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The value of intrarenal resistive index in Diabetic nephropathy

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Abstract

Background. We used duplex Doppler analysis to determine whether the intrarenal RI can be used as an indicator of progression in patients with diabetic nephropathy.
Methods. Intrarenal resistive index (RI) values were obtained from intraparenchimal arteries of both kidneys, either the arcuate or interlobar arteries. Clinical parameters and renal function were also evaluated at baseline and after 12 and 24 months. Seventy patients with diabetic nephropathy were divided based on their intrarenal RI values: group 1 (n=33) had values of <0.68 and group 2 (n=37) had values ≥0.68.
Results. The difference in age between patients in the group 1 (mean, 53 years ± 9) and patients in the group 2 (mean, 63 years ± 6) was statistically significant. There was a significant difference in the duration of diabetes between the groups, 4.4 ± 4.0 years in the group 1 compared to the group (29.2 ± 6.5 years). All patients with RI ≥0.68 had significantly higher serum creatinine and lower creatinine clearance compared with patients with RI<0.68 during the follow up. There were no significant differences between the groups at any check point time with regard to the glicemic control, proteinuria and body mass index. A significant difference was found between the group in the systolic and mean blood pressure,
Conclusions. An intrarenal RI value of ≥0.68 identifies diabetic patients at risk for progressive renal disease. The RI of interlobar arteries seems to be a valuable marker of intrarenal changes and can be used as a non-invasive, easily available parameter of the evolution in patients with advanced clinical diabetic nephropathy.

Keywords: Diabetic nehropathy, progression, resistive index, Doppler ultrasonography.

Introduction

Diabetes mellitus has an epidemical rank and the impact of diabetic renal injury on the incidence of end-stage renal disease continues to grow. It is believed that the total number of people with diabetes will be more than double between the year 2000 and 2030 [1,2]. The most crucial factors for the increasing rate of diabetes are the rise in obesity, the population growth and aging [1]. The increase in DM has been associated with a rise in the prevalence of diabetic chronic kidney disease (CKD) [3]. Nephropathy, the microvascular complications of diabetes, is common and can progress to serious health problems with negative effects on the quality of life. Nephropathy occurs in up to 40% of patients suffering from diabetes and is the single leading cause of ESRD [4-8]. In R. Macedonia diabetic nephropathy is found in 10%, 5-15% in different Dialysis Centers [9]. Now days the effective procedures prevent premature cardiovascular death of the diabetics and they live long enough to develop chronic renal failure and progress to end-stage renal disease. Color Duplex Doppler Sonography (CDDS), available since the 1980s, has allowed noninvasively evaluation of alterations of renal perfusion by interrogating intrarenal arteries or showing general renal perfusion [10]. In the diabetic kidneys histopathologic changes affect mainly the vascular compartment with resultant increase of renal vascular resistance. It is hypothesized that RI demonstrates changes of renal vascular resistance (RVR) in patients with impaired kidney function. Normal ranges for RI values vary from 0.58 to 0.68 in normal kidneys. Platt JF at al suggested 0.70 as a reasonable upper limit for normal RI values in adult population [11]. Among parameters measured by Doppler Ultrasound (US), resistance index (RI) values have been most frequently used in everyday clinical practice. The intraoperator coefficients of variance are small, i.e. less than 4-5%. However, there are not a lot of papers about correlation of intrarenal RI values with serum creatinine and clearance creatinine in DN [12]. Platt *et al*. showed high level of correlation between serum creatinine level and clearance creatinine and intrarenal RI (mean, RI 0.71±0.1; 98 patients) in advanced clinical DN [11,13]. In a recent study Sugiura T *et al*. showed that the progression of chronic kidney disese could be predicted by particular RI value [14]. They demonstrated that the high RI value (RI >0.70) had an equally strong association with the progression of chronic kidney disease as it is proteinuria and hypertension.
The aim of the present study was to determine whether the intrarenal resistance index can be used as an indicator of progression in patients with diabetic nephropathy.

