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PROGRESSION OF DIABETIC NEPHROPATHY: VALUE OF INTRARENAL RESISTIVE INDEX (RI)

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A b s t r a c t: We used duplex Doppler analysis to determine whether the intrarenal RI can be used as a predictor in patients with diabetic nephropathy. 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 three and six months. Forty patients with diabetic nephropathy were divided into two groups based on their intrarenal RI values: group 1 had values of ≥ 70 and group 2 had values < 70. Progression of renal function (delta creatinine clearance, delta CCr) was estimated by linear regression of the slope of decline of CCr plotted against time.

At baseline, sixteen patients (40%) had an intrarenal RI value ≥ 70. Eight patients (50%) of them had a decline in renal function after six months. In comparison, among patients with intrarenal RI values < 70 (n = 24), only 2 had a decline in renal function. In multivariate regression analysis, proteinuria, lower baseline CCr and RI were independent predictors of declining renal function.

An intrarenal RI value of ≥ 70 identifies diabetic patients at risk of progressive renal disease. The RI of interlobar arteries seems to be a dependable 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.

Key words: Diabetic nehropathy, progression, colour duplex Doppler ultrasonography, resistive index.

Introduction

Diabetic nephropathy (DN) is the leading cause of end-stage renal failure (ESRF) in western countries. The prevalence of type 2 *Diabetes mellitus* is increasing probably because of its increased incidence, due to the general aging of population. There are close to 171 million diabetics in the world and will be over 366 million diabetics by 2030 [1]. The progression to clinical nephropathy in 10 years is 20% to 25%. Between 20–50% of patients with DN will develop chronic renal failure. [2, 3, 4]. In R. Macedonia diabetic nephropathy is found in 10%, 5–15% in different Dialysis Centres [5]. There are a lot of diabetics and a lot of diabetics with nephropathy. In the US from 1980 to 2000 the population with Diabetes grew by 45%; the number of diabetics with ESRD grew by 300%. [6]. The effective measures prevent early cardiovascular death of the diabetics and they live long enough to develop chronic renal failure and progress to end-stage renal disease. Available since the 1980s, colour Doppler Duplex sonography (CDDS) has allowed evaluation of alterations of renal perfusion noninvasively by interrogating intrarenal arteries or showing general renal perfusion [7]. Among parameters measured by Doppler ultrasound (US), resistance index (RI) values have been most frequently used in clinical practice. It is hypothesized that RI demonstrates changes of renal vascular resistance (RVR) in patients with impaired kidney function. Histopathological changes affect mainly the vascular compartment in the kidneys of diabetic patients with resultant elevation of renovascular resistance. Normal ranges for RI values vary from 0.58 to 0.68 in normal kidneys. Platt JF *et al*. suggested 0.70 as a reasonable upper limit for normal RI values in adult population [8]. The intraoperator coefficients of variance are small, less than 4–5%. Only a few studies compared intrarenal RI values with serum creatinine and clearance creatinine in DN [9]. Platt *et al*. showed a high level of correlation between SCC and CCR and intrarenal RI (mean, RI 0.71 ± 0.1; 98 patients) in advanced clinical DN [8, 10].

The purpose of the present study was to determine whether the intrarenal resistance index can be used as a predictor of progression in patients with diabetic nephropathy.

Materials and methods

The diagnosis of type 2 *Diabetes mellitus* was based on a previous history of diabetes or criteria according to the WHO. All patients were treated with diet, supplemented by oral hypoglycaemic agents or insulin-treated. A total of forty Macedonian Caucasian (non-smoking) patients with Diabetes mellitus and Diabetic nephropathy (aged 38–72 years) were enrolled and all patients ended the prospective follow-up study. Clinical parameters and renal function were

evaluated at baseline and after three and six months: serum glucose, glycolsylated haemoglobin HbA_{1c}, serum creatinine, blood urea nitrogen, albumin, 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. HbA_{1c} was measured by high-performance liquid chromatography. CCr was calculated from 24-hour urine samples and serum creatinine levels, as follows, Cockroft-Gault formula: [(140-age)-×BW×88.4]/72×sCr, for men and [(140-age)×BWx75.14]/72×sCr, for women. The normal range of GFR for males and females is: males – 97 to 137 ml/min, females – 88 to 128 ml/min. Blood pressure 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.

US examination by a duplex Doppler apparatus was performed with subjects in a supine position after they had 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 scnner. Mean RI value for each kidney is calculated from all measurements. After a proper velocity waveform is obtained, the mean RI is calculated by using six measurements 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). A mean RI value is obtained for each patient by averaging the two kidneys' mean RI values. All the Doppler examinations were performed by the same examiner 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 0.70 were considered pathological [8, 11]. 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 nephro-ureterolithiasis, 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 this study because of poor imaging of blood flow. After the initial presentation, patients were seen at three and at six months.

