

TO STUDY THE CORRELATION OF RENAL RESISTIVE INDEX AND ESTIMATED GLOMERULAR FILTRATION RATE IN DIABETIC NEPHROPATHY

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Abstract:

Background: Renal resistive index is a recognised and early indicator of type II diabetes mellitus-related cardiovascular risk as well as diabetic nephropathy.

Aim: To determine the relationship between resistive index and estimated glomerular filtration rate of subjects with diabetic nephropathy and to determine the frequency of occurrence of high resistive index in subjects with diabetic nephropathy.

Material and methods: The present cross sectional study entitled to study the correlation of renal resistive index and estimated glomerular filtration rate in diabetic nephropathy was conducted on 50 patients of type 2 diabetes mellitus with the diabetic nephropathy with reduced renal function (stage G1-G5), attending outdoor department or admitted in Medicine Department of Guru Nanak Dev Hospital, attached to Government Medical College, Amritsar.

Results: Out of 50 patients, females comprise 22 (44%) and males 28 (56%). The mean egfr in patients with RI <0.7 was 28.5 and in patients with >0.7 was 20.1. The difference was significant (P< 0.05). The mean RI in patients with CKD stage 2 was 0.65, in patients with stage 3 was 0.69, in patients with stage 4 was 0.74 and in patients with stage 5 was 0.78. A significant difference was observed (P< 0.05).

Conclusion: Renal RI could be a useful complementary test for the evaluation of functional alterations in renal hemodynamics in the early stages of diabetic nephropathy.

KEYWORDS: Diabetic nephropathy, Glomerular filtration rate, Renal resistive index

INTRODUCTION

Chronic Kidney Failure (CKD) involves a range of pathophysiologic processes that are associated with impaired renal function. CKD is considered to be associated with cardiovascular morbidity and mortality. Relevant risk factors for CKD include hypertension, type 2 diabetes (T2DM), autoimmune diseases, high age, race, family history of kidney disease, history of acute renal failure and abnormal kidney structure and urinary tract.^{1,2}

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, including the kidney.³

It has been noted that, not all patients of diabetes mellitus are predisposed and are likely to progress to diabetic nephropathy and it has been suggested that only about 20-40% of patients of Type 1 and Type 2 diabetes have renal involvement.⁴ Chronic kidney disease is classified based on the egfr and the level of proteinuria. Patients are classified as G1-G5, based on the egfr:⁵

Renal resistive index (RI) has been described as a duplex ultrasound-derived parameter for exhibiting the arterial waveform, where RI is capable of demonstrating dynamic or structural changes of intrarenal vessels and renal dysfunction,⁶ and is markedly associated with renal arteriosclerosis, and adverse cardiovascular events. Normal RI in adults is ranged from 0.47 to 0.70, showing a difference between 5 to 8% for two kidneys.^{7,8} RI is currently applied as a valuable marker for renal vascular and interstitial damage,^{9,10} where increased value of RI has shown negative progression of renal disease in T2DM patients.¹¹

The present study was performed to determine the relationship between resistive index and estimated glomerular filtration rate of subjects with diabetic nephropathy and to determine the frequency of occurrence of high resistive index in subjects with diabetic nephropathy.

MATERIAL AND METHODS

The present study entitled to study the correlation of renal resistive index and estimated glomerular filtration rate in diabetic nephropathy was conducted on 50 patients of type 2 diabetes mellitus with the diabetic nephropathy with reduced renal function (stage G1-G5), attending outdoor department or admitted in Medicine Department of Guru Nanak Dev Hospital, attached to Government Medical College, Amritsar. The study was carried out after seeking approval from Institutional Ethics Committee, Government Medical College, Amritsar. The nature of study was explained to each patient in their vernacular language, and informed written consent was taken from all who fulfil the inclusion criteria and are willing to participate in the study.

METHOD OF DATA COLLECTION:

- Study Design: Cross Sectional Study.
- Sample Size: 50 patients of type 2 diabetes mellitus with the diabetic nephropathy (stage G1-G5, based on the egfr).

INCLUSION CRITERIA:

- Subjects diagnosed with diabetes mellitus according to either of the ADA criteria with evidence of reduced renal function irrespective of control of blood sugar.

