Original Article

Association of Clinical and Biochemical Parameters with Renal Resistive Index in Type 2 Diabetic Patients with Normal Albuminuria

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ABSTRACT

Objective: To determine the association between the renal resistive index (RRI) and different biochemical and clinical parameters in type 2 diabetic patients with normal albuminuria.

Methodology: This descriptive cross-sectional study was conducted at the Department of Radiology, Shaikh Zayed Hospital, Lahore with a diabetic clinic collaboration for one year from January to December 2023. After ethical approval, 300 type 2 diabetic patients with normal albuminuria <30 mg/g were included by non-probability convenience sampling. After obtaining informed consent, patient demographic and clinical details were noted on the proforma. All the patients underwent renal Doppler ultrasound and RRI was estimated. Various biochemical parameters of the patients were estimated. The data analysis was done using the Statistical Package for the Social Sciences version 25.

Results: The average RRI was ≥0.70 in 64(21.3%) patients who were labeled as having nephropathy, ≥0.65 to <0.7 in 82(27.4%), and 154(51.3%) had normal RRI. There was a significant association of renal resistive index with duration of diabetes mellitus (DM), serum creatinine, urinary albumin-to-creatinine ratio (ACR), glomerular filtration rate (GFR), fasting blood glucose, glycated hemoglobin (HbA1c), and lipid profile in type 2 diabetic patients with normal albuminuria (p-value ≤0.05).

Conclusion: Renal resistive index had a significant association with duration of diabetes, serum creatinine, urinary ACR, GFR, fasting blood glucose, HbA1c, and lipid profile. It can be used for early detection of diabetic nephropathy in type 2 diabetic patients with normal albuminuria.

Keywords: *Diabetes mellitus. Diabetic nephropathy. Ultrasonography. Renal artery.*

INTRODUCTION

The global prevalence of diabetes mellitus is rising, making it a serious health issue. Around 537 million people are suffering from diabetes mellitus worldwide and it is expected that the disease prevalence will increase to 783 million by 2045. The increasing prevalence of disease is attributed to advanced age, obesity, unhealthy lifestyles such as lack of physical activity, and poor quality of diet. The greater burden of disease is in low- and middle-income countries.[1] In Pakistan, the prevalence of diabetes mellitus is 26.7% affecting 33,000,000 people.[2]

Diabetes mellitus is a state of chronic hyperglycemia resulting from defects in insulin secretion, insulin resistance or both. Almost 90% of the cases of DM are of type 2 diabetes mellitus.[2] Chronic diabetes leads to substantial complications affecting almost every body organ. These complications include coronary heart disease, atherosclerosis, stroke, neuropathy, nephropathy, retinopathy, osteoporosis, arthropathy, and myopathy. The disease is linked with a high mortality rate; a greater proportion of these deaths are attributed to kidney and heart diseases.[3,4]

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Diabetic nephropathy is the leading reason for renal disorders, i.e., chronic kidney disease (CKD) and end-stage renal disease across the world. About 40% of diabetic patients develop diabetic nephropathy after 10 years of disease initiation. To prevent the progression of diabetic nephropathy, early-stage detection and effective disease management are required to improve the well-being of patients. The criteria for diagnosing diabetic nephropathy is decreased GFR (<60 ml/min per 1.73 m²) and increased urinary albumin-to-creatinine ratio (≥30 mg/g). These tests cannot detect the disease at early stages and their normal limit deviates only when some structural or functional abnormality occurs. So, there is a need for a more reliable, sensitive, and safe method for the early detection of diabetic nephropathy.[5]

Renal resistive index is considered a potential marker for the early detection of diabetic nephropathy. It can be estimated by utilizing Doppler ultrasonography, which targets renal arteries to find the resistance in blood flow within these arteries. It evaluates perfusion and other renal complications of the kidney's vascular system.[6] In traditional diagnostic methods, only the function of the glomerulus is studied, but RRI reflects the changes in the vascular system of the renal parenchyma.[7] A literature survey of the renal resistive index as a screening tool revealed that it is a reliable, safe, easy, and more accurate early diagnostic method for diabetic nephropathy. It is a highly efficient method, even when the patient has a normal range of albuminuria levels.[8,9]

In Pakistan, studies have evaluated the role of RRI in the diagnosis of diabetic nephropathy in type 2 DM but its association with various clinical and biochemical parameters has not been evaluated. This study was designed to explore the association of clinical and biochemical parameters such as body mass index (BMI), duration of diabetes, smoking & hypertension, lipid profile, fasting blood glucose, HbA1C, and GFR with RRI in type 2 diabetic patients with a normal range of albuminuria. The outcomes of this study would give a more detailed insight into the pathophysiology of the disease and would be beneficial in the early diagnosis & management of diabetic nephropathy.