Results are presented as means ± SD. Student's *t* test was used to compare parametric values, the Mann-Whitney rest to compare nonparametric values. Correlations between intrarenal RI and diabetic years, sCr, and CCr were calculated. Multiple regression analysis was performed to assess the combined influence of clinical variables on the RI values. Progression of renal function (delta creatinine clearance, delta CCr) was estimated by linear regression of the slope of decline of CCr plotted against time.

Results

Patients were divided into two groups based on their intrarenal RI values. Group 1 (n = 16) had values of ≥ 70. Group 2 (n = 24) had values < 70. The difference in age between patients in group 1 (mean, 53 years ± 8) and patients in group 2 (mean, 55 years ± 11) was not statistically significant. There was no significant difference in the duration of diabetes between the groups, 14.3 ± 8.2 years in group 1, 11.2 ± 7.3 years in group 2 (Table 1). There were no significant differences in the serum glucose, glycosylated hemoglobin HbA_{1c}, blood urea nitrogen, albumin and electrolytes (data not shown).

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 Table 1. All our patients at baseline had higher serum creatinine and lower CCr. In patients with RI ≥ 70, sCr was 165 ± 52 μmol/l with CCr of 50.9 ± 8.8 ml/min. In patients with RI < 70, sCr was 150 ± 20 μmol/l with CCr of 54.9 ± 6.7 ml/min At the end of follow-up, after 6 months, serum creatinine and CCr expressed statistically significant differences between the two groups of patients. Eight patients (50%) from group 1 had a decline in renal function after six months. In comparison, among patients with intrarenal RI values < 70 (n = 24), only 2 had a decline in renal function (data not shown).

Regarding proteinuria, there were statistically significant increases and differences between the groups after three and six months. Mean blood pressure was significantly higher in the patients with RI ≥ 70 at baseline (107 ± 12 mmHg vs. 97 ± 11 mmHg) and after six months (115 ± 7 mmHg vs. 103 ± 10 mmHg). Body mass index showed no significant differences between the two groups of patients at any check point time. The statistical significance of differences for RI values was observed between the groups during the follow-up period.

Results of multiple regression analysis examining possible predictors independently affecting RI are shown in Table 2. RI values in DN patients were significantly affected by DeltaCCr, proteinuria and mean blood pressure. The relationship between the RI values and CCr (Delta CCr) in DN patients showed a negative correlation coefficient of $r = -0.388$ ($P < 0.01$). There was no relation-

Table 2 – Табела 2

Factors affecting the resistive index
Фактори кои влијаат на индексот на резистенција

Variables Dependent	Independent	β	*P* <	R2
Resistive Index	DeltaCCr	-0.388	0.01	
	Proteinuria	0.256	0.01	
	Mean blood pressure	0.232	0.05	
	HbA1c	-0.102	0.2	
	Age	0.055	0.59	0.505 (*P* < 0 .01)

ship between CCr and age and RI and age in DN patients. Linear regression analyses were performed to examine the relationship between the RI values and creatinine clearance in DN patients. A significant, negative correlation existed between the two measurements, r = -630 (P < 0.01, Figure 1).

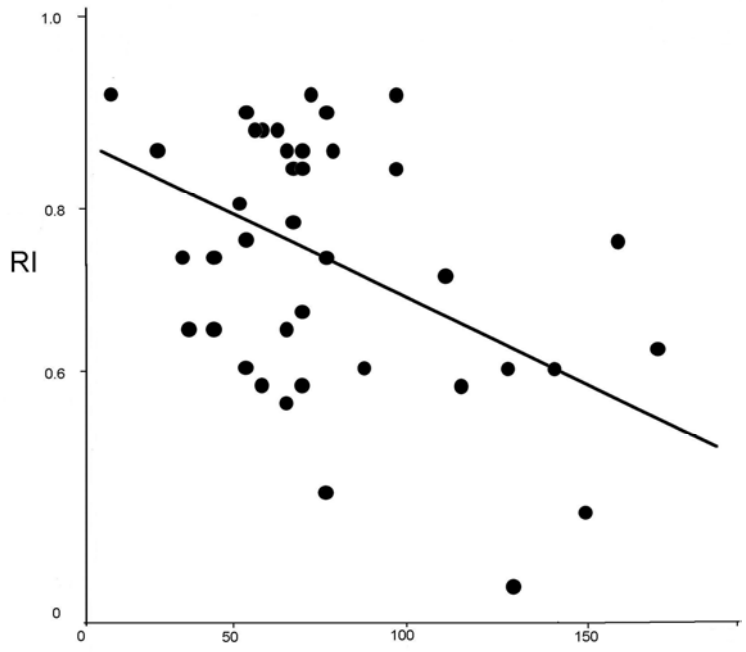

Figure 1 – Correlation between RI values and creatinine clearance in DN patients
Слика 1 – Корелација помеѓу вредноста на ИР и креатинин клиренсот кај пациенти со ДН