EXCLUSION CRITERIA:

- Subjects with known history of renal disease other than diabetic nephropathy.
- Subject with a single kidney
- Subjects with known or demonstrated renal arterial stenosis (excluded by the clinical findings, including physical examination and radiological examination of the kidney carried out during the course of the study)
- Subjects with a history of renal ultrasound features suggestive of urinary tract abnormalities
- Subjects with evidence of dehydration, hypotension (blood pressure $\leq 90/60$ mmhg)
- Subjects with bradycardia (Pulse rate < 60 beats per minute)
- Non consenting subjects

METHODS:

1. Confirmation of presence of diabetes mellitus was based on a documented history of diabetes, which includes objective evidence of degree of control as assessed by HAlC of $\geq 6.5\%$.¹⁹
2. Creatinine clearance as measured by the Abbreviated four variable Modification of Diet in Renal Disease (MDRD) equation as follows; $GFR (ml/min/1.73 m^2) = 175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$.
3. Subjects who were diagnosed with diabetes mellitus and have evidence of reduced renal function will be referred to an ultrasound unit and value of intrarenal resistive index was measured.

STATISTICAL ANALYSIS:

The data was systematically collected, tabulated and subjected to quantitative statistical analysis and relevant conclusions was drawn. SPSS version 21.0 was used. Chi-square test and Mann Whitney tests were applied. Results were expressed as frequency, percentages, mean \pm SD. P value less than 0.05 was considered significant.

RESULTS & OBSERVATIONS

Age group <30 years comprises of 4 (8%), 31-40 years 10 (20%), 41-50 years 22 (44%), 51-60 years 3 (6%), 61-70 years 10 (20%) and >70 years 1 (2%). The mean age was 45 \pm 9.87 years (Table 1).

Out of 50 patients, females comprise 22 (44%) and males 28 (56%).

There were 7 (14%) patients with hba1c <7, 11 (22%) patients with hba1c between 7-7.9, 18 (36%) patients with hba1c between 8-8.9, 14 (28%) patients with hba1c between 9-9.9.

Out of 50 patients, 18 (36%) were having hypertension and 32 (64%) did not have hypertension.

Out of 50 patients, 5 (10%) were having history of smoking and 45 (90%) did not have history of smoking.

Out of 50 patients, 36 (72%) were normal, 3 (6%) were overweight and 11 (22%) were obese.

The mean TC was 195 \pm 15.2 mg/dl, TG was 129 \pm 11.4 mg/dl and LDL was 129 \pm 10.7 mg/dl.

Duration of disease was 5 years in 8, (16%), 5-10 years in 12 (24%) and >10 years in 30 (60%).

24 hours urinary albumin <30 mg/24 hours was seen among 11 (22%), 30-300 mg/24 hours in 19 (38%) and >300 mg/24 hours in 20 (40%) patients.

There were 12 (24%) patients with serum creatinine <5 mg/dl, 30 (60%) with 5-10 mg/dl and 8 (16%) with serum creatinine >10 mg/dl.

