

Resistive Index for the Evaluation of Renal Damage in Diabetes Mellitus Type 2

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Abstract

Background: One of the most common causes of renal impairment and development of chronic kidney disease is diabetes mellitus type 2 (DM 2). The aim of this prospective study was to determine the role of Resistive Index (RI) as a non-invasive marker for the evaluation of renal impairment in patients with DM 2. **Material and Methods:** 47 patients with DM 2 in mean age 62.66 ± 10.081 years were included in the study for the period of one year. All of them were with well-compensated diabetes mellitus ($HbA1c < 7.0\%$) and optimal control of arterial hypertension. Hematological analysis of blood were carried out. Serum and urine biochemical parameters were tested, glomerular filtration rate (GFR) was calculated, and abdominal ultrasound with measure of RI was done. **Results:** Patients with $RI < 0.7$ and those with $RI \geq 0.7$ did not differ significantly in terms of their age, sex, body mass index (BMI), duration of DM 2 and arterial hypertension, use of antihypertensive drugs and HbA1c ($p > 0.05$ for all). There was significant difference between the groups according to serum creatinine ($p = 0.026$), GFR ($p = 0.044$) and the degree of proteinuria ($p = 0.001$). There was a positive correlation between RI and serum creatinine ($r = 0.418$; $p = 0.001$) and between RI and proteinuria ($r = 0.396$; $p = 0.004$). A negative correlation relationship between RI and GFR values was found ($r = -0.413$; $p = 0.011$). **Conclusions:** RI may be used as an indicator for the assessment of the severity of renal impairment in patients with DM 2. It correlates well with serum creatinine, GFR and proteinuria, which are proven biochemical parameters indicating the degree of renal damage in patients with DM 2.

Keywords

Diabetes Mellitus Type 2, Resistive Index, Serum Creatinine, Proteinuria, Glomerular Filtration Rate

1. Introduction

One of the most common causes of renal impairment and the development of chronic kidney disease is diabetes mellitus type 2 (DM 2) [1]. Around 20% - 40% of patients with DM 2 and microalbuminuria have progression of renal damage and are diagnosed with nephropathy about 20 years after the onset of diabetes. Approximately 20% of them develop end-stage renal disease (ESRD) [2]. Microalbuminuria and proteinuria can be considered as important signs of the progression of glomerular abnormalities [3]. Other kidney function measures, such as estimated glomerular filtration rate (GFR) and serum creatinine are used as markers to assess mortality risk or to predict these outcomes in kidney disease [4].

The resistive index of an artery (RI) is a hemodynamic measure considered to reflect its vascular impedance [5]. Higher resistive index values consist in a manifestation of local arteriopathy [6]. Evaluation of vascular impedance at different sites of the renal parenchyma may suggest functional or structural changes within the kidneys and could provide useful diagnostic and prognostic information [7]. Elevated RI is associated with adverse outcomes in different diseases like diabetes mellitus or hypertension [4].

The aim of the study was to establish the role of RI as a non-invasive marker for the evaluation of renal damage in patients with DM 2.

2. Material and Methods

2.1. Patients

47 patients with DM 2, hospitalized in Clinic of nephrology, University Hospital "St. Ivan Rilski", Sofia, from February 2017 to March 2018 were enrolled in this prospective study. The mean age of the patients was 62.66 ± 10.081 years. The male-to-female ratio was 21/26 (44.7% men and 55.3% women). Written informed consent was obtained from the participants. The protocols conformed to the guidelines of the 1975 Helsinki Declaration. All patients were with well controlled DM 2 and without history of any other renal diseases. 36 of participants (76.6 %) were with anamnesis for arterial hypertension on medical treatment. Patients younger than 18 years old, oncology or systemic diseases, glycated haemoglobin (HbA1c) > 7.0% or suboptimal control of arterial hypertension (Blood pressure > 140/90mmHg) were excluded [8].

2.2. Testing Procedures

All patients were clinically examined and body mass index (BMI) was calculated.

Hematological analysis and tests of serum glucose, HbA1c, serum creatinine, blood urea nitrogen, albumin, electrolytes, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL), very low-density lipoprotein (VLDL), and high-density lipoprotein cholesterol (HDL) were done. 24-hour urine samples were obtained for proteinuria. GFR was calculated using Cockcroft-Gault formula $(140 - \text{age}) \times (\text{weight in kg}) / (\text{serum creatinine} \times 72) \times (0.85 \text{ for women})$ for all

patients and later adjusted by body surface [9].