Patients and methods

A total of seventy Macedonian Caucasian patients with Diabetes mellitus and Diabetic nephropathy (aged 38-72 years) were enrolled; 68 patients ended the prospective follow-up study (one patients died because of cancer, one due to a heart attack). The diagnosis of type 2 Diabetes mellitus was based on a previous history of diabetes or criteria according to the WHO. All patients were in good clinical condition, treated with diet (special attention was paid on adequate protein intake), supplemented by oral hypoglycemic agents or insulin-treated. Clinical parameters and renal function were evaluated at baseline and after 12 and 24 months: serum glucose, serum creatinine, blood urea nitrogen, total protein, albumin, serum cholesterol, high density lipoprotein (HDL), triglycerides, electrolytes, 24-hour urine samples were obtained for creatinine clearance rate (CCr) and proteinuria. Standard laboratory methods were used. Blood samples were collected after an overnight fast. CCr was calculated from 24-hour urine samples and serum creatinine levels, as follows, Cockroft-Gault formula: [(140-age) xBWx88.4]/72xsCr, for man and [(140-age) xBWx75.14]/72xsCr, for woman. The normal range of GFR for males and females is: males - 97 to 137 ml/min, females - 88 to 128 ml/min. Systolic and diastolic blood pressure (BP) was measured three times with a standard mercury sphyngomanometer and a cuff around the right arm after a subject had rested in the supine position for at least 15 minutes. An average of the three measurements was documented. For the mean BP the following formula was used: MBP = DBP + SBP-DBP/3. Because DM patients are often obese, a body mass index (BMI) was calculated by dividing the subject's weight by the square of the subject's height: BMI = kg/m².

Table 1: Clinical data of patients with Diabetic nephropathy

	At baseline			After 12 months			After 24 months		
	I	II	*P*<	I	II	*P*<	I	I	*P*<
n	33	37							
Age (years)	53±9	63±6	0.01						
Duration of diabetes (years)	4.4±4.0	9.2±6.5	0.01						
Duration of hypertension (years)	3.4±5.9	5.4±8.3	NS						
sCr (mmol/l)	78.7±15.0	103.0±42.0	0.01	84.2±17.1	124.3±25.0	0.01	85.4±11.7	136.2±84.2	0.03
CcR (ml/min)	105.8±20.3	75.4±17	0.01	102.8±25	64.6±26.7	0.01	103.8±26.7	64.2±26.7	0.01
Proteinuria (g/24h)	1.1±0.9	1.9±1.9	0.05	1.2±0.8	2.0±1.7	0.03	1.3±0.7	1.8±1.2	NS
SBP (mmHg)	143.8±25.3	156.6±26.3	0.05	126.5±12.0	138.9±16.5	0.01	125.6±14.1	135.2±12.5	0.03
DBP (mmHg)	87.6±15.6	89.2±150	NS	80.0±7.2	80.9±6.3	NS	77.2±6.3	79.7±5.5	NS
Mean BP (mmHg)	66.7±13.6	74.7±14.3	0.03	57.7±7.1	67.3±12.3	0.01	58.0±8.7	64.1±9.3	0.03
Body mass index (kg/m²)	26.9±3.0	27.2±4.0	NS	26.1±2.8	26.4±3.7	NS	25.3±2.2	25.6±3.5	NS
Glycemia (mmol/l)	8.1±3.5	8.8±3.4	NS	6.9±1.7	7.0±1.9	NS	6.2±1.7	6.5±2.2	NS
RI	0.6194± 0.003943	0.7154± 0.003860	0.01	0.6322± 0.004022	0.7320± 0.003871	0.01	0.6613± 0.004463	0.7600± 0.004472	0.01
TG (mM/l)	2.7±1.6	2.7±1.7	NS	2.2±0.5	2.5±2.0	NS	1.9±0.4	1.8±0.4	NS
TC (mM/l)	5.7±1.1	6.0±1.6	NS	4.9±0.7	5.3±1.7	NS	4.5±0.6	4.8±0.6	NS
HDL (mM/l)	1.5±0.7	1.5±0.9	NS	2.0±0.5	1.8±0.5	NS	1.9±0.4	1.8±0.5	NS
LDL (mM/l)	3.2±1.1	3.6±1.4		2.5±0.5	2.7±0.5		2.4±0.2	2.9±1.5	NS

Group I, RI ≤0.68; Group II, RI ≥0.68; Cr, creatinine; CCr, creatinine clearance rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL, high density cholesterol; LDL, low density cholesterol; RI, resistive index; NS, not significant.