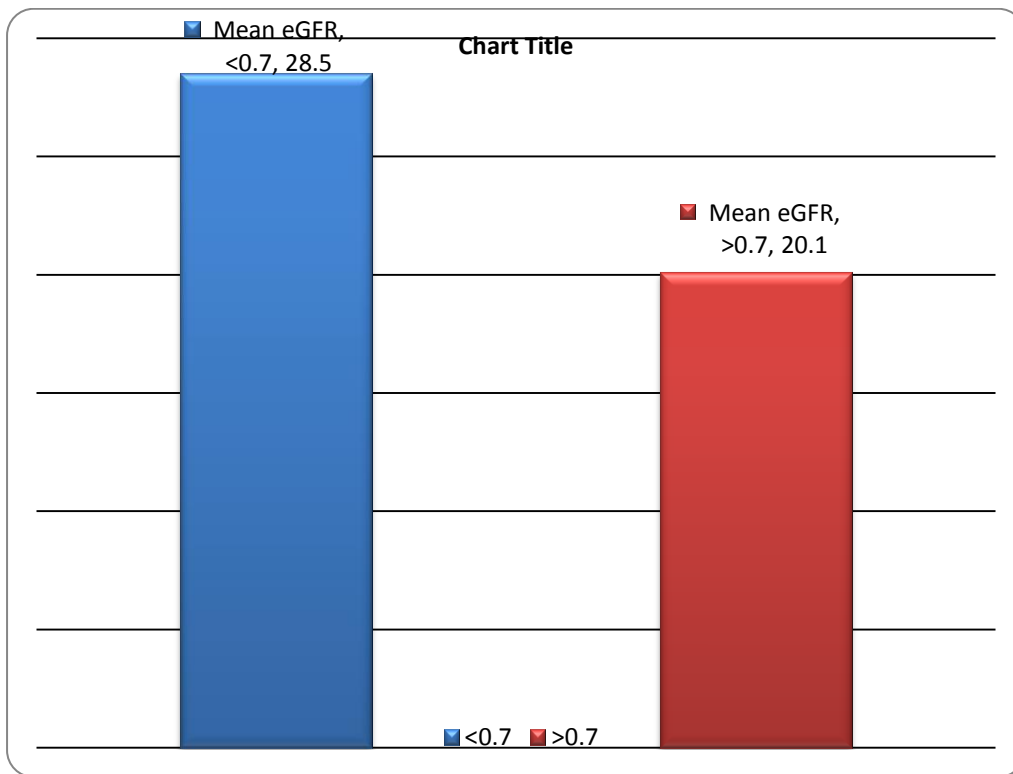
TABLE 1 DISTRIBUTION OF PATIENTS ACCORDING TO STAGE OF CKD AND GFR

CKD stage	Number	Percentage
2 (egfr 60-89)	1	2%
3 (egfr 30-59)	5	10%
4 (egfr 15-29)	16	32%

5 (<egfr 15)	28	56%
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There were 1 (2%) patients of CKD stage 2, 5 (10%) with stage 3, 16 (32%) with stage 4 and 28 (56%) with stage 5. As early stages of Diabetic Nephropathy are usually asymptomatic, the maximum number of patients usually present to the hospital during later stages.

GRAPH 1 CORRELATION OF RI ACCORDING TO egfr



The mean egfr in patients with RI <0.7 was 28.5 and in patients with >0.7 was 20.1. The difference was significant (P< 0.05).

TABLE 3 CORRELATION OF RI ACCORDING TO STAGE OF CKD AND GFR

CKD stage	Mean	P value
2 (egfr 60-89)	0.65	0.037
3 (egfr 30-59)	0.69	
4 (egfr 15-29)	0.74	
5 (<egfr 15)	0.78	

The mean RI in patients with CKD stage 2 was 0.65, in patients with stage 3 was 0.69, in patients with stage 4 was 0.74 and in patients with stage 5 was 0.78. A significant difference was observed ($P < 0.05$).

DISCUSSION

In our study age group <30 years comprises of 4 (8%), 31-40 years 10 (20%), 41-50 years 22 (44%), 51-60 years 3 (6%), 61-70 years 10 (20%) and >70 years 1 (2%). The mean age was 45 ± 9.87 years. In a similar study by Peterson et al, the mean age was 52 years (24-74).¹² Taniwaki et al included 61 patients with type 2 diabetes.¹³ The age ranged from 40 to 69 years. Sperandeo et al included 262 patients (age range: 48-81 years) with type 2 diabetes mellitus and 100 healthy volunteers (age range: 50-80 years).¹⁴ In a study by Raut et al the mean age in group I was 50.42 ± 4.89 and in group II was 60.34 ± 7.92 ($P = 0.000$).¹⁵ In a study by Shirin et al majority (45.3%) patients were in 6th decade with the mean age of 52.66 ± 7.4 years.¹⁶ Genov et al (studied 47 patients with DM 2 with mean age 62.66 ± 10.081 years).¹⁷

In our study out of 50 patients, females comprise 22 (44%) and males 28 (56%). Mean RI in females was 0.68 and in male was 0.76. Peterson et al in their study had twenty-five patients (10 females, 15 males).¹² Ishimura et al in their study had 112 in patients with type II diabetes mellitus (DM; 65 males, 47 females, 58 ± 13 years old).¹⁸ In another study conducted by Taniwaki et al included 61 patients with type 2 diabetes with 28 men and 33 women.¹³ Shirin et al in their study had 54.7% of diabetic patients as males with male to female ratio 1.2:1.¹⁶

It was seen that out of 50 patients, 18 (36%) were having hypertension and 32 (64%) did not have hypertension. Out of 50 patients, 5 (10%) were having history of smoking and 45 (90%) did not have history of smoking. Out of 50 patients, 36 (72%) were normal, 8 (16%) were overweight and 6 (12%) were obese. The mean TC was 195 ± 15.2 mg/dl, TG was 129 ± 11.4 mg/dl and LDL was 129 ± 10.7 mg/dl.