2.3. Doppler Ultrasonography

Doppler ultrasound was performed using an ultrasound machine Prosound Alpha 7 (Hitachi Aloka Medical, Ltd., Tokyo, Japan) in all subjects. RI was measured in each kidney and mean RI value was obtained for each patient by averaging the two kidneys' mean RI values. The RI was determined as follows: $RI = (PSV - EDV)/PSV$ where: PSV = peak systolic flow velocity, EDV = end-diastolic flow velocity. Values of RI higher than 0.70 were considered pathological [10].

2.4. Statistical Analysis

The statistical analysis was performed using SPSS version 16. A variational analysis of the quantitative variables was used, as well as the Fisher's exact test, the method of Kolmogorov-Smirnov and the method of Mann-Whitney. Regression analysis was applied to establish the relationship between dependent variable RI and other analyzed variables as independent variables. A value of $p \leq 0.05$ was considered statistically significant.

3. Results

According to the RI index all subjects were divided into two groups. Group 1 consisted of 19 patients with normal RI values ($RI < 0.7$). Group 2 ($n = 28$) had elevated values of $RI \geq 0.7$. The main demographic and laboratory data of both groups were shown in **Table 1**.

There was no significant difference between the groups according to sex, age, BMI, duration of DM 2 and HbA1c ($p > 0.05$ for all). The systolic and diastolic blood pressure were similar in two groups ($p > 0.05$ for both). There was no statistical difference in the presence of arterial hypertension. 13 (68.4%) patients in Group 1 were with anamnesis of high blood pressure compared to 23 (82.1%) patients in Group 2 ($p = 0.312$). Duration of the disease was similar (13.71 ± 8.94 years vs. 17.33 ± 10.86 years, $p = 0.499$). The use of antihypertensive drugs was not different in patients with $RI < 0.7$ than those with $RI \geq 0.7$ ($p > 0.05$ for all) (**Table 2**).

There were no significant differences in the haematology, serum glucose, blood urea nitrogen, albumin, total cholesterol, triglyceride, LDL, VLDL, HDL and electrolytes (data not shown). The significantly higher serum creatinine and lower GFR were found in the group with $RI \geq 0.7$ ($p < 0.05$ for all) (**Table 1**). The serum creatinine in Group 1 was 94.26 ± 21.512 $\mu\text{mol/l}$ and mean GFR calculated for this group was 77.80 ± 28.25 ml/min/1.73m^2 . In Group 2 serum creatinine was 165.04 ± 34.603 $\mu\text{mol/l}$ and GFR was 50.13 ± 14.60 ml/min/1.73m^2 .

The prouteinuria was significantly higher in patients with $RI \geq 0.7$ ($p = 0.001$) (**Table 1**). Five patients in Group 1 had albuminuria less than 30 mg/24h and 11 patients were with albuminuria between 30 - 299 mg/24h . In this group only 3

patients were with greater than 300 mg of urinary albumin excretion in 24 hours. In comparison, among patients in Group 2 only one patient had albuminuria < 30 mg/24h and another one was with urinary albumin excretion in 24 hours between 30 - 299 mg. The most patients (n = 26) in the Group 2 had proteinuria \geq 300 mg/24h.

Linear regression analyses were performed to examine the relationship between the RI values with serum creatinine, proteinuria and GFR (**Table 3**). A strongly positive correlation was found between RI and serum creatinine ($r = 0.418$; $p = 0.001$). There was a positive correlation between RI and proteinuria as well ($r = 0.396$, $p = 0.004$). The same analysis found negative correlation between RI and GFR ($r = -0.413$, $p = 0.011$).

Table 1. Demographics of groups according to the Resistive Index.

	Group 1 N = 19	Group 2 N = 28	P
Male	7 (36.8%)	14 (50%)	0.551
Age (yrs)	61.58 \pm 8.572	63.39 \pm 11.080	0.389
BMI	29.90 \pm 6.395	30.34 \pm 3.687	0.862
Diabetes duration (months)	97.95 \pm 57.56	135.21 \pm 100.81	0.246
HbA1c (%)	6.167 \pm 0.726	6.2 \pm 0.613	0.919
Systolic blood pressure (mmHg)	121.05 \pm 9.94	125.60 \pm 14.87	0.187
Diastolic blood pressure (mmHg)	77.95 \pm 11.26	81.77 \pm 13.24	0.346
Creatinine μ mol/l	94.26 \pm 21.512	165.04 \pm 34.603	0.026*
Proteinuria g/24h	0.8947 \pm 0.258	1.8929 \pm 0.416	0.001*
GFR ml/min/1.73m ²	77.80 \pm 28.25	50.13 \pm 14.60	0.044*

Data are expressed as mean \pm standard deviation (SD) and number (percent). Statistical analysis: Fisher's exact test, method of Mann-Whitney. *p-value with statistic significant difference.