Discussion

Diabetic nephropathy is a frequent microvascular complication of *Diabetes mellitus*. Early functional and structural abnormalities may be present a few years after the onset of the disease. In these last decades, Doppler ultrasonography has provided an easily applicable and noninvasive method for investigating renal haemodynamics. The renal resistive index reflects intrarenal vascular resistance [7, 8]. The mechanisams for increased RI values in patients with decreased glomerular function is unknown. In advanced DN, glomeruli become sclerotic, tubuli become atrophic, and interstitial fibrosis is increased. Sclerotic glomeruli may cause increased blood flow resistance measurable at an upstream interlobar artery. Increased interstitial fibrosis may cause elevated RI values. The RI of interlobar arteries seems to be a dependable marker of intrarenal changes. Activation of the renin-angiotensin system is reported to contribute to inrarenal haemodynamic abnormality in diabetic patients. ACE inhibitors have been shown to delay the progression of DN by decreasing the intraglomerular capillary pressure. Recently, Taniwaki *et al*. evaluated the effect of RAS blocade on intrarenal haemodynamic changes by examing changes in RI in normotensive patients with type 2 DM. They showed that in diabetic patients, RI values after the test were significantly lower than baseline values, which is not the case with healthy subjects. With multiple regression analysis HbA1c and baseline plasma renin activity significantly and independently affected the magnitude of decrease in RI values after captopril administration in diabetic patients [12]. 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. The intrarenal RI of diabetics is greater than the RI in patients with nondiabetic renal disease [13]. Recently, Ohta *et al*. evaluated the relationship between RI and pulse wave velocity (PWV, a measure of arterial stiffness), which reflects atherosclerosis, and determined whether renal RI differed depending on the underlying renal disease in 245 patients. They 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 [14]. The potential of Doppler ultrasonography to serve as a useful adjunct for the assesment of renal disease was advanced in a series of articles published recently. Boddi *et al*. studied renal RI in patients with chronic tubulointerstitial nephritis. They found that RI measurement allows the early identification of both normotensive and hypertensive patients with chronic TIN, when renal function is still preserved. Renal RI values were linearly related to uricaemia and to filtration ratio values [15]. Other authors have 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 renal outcome in patients followed up for more than 2 years. They show a direct relationship between RI and arteriosclerosis in damaged kidneys. 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 [13]. In a series published more recently 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 [16].

In the present study we followed-up patients for six months. This study is a part of a longitudinal study (for 2 years) in which we follow-up patients with DM and DN and we ask whether serial periodic RI measurements offer advantages over well-proved clinical or laboratory parameters in predicting the progress of the disease. The present study confirms a very good correlation between RI and renal functional parameters. The RI index was significantly affectted by DeltaCCr, proteinuria and mean blood pressure. The relationship between the RI values and CCr (Delta CCr) in DN patients showed a negative correlation coefficient. We were not able to confirm the relationship between CCr and age and RI and age in DN patients like Pearce *et al*. [17]. Our results are in agreement with others [18]. 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 [19]. However, intrarenal RI does not offer any advantage over sCC and CCR in patients with early-stage DN with normal renal function [20]. Nosadini *et al*. 2006 tested wheather a renal RI >= 80 was predictive to worsening renal function in 157 microalbuminuric, hypertensive, type 2 diabetic patients after a 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 predicts the outcome of renal function in these patients, even when GFR is still normal [10]. However, the correlation between increased intrarenal RI and altered renal haemodynamics in children and adolescents with diabetes remains unclear. In their study Savino *et al*. observed that children with diabetes had significantly increased values of Doppler RI [21 Savino A, Pelliccia P, Schiavone C., Primavera A, Tumini S., Mohn A., Chiarelli F. (2006): Serum and urinary nitrites and Doppler sonography in children with diabetes. Diabetes Care; 29: 2676–2681]. Nevertheless, there is still no general agreement on the predicttive value of Doppler ultrasonography in patients with diabetic nephropathy. There are additional important covariables, however, that affect renal vascular resistance and their complex interrelations cannot be easily evaluated in clinical practice.