Doppler US examination was performed with subjects in a supine position after they rested for 15 minutes. For the Doppler study, the wall filter is set to the minimum (50 Hz) and the sample volume is set at 2-5 mm. Resistive indexes (RIs) are measured in each kidney using existing software (automated algorithm) capabilities of the scanner. After a proper velocity waveform is obtained, the mean RI is calculated by using six measure-

ments taken for each patient. Intrarenal RI values were obtained from intraparenchimal arteries of both kidneys, either the arcuate or interlober arteries. Three different measurements are obtained for each kidney in different portions of the organ (upper, middle and lower pole). Mean RI value for each kidney is calculated from all measurements. A mean RI value is obtained for each patient by averaging the two kidneys' mean RI values. All Doppler examinations were performed by the same examiner (blinded to renal status of the patients) to avoid interobserver variability. The RI is determined as follows: RI = (PSV-EDV)/PSV (PSV=peak systolic flow velocity, EDV=end-diastolic flow velocity).

Values of RI higher than 0.68 were considered pathologic. The patients with nondiabetic or obstructive kidney diseases, the patients with microscopic or macroscopic hematuria, or an abnormal urinary sediment, a past history of glomerulonephritis or nephroureterolithiasis, or dilated renal pelvis on real-time US, were excluded from this study. The patients who had severely atrophied kidney(s), either unilateral or bilateral, were also excluded from the study because of poor imaging of blood flow.

Descriptive statistics (mean, standard deviation, minimum, median, maximum) was performed for all examined variables. Results are presented as means ± SD. Student's *t* test was used to compare parametric values, the Mann-Whitney rest to compare nonparametric values.

Results

Clinical data of the studied patients are shown in Table 1. Patients were divided based on their intrarenal RI values. Group 1 (n=33) had values of <0.68. Group 2 (n=37) had values ≥0.68. The difference in age between patients in the group 1 (mean, 53 years ± 9) and patients in the group 2 (mean, 63 years ± 6) was statistically significant. There was also a significant difference in the duration of diabetes between the groups, 4.4 ± 4.0 years in the group 1, compared to the group 2 (9.2 ± 6.5 years). There were no significant differences in the blood urea nitrogen, total protein, albumin and electrolytes (data not shown) at all time points.

Changes in serum creatinine, creatinin clearance rate, proteinuria, mean blood pressure, body mass index, and resistive index during the follow-up period are shown in the Table 1. All patients with RI ≥0.68 had statistically significant higher serum creatinine and lower CCr compare with patients with RI<0.68 during the follow up. Regarding glicemia, proteinuria and body mass index there were no significant differences between the groups at any time point. A significant difference was found between the groups in the systolic and mean blood pressure, but not in the diastolic blood pressure. A significant difference for RI values was also observed between the groups during the whole follow-up period.