METHODOLOGY

This descriptive cross-sectional study was conducted at the Department of Radiology, Shaikh Zayed Hospital, Lahore with a diabetic clinic collaboration for one year from January to December 2023. The ethical approval was obtained from the institutional review board (Letter No. UHS/Reg-20/2829, 26-11-2022). A sample size of 291 was calculated using the expected proportion of higher RRI in 25.3% of type 2 diabetic patients, 5% margin of error and 95% confidence interval.[10] After obtaining written informed consent, 300 type 2 diabetic patients with age >18 years and normal albuminuria (ACR below 30 mg/g) were enrolled by nonprobability convenience sampling. Pregnant females, patients with renal stones, CKD and GFR <60ml/minute/1.73 m^2 were excluded. Patients were diagnosed with type 2 diabetes mellitus if the fasting blood glucose was ≥126 mg/dl (7.0 mmol/l) after an 8 hour fast or blood glucose level >200 mg/dl (11.1 mmol/l) 2 hours after an oral glucose tolerance test or HbA1c ≥6.5%.[11]

The demographic and clinical details of patients including age, gender, BMI, duration of diabetes, smoking, and hypertension status were noted on the proforma. All the patients underwent renal Doppler ultrasound (General Electronics LogiqS7 ultrasound machine with linear 6-10 MHz and curvilinear 2-5 MHz transducers) and RRI was estimated to determine the resistance to blood flow in renal arteries using the following formula:

$$\text{Renal Resistive Index} = \frac{(\text{Peak systolic velocity} - \text{End diastolic velocity})}{\text{Peak systolic velocity}}$$

Readings were taken from three renal arteries for each kidney and then their average was calculated to find RRI. The value of normal RRI was <0.65, ≥0.65 to <0.7 was borderline and ≥0.7 was considered high (nephropathy).[6] The RRI >0.7 is indicative of diabetic nephropathy with 100% probability.[12] Fasting blood samples of patients were collected and sent to the Pathology department for the estimation of different biochemical parameters such as fasting blood glucose, HbA1c, lipid profile, and serum creatinine. In the lipid profile, total cholesterol, triglycerides, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and high density lipoproteins (HDL) were measured. The urine samples of patients were also sent to the laboratory for determining the urinary albumin-to-creatinine ratio. The GFR was calculated using the Cockcroft-Gault equation using age, weight, and serum creatinine.[13] The reference values for various biochemical parameters were taken as follows: urinary ACR <30 mg/g, serum creatinine=0.6-1.1 mg/dl in females and 0.7-1.3 mg/dl in males, GFR >90 ml/min/1.73 m^2, fasting blood glucose <126 mg/dl, HbA1c=4-5.6%, total cholesterol <200 mg/dl, triglycerides <150 mg/dl, LDL <100 mg/dl, VLDL <40 mg/dl, and HDL >40 mg/dl.[3,14,15]

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) version 25 was used to enter and analyze the data. The biochemical parameters such as fasting blood glucose, serum creatinine, etc. were reported using mean±standard deviation (SD). The qualitative variables such as gender, age groups, smoking, and hypertension status were presented as frequency and percentage. The association of RRI with qualitative and quantitative variables was measured using Chi-square and Analysis of Variance (ANOVA) tests, respectively. A p-value of ≤0.05 was taken as statistically significant.

RESULTS

In our study, there were 177(59%) males and 123(41%) females. Most of the patients were <60 years old with 131(43.7%) patients in each group (<45 and 46-60 years), respectively. The majority of the patients (57.7%) had a normal BMI of <25 kg/m^2 followed by 90(30%) with overweight BMI of 25-29.9 kg/m^2 and 37(12.3%) patients were obese with BMI of ≥ 30 kg/m^2. The duration of DM was <5 years in 180(60%), 5-10 years in 55(18.3%), and more than 10 years in 65(21.7%) patients. Most of the patients were non-smoker (80%) and non-hypertensive (64.7%).

The mean±SD value of urinary ACR was 18.6±0.04 mg/g, serum creatinine was 0.9±0.05 mg/dl, and GFR was 102.6±0.3 ml/min/1.73 m^2. Patients had mean fasting blood glucose of 153.9±0.02 mg/dl and HbA1c of 8.2%. Regarding lipid profile, the average total cholesterol was 208.3±0.2 mg/dl, triglycerides were 148.3±0.03 mg/dl, LDL of 88.3±0.02 mg/dl, VLDL of 24±0.1

mg/dl, and HDL of 51.6±0.05 mg/dl. Most of the parameters were within normal range except fasting blood glucose, HbA1c, and total cholesterol.