It was seen that mean RI was 0.70 ± 0.03 . A significant increase of mean RI was observed with every increase in age group. Maximum mean RRI was in age >70 yr (0.80). Our findings were supported by another study conducted by Ishimura et al revealed that RI values in DM patients were significantly affected by age.¹⁸ In a study by Taniwaki et al GFR was significantly correlated with the patient's age ($r = -0.256$, $P < 0.05$) and renal arterial RI ($r = -0.365$, $P < 0.05$).¹³ In a study by Pontremoli et al renal resistive index (RI) positively correlated with age ($r = 0.25$, $P = 0.003$).¹⁹ In a study by Hamano et al RI there was a significant associations with age ($r = 0.398$, $P < 0.0001$), diastolic blood pressure ($r = -0.398$, $P < 0.0001$), egfr ($r = -0.373$, $P < 0.0001$) respectively.²⁰ Ishimura et al revealed that RI values in DM patients were significantly affected by age ($R^2 = 0.554$, $P < 0.0001$).¹⁸

In our study the duration of disease was 5 years in 8, (16%), 5-10 years in 12 (24%) and >10 years in 30 (60%). The mean RI in patients with 5 years of duration was 0.68, in patients with 5-10 years was 0.72 and in patients with >10 years was 0.79. There was significant increase

in RI as age advances ($P < 0.05$). In concordance to our study a in a study by Ishimura et al RI values in DM patients were significantly affected by duration of diabetes ($R^2 = 0.554$, $P < 0.0001$). In a study by Youssef et al increase in RI had a positive correlation with duration of the disease.¹³ In a study by Maksoud in 2019 a progressive increase in RI was significantly associated with increased disease duration more than 10 years.²¹

In our study there were 12 (24%) patients with serum creatinine <5 mg/dl, 30 (60%) with 5-10 mg/dl and 8 (16%) with serum creatinine >10 mg/dl. There was significant increase in RI with the increase in serum creatinine. Mean RI in patients having serum creatinine <5 mg/dl was 0.67, in serum creatinine between 5-10mg/dl was 0.71 and in serum creatinine >10 mg/dl was 0.79.

Our findings were supported by a study conducted by Sari et al in which serum creatinine concentration showed high correlations ($r = 0.84$ and $r = -0.76$, respectively) with intrarenal RI values. In another study by Afsar et al renal resistive index levels were highest in patients with type 2 diabetes with both decreased 24- h creatinine clearance whereas they were lowest in patients with normal creatinine clearance and normal urinary albumin excretion.²² In a study by Shirin et al (2015) a positive correlation was seen between resistive index with serum creatinine ($r=0.581$, $p<0.01$) and albuminuria ($r=0.725$, $p<0.01$).¹⁶ In a study by Genov et al there was a positive correlation between RI and serum creatinine ($r = 0.418$; $p = 0.001$).¹⁷ Ishimura et al revealed that RI values in DM patients were significantly affected by creatinine clearance ($R^2 = 0.554$, $P < 0.0001$).¹⁸

The mean systolic blood pressure (SBP) in patients with RI (<7) was 120.4 mm Hg and in patients with RI (>7) was 138.2 mm Hg. As the RI increases, SBP increases ($P < 0.05$).

Our findings were supported in a study by Pontremoli et al where RI was positively correlated with systolic blood pressure (SBP) ($r=0.2$, $P=0.02$). In a study by Sistani et al (2019) a significant correlation of RI with systolic BP ($p=0.04$ $R=0.75$) was established.²³

The mean diastolic blood pressure (DBP) in patients with RI (<7) was 76.2 mm Hg and in patients with RI (>7) was 88.4 mm Hg. As the RI increases, DBP increases ($P < 0.05$). In a study by Hamano et al RI had significant associations with diastolic blood pressure ($r = -0.398$, $P < 0.0001$).²⁰ Sistani et al indicated a significant correlation of RI with diastolic BP ($P=0/45$ $R=0/32$).²³

The well-known mechanism for increasing RRI in essential hypertension has not been explained. But various process can be likely involved in this event. Hypertensive arteriopathy has been described to be linked to constriction of arterioles and its hemodynamic modulation, thus both functional alteration and, renal atherosclerotic lesions has been attributed to an increase in RI value.