Disscussion

Doppler ultrasonography has provided an easily applicable and noninvasive method for investigating renal hemodynamic. The renal resistive index reflects intrarenal vascular resistance [11]. In patients with decreased glomerular function the mechanisams for increased RI values is still not exactly clarified. A frequent microvascular complication of Diabetes mellitus is the development of Diabetic nephropathy. While early functional and structural abnormalities may be present a few years after the onset of the disease, in advanced DN, glomeruli become sclerotic, tubules become atrophic, and interstitial fibrosis is evident [15]. Sclerotic glomeruli may cause an increased blood flow resistance measurable at an upstream interlobar artery and increased interstitial fibrosis may cause elevated RI values. The RI of interlobar arteries seems to be a dependable marker of intrarenal changes. Intrarenal arteriosclerosis, as opposed to other forms of renal damage, has been shown to be an independent risk factor for an increased intrarenal RI in nondiabetic subjects. In addition, the intrarenal RI of diabetics is greater than the RI in patients with nondiabetic renal disease [16]. Ohta *et al*. recently found that the RI of the main renal arteries was significantly higher in patients with DN than in other patients. The intrarenal vascular resistance appears to increase to a greater extent in DN. Their results indicate that the increased RI of the renal arteries is associated with the severity of systemic atherosclerosis [17]. In a series of articles recently published, the potential of Doppler ultrasonography as useful adjunct for the assessment of the renal disease was markedly advanced. Boddi *et al*. found that RI measurement allows the early identification of both normotensive and hypertensive patients with chronic tubulointerstitial nephritis when renal function is still preserved. Renal RI values were linearly related to uremia and to filtration ratio values [18]. Other authors investigated whether RI at biopsy could be related directly to vascular or tubulointerstitial changes in the kidney, to the clinical and histopathologic parameters and to the renal outcome in patients followed up for more than 2 years. A direct relationship between RI and arteriosclerosis in damaged kidneys has been shown. RI at renal biopsy may be useful as one of the prognostic markers for renal outcome; patients with progression of renal impairment had a significantly increased RI at biopsy compared with patients without progression [16]. Series published from Heine *et al*. showed that in patients with chronic kidney disease, intrarenal RI linearly increased with a progressive impairment of renal function and independently reflect both local renal damage and systemic vascular disease [19]. In the present study we followed-up patients for two years and we hypothesized whether serial periodic RI measurements can be used as indicators of progression of the disease. The present study confirms the excellent correlation between RI and renal functional parameters. We were able to confirm relationship between CCr and age and RI and age in DN patients as it was

done previously by Pearce *et al*. [20]. Initialy higher RI may reflect accelerated impairment of the renal function. Beside good glycemic control, control of the weight and the decreased blood pressure there is no effect of protection if initial RI is >0.68. When RI increases to the value of 0.68, the risk of further impairment of renal function continues to escalate. In both groups BMI and glycemia declined during the folow up period almost to the normal values. We can explain this with fact that once patients enrolled the study they were under tight control and followed recomendations about the importance of the diet and medications.

We were not able to confirm relationship between RI and proteinuria previously done by Sugiura *et al*. since we could not find such differences between the groups. Finally, the RI is not a good indicator for changes in proteinuria [14]. Despite proteinuria was lower after two years in the group of patients with RI > 0.68, RI extended to rise. An explanation for this result maybe that proteinuria is a result of damaged glomerular capilaries and RI more reflects upon changes of intrarenal, extraglomerular arteries. Patients with DM and DN have particularly high risk of atherosclerosis. Intriguing question is whether or not reduction of RI predicts delay and/or even improved renal function. This question is very important and deserves long prospective examination.

Increased intrarenal RI has been shown in adults with diabetic nephropathy as a function of creatinine clearance, age, and diabetes duration and could represent a useful indication of renal function in diabetic kidney disease, especially in advanced clinical diabetic nephropathy [21]. However, intrarenal RI does not offer any advantage over serum creatinine and CCr in patients with early-stage DN with normal renal function [22]. Nosadini *et al*. 2006 tested whether the renal RI ≥80 was predictive to worsening renal function in 157 microalbuminuric, hypertensive, and type 2 diabetic patients after 7.8 year follow-up period. Overt proteinuria did develop in 24% of patients with RI ≥80 and in 5% of patients with RI <80. They found that RI strongly predicted the outcome of renal function in these patients, even when GFR is still normal [13]. Nevertheless, there is still no general agreement for the predictive value of Doppler ultrasonography in patients with diabetic nephropathy. Moreover, there are additional important covariables that affect renal vascular resistance and their complex interrelations cannot be easily evaluated in clinical practice.

In conclusion, an intrarenal RI ≥0.68 reflects damage of the microcirculation and can be used as a indicator of progression in patients with advanced clinical DN. Elevated RI might be observed in type 2 diabetic patients even in earlier stages of DN. An intrarenal RI value of ≥0.68 identifies diabetic patients at risk for progressive renal disease. Doppler US allows rapid, noninvasive evaluation of the intrarenal vasculature and can be used as easily available parameter of the evolution and a predictor in patients with advanced clinical diabetic nephropathy.

Conflict of interest statement. None declared.

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