In conclusion, intrarenal RI shows a high level of correlation with serum creatinine and clearance creatinine rate and can be used as a predictor in patients with advanced clinical DN. An intrarenal RI value of ≥ 70 identifies diabetic patients at risk of progressive renal disease. Duplex Doppler US allows the rapid, noninvasive evaluation of the intrarenal vasculature and can be used as an easily available parameter of the evolution and a predictor in patients with advanced clinical diabetic nephropathy.

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Резиме

ПРОГРЕСИЈА НА ДИЈАБЕТИЧНАТА НЕФРОПАТИЈА: ПРЕДИКТОРНА ВРЕДНОСТ НА ИНТРАРЕНАЛНИОТ ИНДЕКС НА РЕЗИСТЕНЦИЈА (ИР)

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Користевме дуплекс доплер анализа за да детерминираме дали интрареналниот индекс на резистенција може да се користи како предитор кај пациенти со дијабетична нефропатија. Интрареналниот индекс на резистен-

ција (ИР) беше добиен од интрапаренхимните артерии на обата бубрега, аркуатните или интерлобарните артерии. Клиничките параметри и бубрежната функција беа исто така испитувани на почеток и по три и шест месеци. Четириесет пациенти со дијабетична нефропатија беа поделени врз основа на вредноста на интрареналниот ИР: група1 имаа вредност >= 70 и група 2 со вредност < 70. Прогресијата на бубрежната функција (делта клиренс креатинин, делта ККр) беше пресметувана со линеарна регресија на опаѓањето на ККр во функција на време.

На почеток, шеснаесет пациенти (40%) имаа интраренален ИР >+ 70. Осум пациенти (50%) од нив имаа пад на бубрежната функција по шест месеци. Помеѓу пациентите со интраренален ИР < 70 (н = 24), само двајца пациенти имаа пад на бубрежната функција. Со мултиваријантна регресиона анализа, протеинуријата, понискиот почетен ККр и ИР беа независни предиктори на падот на бубрежната функција.

Вредноста на интрареналниот ИР >+ 70 ги идентификува дијабетичните пациенти со ризик за прогресивна бубрежна болест. ИР на интерлобарните артерии се чини дека е зависен маркер на интрареналните промени и може да се користи како неинвазивен, лесно достапен параметар на еволуцијата на пациентите со напредната клиничка дијабетична нефропатија.

Клучни зборови: дијабетична нефропатија, прогресија, колор дуплекс доплер ултрасонографија, индекс на резистенција.

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Table 1 – Табела 1

Clinical data of patients with Diabetic nephropathy
Клинички податоци за пациентите со дијабетична нефропатија
BP, blood pressure

	At baseline			After 3 months			After 6 months		
	I	II	P	I	II	P	I	II	P
n (%)	16 (40%)	24 (60%)							
Age (years)	53 ± 8	55 ± 11	NS			NS			NS
Duration of diabetes (years)	14.3 ± 8.2	11.2 ± 7.3	NS			NS			NS
sCr (μmol/l)	165 ± 52	150 ± 20	NS	188 ± 48	167 ± 48	NS	202 ± 33	167 ± 48	< 0.01
Proteinuria (g/24h)	2.1 ± 1.2	1.3 ± 0.9	< 0.01	2.7 ± 0.7	1.4 ± 0.8	< 0.01	3.0 ± 0.4	1.5 ± 0.8	< 0.01
Creatinin clearance rate (ml/min)	50.9 ± 8.8	54.9 ± 6.7	NS	49.4 ± 8.3	55.4 ± 2.7	NS	47.4 ± 4.9	51.4 ± 7.6	< 0.03
Mean BP (mmHg)	107 ± 12	97 ± 11	< 0.03	109 ± 8	101 ± 5	NS	110 ± 7	103 ± 10	< 0.05
Body mass index (kg/m2)	30 ± 3.8	28 ± 1.9	NS	30 ± 4.5	29 ± 0.8	NS	32 ± 1.7	29 ± 2.6	NS
Resistive index	0.78 ± 0.02	0.62 ± 0.04	< 0.05	0.79 ± 0.08	0.59 ± 0.23	< 0.05	0.79 ± 0.1	0.68 ± 0.03	< 0.05

Table 2 Factors affecting the resistive index.
Табела 2. Фактори кои влијаат на индексот на резистенција.

Variables				
Dependent	Independent	β	*P* <	R2
Resistive Index	DeltaCCr	-0.388	0.01	
	Proteinuria	0.256	0.01	
	Mean blood pressure	0.232	0.05	
	HbA1c	-0.102	0.2	
	Age	0.055	0.59	0.505 (*P*<0.01)

Figure 1. Correlation between RI values and creatinine clearance in DN patients.
Слика 1. Корелација помеѓу вредноста на ИР и креатинин клиренсот кај пациенти со ДН.