There were 7 (14%) patients with hba1c <7 , 11 (22%) patients with hba1c between 7-7.9, 18 (36%) patients with hba1c between 8-8.9, 14 (28%) patients with hba1c between 9-9.9. The mean RI in patients with hba1c <7 was 0.62, in patients with hba1c 7-7.9 was 0.64, in

patients with hba1c 8-8.9 was 0.70, in patients with hba1c 9-9.9 was 0.72 and in patients with hba1c >10 was 0.78.

In concordance to our study Youssef et al found increase in RI had a positive correlation with hba1c levels.¹³ In a study by Maksoud et al progressive increase in RI was significantly associated with, elevated serum hba1c more than 7.5%.²¹

Poor control of blood glucose, as shown by elevated hba1c and basal plasma renin activity (PRA) had an effect on the magnitude of reduction in RI among subjects suffering from T2D.

Early functional and structural abnormalities which occur after a few years of diabetes might be responsible for the precocious alteration in renal hemodynamics , and this might be reflected in increased RI

The mean RI in patients with 24 hours urinary albumin <30 mg/24 hours was 0.64, in patients with 30-300mg/24 hours was 0.72 and in patients with >300 mg /24 hours was 0.78. A significant difference was observed (P< 0.05).

In a study by Afsar et al renal resistive index levels were highest in patients with type 2 diabetes with increased 24- h urinary albumin excretion.²² In a study by Falah et al RI was highest in the group with macroalbuminuria.²⁴ Thus, increasing the excretion of albumin has led to an increase in the resistance of the renal interlobular arteries.

The association of RI with microalbuminuria in some investigations could suggest the impact of increased pulsatility on aorta, resulting in accelerating the gradual microvascular damage. Furthermore, increased RI has been revealed in diabetic nephropathy, when the kidneys become smaller in size, followed by microalbuminuria. On the other hand, recent evidence indicates that that albuminuria and albuminuric nephropathy cannot be always linked to impaired renal function and renal failure. A growing body of evidence suggests that high level of albuminuria or mild decrease in glomerular filtration rate (GFR) can be capable of assessing cardiovascular risk at the initial stage.

In our study there was 1 (2%) patient of CKD stage 2, 5 (10%) patients with stage 3, 16 (32%) patients with stage 4 and 28(56%) patients with stage 5. The mean RI in patients with CKD stage 2 was 0.65, in patients with stage 3 was 0.69, in patients with stage 4 was 0.74 and in patients with stage 5 was 0.78. A significant difference was observed (P< 0.05).

Our findings were supported In a study by Spomenka et al in which a significant positive correlation was found between intra-renal RI and diabetic nephropathy.²⁵ In another study by Priyono et al there was a strong correlation between RI and e GFR (CKD –EPI) in diabetic kidney disease.²⁶

The mean egfr in patients with RI <7 was 28.5 and in patients with >7 was 20.1. In a study by Peterson et al RI correlated significantly to GFR (r = -0.5, P = 0.02)¹². In a study by Taniwaki et al GFR was significantly correlated with the patient's renal arterial RI (r = -0.365, P < 0.05).¹³ In a study by Youssef et al increase in RI had a positive correlation with GFR.²⁷ In another study by Priyono et al correlation was seen between RI and e GFR (CKD-EPI) in

diabetic kidney disease, $r = -0,84$ with $p = 0,000$.²⁶ In a study by Sistani et al (2019) a significant correlation of RI with GFR ($P=0.001$ $R=0.76$) was seen.²³

CONCLUSION

In our study we concluded that

- RI values increase as the serum creatinine rises.
- RI correlates well with degree of albuminuria
- As the egfr decreases during the course of the diabetic nephropathy RI increases in a significant manner.

All of the above are proven biochemical parameters indicating the degree of renal damage in patients with diabetic nephropathy. Renal RI could be a useful complementary test for the evaluation of functional alterations in renal hemodynamics in the early stages of diabetic nephropathy. Thus, renal resistive index can be declared as reliable and early marker of diabetic nephropathy as well as other cardiovascular risk associated with type II diabetes mellitus.

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