The average RRI was ≥0.70 in 64(21.3%) of the patients labeled to have nephropathy, ≥0.65 to < 0.70 in 82(27.4%), and 154(51.3%) had normal RRI. These results are shown in Table 1.

The renal resistive index had a significant association with duration of diabetes (p-value=0.00001) showing that nearly half of the patients with duration more than 10 years had nephropathy and the majority of those with less than 5 years duration were normal. Most of the patients with 5-10 years duration were borderline. Renal resistive index showed no significant association with gender, age, BMI, smoking, and hypertension status (Table 2).

When the association of RRI was seen with various biochemical parameters, a significant relation was found with serum creatinine, urinary ACR, GFR, fasting blood glucose, HbA1c, and lipid profile. The mean of all biochemical parameters except GFR were increased in borderline and nephropathy groups as compared to normal RRI. However, the mean GFR was decreased in both nephropathy and borderline groups (Table 3).

Table 1: Renal Resistive Index in the Arteries of Left and Right Kidneys

Renal Artery	RRI <0.65 (Normal)	RRI ≥0.65 to <0.7 (Borderline)	RRI ≥0.70 (Nephropathy)
Main Renal Artery (R)	191(63.7%)	64(21.3%)	45(15%)
Segmental Artery (R)	182(60.7%)	74(24.7%)	44(14.6%)
Interlobar Artery (R)	186(62%)	74(24.7%)	40(13.3%)
Main Renal Artery (L)	202(67.3%)	59(19.7%)	39(13%)
Segmental Artery (L)	200(66.7%)	69(23%)	31(10.3%)
Interlobar Artery (L)	211(70.3%)	69(23%)	20(6.7%)
Average	154(51.3%)	82(27.4%)	64(21.3%)

Table 2: Association of Renal Resistive Index with Various Demographic & Clinical Parameters

Variables		RRI <0.65 (Normal)	RRI ≥0.65 to <0.7 (Borderline)	RRI ≥0.70 (Nephropathy)	Total	p-value
Gender	**Male**	93(31%)	48(16%)	36(12%)	177(59%)	0.847
	Female	61(20.3%)	34(11.4%)	28(9.3%)	123(41%)	
	Total	154(51.3%)	82(27.4%)	64(21.3%)	300(100%)	
Age (Years)	**≤45**	75(25%)	32(10.7%)	24(8%)	131(43.7%)	0.464
	46-60	60(20%)	40(13.4%)	31(10.3%)	131(43.7%)	
	>60	19(6.3%)	10(3.3%)	9(3%)	38(12.6%)	
	Total	154(51.3%)	82(27.4%)	64(21.3%)	300(100%)	
BMI (kg/m^2)	**<25**	89(29.7%)	50(16.7%)	34(11.3%)	173(57.7%)	0.169
	25-29.9	52(17.3%)	20(6.7%)	18(6%)	90(30%)	
	≥30	13(4.3%)	12(4%)	12(4%)	37(12.3%)	
	Total	154(51.3%)	82(27.4%)	64(21.3%)	300(100%)	
Duration of DM (Years)	**<5**	126(42%)	40(13.3%)	14(4.7%)	180(60%)	0.00001*
	5-10	7(2.3%)	28(9.3%)	20(6.7%)	55(18.3%)	
	>10	21(7%)	14(4.7%)	30(10%)	65(21.7%)	
	Total	154(51.3%)	82(27.4%)	64(21.3%)	300(100%)	
Smoking	**Smoker**	36(12%)	10(3.3%)	14(4.7%)	60(20%)	0.113
	Non-Smoker	118(39.3%)	72(24%)	50(16.6%)	240(80%)	
	Total	154(51.3%)	82(27.4%)	64(21.3%)	300(100%)	
Hypertension	**Hypertensive**	50(16.7%)	32(10.7%)	24(8%)	106(35.3%)	0.556
	Non-Hypertensive	104(34.6%)	50(16.7%)	40(13.3%)	194(64.7%)	
	Total	154(51.3%)	82(27.4%)	64(21.3%)	300(100%)	

**Significant p-value*

Table 3: Association of Renal Resistive Index with Various Biochemical Parameters

Biochemical Parameters (Mean±SD)	RRI			p-value
	<0.65 (Normal)	≥0.65 to <0.7 (Borderline)	≥0.70 (Nephropathy)	
Urinary ACR	7.7±0.04	19.1±0.04	29±0.04	0.001*
Serum Creatinine	0.7±0.05	0.96±0.05	1.2±0.05	0.001*
GFR	116±0.3	100±0.3	92±0.3	0.001*
Fasting Blood Glucose	143.1±0.02	150.6±0.02	168.2±0.02	0.001*
HbA1c	6.9±0.5	8.2±0.5	9.5±0.5	0.001*
Total Cholesterol	175±0.2	200±0.2	250±0.2	0.001*
Triglycerides	115±0.03	140±0.03	190±0.03	0.001*
LDL	80±0.02	95±0.02	90±0.02	0.001*
VLDL	25±0.1	27±0.1	20±0.1	0.001*
HDL	45±0.05	50±0.05	60±0.05	0.001*

