056	0.0579	0.6200	0.6700	0.6900	0.7200	0.8800
Systolic blood pressure (mm Hg)	43	186.3953	16.7731	150.0000	180.0000	190.0000	200.0000	220.0000
Diastolic blood pressure (mm Hg)	43	102.3256	7.6647	85.0000	95.0000	100.0000	110.0000	125.0000
AER (mg/24 h)	43	38.7698	45.3181	1.2000	8.3000	16.8000	63.1000	191.0000
HbA _{1c} (%)	43	8.4223	2.2653	4.7000	6.8900	8.0200	9.3300	14.3000
Creatinine clearance (mL/s)	43	1.6491	2.8743	0.7300	1.2400	1.6600	2.0800	2.3000
Cholesterol (mM/L)	43	6.6026	1.5809	2.5900	5.3000	6.6900	7.5500	10.2600
HDL (mM/L)	43	1.7421	5.1921	0.6000	1.1000	1.3100	1.7400	1.9500
LDL (mM/L)	43	4.3223	1.4220	1.3400	3.4400	4.3800	5.2300	8.7000
Triglycerides (mM/L)	43	2.1472	1.4685	0.5200	1.3200	1.7100	2.6700	9.0100

AER=albumin excretion rate; THPER, HbA_{1c}, glycated hemoglobin

creatinine clearance, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides on RI elevation was assessed. Results of the stepwise regression method showed that systolic blood pressure, disease duration and AER together explained nearly 53% of RI variation. Systolic blood pressure explained almost 24% of RI variation (Table 2). Disease duration explained nearly 21% and AER nearly 8.5%. Results of the final model (systolic blood pressure, disease duration, AER) are shown in Table 3.

In the group of 24 normoalbuminuric patients, 16 (66.7%) patients had RI <0.70 and eight (33.3%) patients had RI ≥0.70 (Table 4). A statistically significant difference was observed between the group of patients with RI <0.70 and the group of patients with RI ≥0.70 in disease duration (8.00 ± 6.66 vs. 14.25 ± 7.70 ; $p < 0.05$) (Fig. 2), but not in systolic blood pressure (181.87 ± 16.21 vs. 181.87 ± 16.67 ; $p = 1.000$) (Fig. 3).

Table 2. Summary of stepwise procedure for dependent variable resistance index (RI)

Step	Variable	Number In	Partial R**2	Model R**2	C(p)	F	p>F
1	Systolic blood pressure	1	0.2385	0.2385	14.1036	11.5891	0.0016
2	Disease duration	2	0.2097	0.4482	2.5832	13.6799	0.0007
3	Albumin excretion rate	3	0.0845	0.5327	-0.8657	6.3277	0.0166

Table 3. Results of stepwise regression method for dependent variable resistance index (RI)

	Parameter estimate	Standard error	F	p>F
Intercept	0.42601	0.07156	35.44	0.0001
Systolic blood pressure	0.00123	0.00038	10.09	0.0031
Disease duration	0.00327	0.00087	14.17	0.0006
Albumin excretion rate	0.00034	0.00013	6.33	0.0166

Table 4. Number of patients according to albumin excretion rate (AER) and resistance index (RI)

	RI <0.70	RI ≥0.70	Total
AER <20 mg/24 h	16	8	24
AER ≥20 mg/24 h	8	11	19
Total	24	19	43

Figure 2. Diabetes duration in the group of patients according to RI

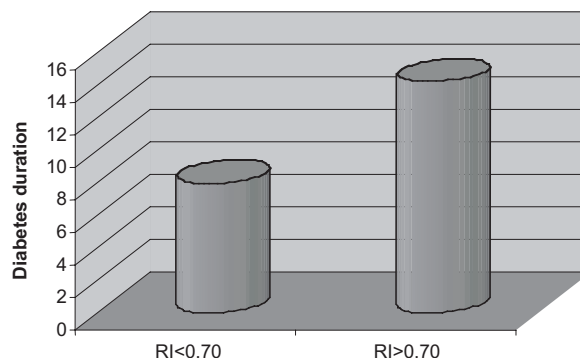
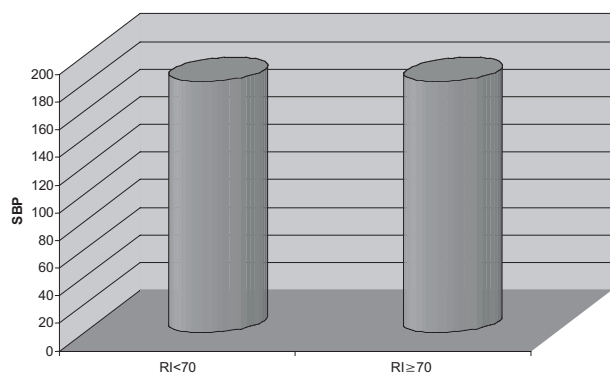


Figure 3. SBP in the group of patients according to RI



DISCUSSION AND CONCLUSION

Endothelial dysfunction and widespread vascular damage can be found in the first stage of diabetic nephropathy in type 2 diabetes (27,28). It may be accompanied by usually transient microalbuminuria (13). These changes in the kidneys were found predominantly in vascular compartments, leading to RVR elevation reflecting in an increase of Doppler US RI values in intrarenal arteries (21,22,29). Our study group consisted of 24 normoalbuminuric and 19 microalbuminuric patients. A statistically significant difference was found in RI between these two groups (Fig. 1). This could be compared with the observation reported by Derchi *et al.*, comparing RI values between the groups of normoalbuminuric type 2 diabetic patients and control subjects, who found a significant RI increase in type 2 diabetic patients (30).

Cholesterol and LDL-cholesterol levels are considered to be good predictors for the development of atherosclerotic changes in diabetes (31,32). Atherosclerotic changes occur early in diabetic patients and can contribute to the elevation of systolic and diastolic blood pressure (32-34). It is known that optimal blood pressure regulation is very important for the prevention of histopathologic changes in vascular compartments and consequently for the onset of microalbuminuria (2,20,31). Changes in vascular compartments might result in RI elevation (21,22,29).

In the studies by Mostbeck *et al.* and Becker, diabetes duration was established as a statistically significant covariable which affected renal RI of diabetic patients (35,36). Previous studies showed a significant correlation between RI and serum creatinine and clearance creatinine values in patients with microalbuminuria and clinically evident proteinuria (21,29). The Diabetic Control and Complications Trial (DCCT) showed that an improvement of glycemic control is beneficial in type 1 diabetic patients with respect to microvascular complications (37). The UK Prospective Diabetes Study showed the same results in type 2 diabetic patients (38). When we investigated the influence of the previously mentioned variables, we observed that diabetes duration, systolic blood pressure and AER were statistically significant covariables that affected RI (Table 2). Based on the value of systolic blood pressure the variation of RI can be explained in the highest percentage.

We observed RI elevation in 8 of 24 (33.3%) normoalbuminuric patients (Table 4). A significant difference was observed in diabetes duration but not in systolic blood pressure between the groups of normoalbuminuric patients with and without RI elevation, suggesting that diabetes duration and systolic blood pressure are important variables in the prediction of RI (Table 2).

In conclusion, many factors are included in the development of small vessel abnormalities of the kidney as part of the widespread vascular damage in type 2 diabetes. The consequence of these abnormalities can be the elevation of Doppler US renal RI. As demonstrated in the present study, elevated RI might be observed in type 2 diabetic patients even in earlier stages of diabetic nephropathy. Diabetes duration, systolic blood pressure and microalbuminuria were shown to be statistically significant covariables influencing RI. The predictive value of markers of tubular abnormalities for RI elevation was not proved.

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