Table 2. Antihypertensive drugs of groups according to the Resistive Index.

Antihypertensive drugs	Group 1 N = 19	Group 2 N = 28	P
ACEIs	9 (47.4%)	12 (42.9%)	0.775
ARBs	3 (15.8%)	6 (21.4%)	0.720
CCBs	5 (26.3%)	13 (46.4%)	0.226
beta-blockers	5 (26.3%)	15 (53.6%)	0.079
Diuretics	4 (21.1%)	11 (39.3%)	0.220
Alpha-blockers	1 (5.3%)	6 (21.4%)	0.215

Data are given as n (%). Statistical analysis: Fisher's exact test. ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin-receptor blockers; CCBs, calcium channel blockers.

Table 3. Relationship between the RI values with serum creatinine, proteinuria and GFR.

	RI	
	r	p
serum creatinine	0.418	0.001*
proteinuria	0.396	0.004*
GFR	-0.413	0.011*

Statistical analysis: Linear regression analyses. *p-value with statistic significant difference.

4. Discussion

The RI increases in various kidney diseases and a lot of studies have shown the associations between RI, renal function and patient prognosis [7] [11]. The most studies agree that RI 0.70 should be the upper limit of normal intrarenal vascular resistance and higher values are associated with different renal pathologies [3].

Renal pathological changes in DM2 are as a result of atherosclerosis of the intra and extra renal arteries in a combination of microangiopathy of the glomerular capillaries, afferent arterioles and efferent arterioles. Renal RI is tightly related to renal arteriosclerosis and most studies show that RI is increased in DM2 [12]. According to some authors the severity of renal damage correlates well with the increasing of RI [12] [13].

In our study 28 of all patients are with increased RI. On the other hand only 19 of patients with DM 2 included in the study are with RI < 0.7. We find significantly higher serum creatinine in patients with RI \geq 0.7 than in other group ($165.04 \pm 34.603 \mu\text{mol/l}$ vs. $94.26 \pm 21.512 \mu\text{mol/l}$, $p = 0.026$). Strongly positive correlation between RI and serum creatinine ($r = 0.418$; $p = 0.001$) that we observe is prove by previous studies [14] [15]. For example Sari *et al.* reports higher correlation ($r = 0.84$) between serum creatinine and RI values in diabetic nephropathy [16].

According to our results there is a positive correlation between RI and proteinuria. Most of the patients with RI \geq 0.7 are with significant proteinuria ($\geq 300 \text{ mg/24h}$) while in the other group patients are with proteinuria < 300 mg/24h predominantly. The increase in proteinuria is associated with an increase in the RI ($r = 0.396$, $p = 0.004$). Our results are comparable to a similar study conducted [17] [18]. Ishimura *et al.* found that patients with diabetic nephropathy and increased values of albuminuria and serum creatinine have increased RI values although statistical significance was not reached [19]. In Milovanceva-Popovska *et al.* study proteinuria was associated with increased RI indicating nephropathy though this relation was not statistically significant until follow up after 3 and 6 months and further decline in creatinine clearance [13]. Shirin *et al.* also observed positive correlation between RI with albuminuria ($r = 0.725$, $p < 0.01$) [14].

We find that patients with RI < 0.7 have significantly lower GFR than patients with RI \geq 0.7 ($77.80 \pm 28.25 \text{ ml/min/1.73m}^2$ vs. $50.13 \pm 14.60 \text{ ml/min/1.73m}^2$, p

= 0.044). Negative correlation is found between RI and GFR ($r = -0.413$, $p = 0.011$). Our results are similar to those received by MacIsaac *et al.* They also find negative relationship between GFR and RI [20]. Parolini *et al.* establish that initial RI correlates with final GFR ($r = -0.4$, $p < 0.001$) [21]. Another authors observe the same relationship [3] [17].

5. Study Limitations

The current study has several limitations. First, the number of cases is small. No follow-up of patients is performed in the study, and the change in the RI over time is not assessed. This will be the subject of further research.

6. Conclusion

RI may be used as an indicator for assessing the severity of renal damage in patients with DM 2. It correlates correctly with serum creatinine, GFR and proteinuria, which are proven biochemical parameters showing the extent of renal impairment in patients with DM 2.

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