**Significant p-value*

DISCUSSION

The renal resistive index is recognized as a sensitive early diagnostic marker for diabetic nephropathy and is routinely included in the diagnostic evaluation of chronic kidney disease to assess kidney damage.[16,17] However, the association of RRI with demographic, clinical, and biochemical parameters has been explored in only a limited number of studies, primarily among patients with elevated albumin-to-creatinine ratio. In contrast, our study assessed this association in patients with normal ACR levels.

In our study, most of the patients (87.4%) were <60 years old. There were 59% males and 41% females. However, RRI groups (normal, borderline, and nephropathy) showed no significant association with the age and gender of the patients. In a study conducted by Kharsa et al., 78.1% were males, majority of the patients were >60 years old and only age showed a significant association with RRI.[18] Another study reported 60% males with age <60 years.[19] Most of the patients (37%) had an age range of 41-50 years with 63% males in a study by Joseph et al.[20] In contrast, study by Khan et al., had a majority (52%) of females with a mean age of 49.15±11.91 years.[21] In our study, the majority of the patients (57.7%) had normal BMI. Most of the patients were non-smoker (80%) and non-hypertensive (64.7%). Smoking, hypertension status, and BMI showed no significant association with RRI. Kharsa et al. reported 43.2% smokers, 33.9% obese, and 95.8% hypertensive patients. Similar to our results, RRI showed no significant association with any of these clinical parameters.[18] Our results revealed that RRI showed a significant association with duration of DM and abnormal RRI was observed in most patients with more than 5 years of duration. Similar to our results, Tahir et al. reported that RRI increased significantly among patients with >5 years duration of diabetes.[16] Joseph et al. reported that patients with increased RRI had a mean duration of diabetes of 7.41±4.9 years. However, these results were not statistically significant.[20] A study by Fatima et al. showed that the patients with illness duration of 5-10 years had a significant correlation with RRI.[22]

Our results showed a significant association of RRI with serum creatinine, urinary ACR, GFR, fasting blood glucose, HbA1c, and lipid profile. In another study, a significant increase in HbA1c was seen in patients with RRI >0.7.[16] A study by Romano et al. determined the prognostic role of RRI in CKD showing that renal function tests deteriorate rapidly in patients with higher RRI. Renal resistive index was considered an independent marker of the progression of CKD and its associated deaths.[23] Another study reported that higher RRI was significantly associated with higher serum creatinine and decreased GFR.[18] Nasir et al. reported a significant positive correlation of RRI with serum creatinine and microalbuminuria. However, results for HbA1c correlation with RRI were not statistically significant.[19] Another study also reported a significant increase in serum creatinine, microalbuminuria, and HbA1c in patients with elevated RRI. The GFR was significantly decreased in patients with high RRI. However in this study, only 12% of the patients had normal albuminuria.[20] In contrast, a study reported a significant positive correlation of RRI with serum creatinine but no significant correlation of RRI with albuminuria & HbA1c was observed. [21] Fatima et al. also showed a positive link between RRI and serum creatinine and albuminuria.[22] In contrast to our results, in which patients with high RRI showed a significant increase in total cholesterol and triglycerides, a study conducted at the University of Udine, Italy, observed lower levels of total cholesterol and non-HDL cholesterol in patients with an elevated RRI.[23]

CONCLUSION

Renal resistive index had a significant association with duration of diabetes, serum creatinine, urinary ACR, GFR, fasting blood glucose, HbA1c, and lipid profile. It can be used for early detection of diabetic nephropathy in type 2 diabetic patients with normal albuminuria.

LIMITATIONS & RECOMMENDATIONS

Our study had a few limitations. It was conducted at a single-center limiting the generalization of the results. The study did not determine the association of RRI with long-term outcomes such as adverse events and mortality. In light of our results, it is recommended that the renal resistive index should be used as a non-invasive screening marker for early detection of diabetic nephropathy in type 2 diabetic patients.

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Authors' Contributions:
A.S: Study design, patient recruitment, and data collection
M.N: Data analysis, result interpretation, and manuscript drafting
S.K.T: Literature review and referencing
M.F: Data verification and tabulation
S.S: Critical revision, statistical supervision, and final approval of the manuscript

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