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A comprehensive study to find the association between biochemical markers and renal resistive index in patients with diabetes mellitus

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Abstract
Context: Renal Doppler sonography provides an easily applicable and non-invasive method for investigating renal morphologic characteristics and measuring vascular resistance in the renal parenchyma which is defined by the renal resistive index (RI). RI is elevated in tubule interstitial and vascular pathologies. Estimation of RI and its role in the diagnosis of diabetic nephropathy in diabetes mellitus is not well defined.
Aim of the study: To evaluate the association between renal resistive index, microalbuminuria and serum biochemical markers in patients with diabetes mellitus.
Material and Methods: A cross sectional study was done in Department of Radiodiagnosis in Government medical college Baroda from December 2018 to September 2020. 100 diabetic patients without other comorbidities were enrolled in the study. Renal Doppler was done using a 3.5 MHz convex array probe. SPSS 16 software was used for statistical analysis.
Results: Majority of patients belonged to the age group of 41- 50 years. Majority of patients were males (63%). The mean duration of diabetes in our study was 6.17 ± 5.16 years. 71% of our patients had uncontrolled diabetes mellitus (HbA1c >= 6.5) and 29% had controlled diabetes mellitus (HbA1c < 6.5). Statistically significant association was found between microalbuminuria and RI (P value of < 0.0001). Statistically significant correlation was found between RI and HbA1C (P=0.008), serum creatinine (P<0.0001), e-GFR (P<0.0001) and duration of diabetes mellitus (P= 0.0001).
Conclusions: Out of the 100 patients, RI was elevated in 57 patients. RI had a statistically significant association with microalbuminuria. Statistically significant correlation was found between RI and serum creatinine, HbA1C, eGFR and duration of diabetes. Of the 57 patients with raised RI, 37 patients had normal serum creatinine levels, implying that RI is elevated before serum creatinine is elevated.

Keywords: Resistive index, diabetes, microalbuminuria, association

Introduction
Diabetes is the most common cause of end stage renal disease. Diabetic nephropathy is one of the most frequent microvascular complications of diabetic patients that occurs in nearly 30% of diabetics. Microalbuminuria is one of the earliest predictors of onset of diabetic nephropathy [1].
Microalbuminuria is considered as a risk factor for progression to macroalbuminuria and subsequently overt nephropathy in later stages of the disease. Renal resistive index by duplex Doppler ultrasound was recognized to be a rapid, noninvasive, diagnostic method to study the characteristics of intra renal blood flow, which strongly indicates outcome of renal function in diabetics even when glomerular filtration rate patterns were still within normal limits and also to assess the progression to end stage renal disease [11].
Renal Resistive Index estimated by renal duplex Doppler ultrasonography, can be used as an additional diagnostic tool in diagnosing diabetic nephropathy and to assess the progression to end stage renal disease.

Materials and Methods
Source of data
Type 1 and 2 DM patients visiting Medical College Baroda over a period of 1 year and 9 months extending from December 2018 to September 2020.

Method of collection of data

Patient's informed consent was taken. A detailed history regarding the duration of diabetes, hypertension, history of diabetic complications, and presence of other macro vascular complications was taken. General and systemic clinical examination were checked through patient records.

Following investigations were obtained:

a. HbA1c
b. Urine Dipstick
c. Serum creatinine
d. Microalbuminuria was estimated by urine albumin / creatinine ratio in all patients in whom overt proteinuria was absent by urine dipstick.
e. GFR-calculated by using the formula of MDRD(modification of diet in renal disease) eGFR $=186*s.creat^{(-1.154)}*age^{(-0.203)}*$[0.742 if females]
f. Duplex Doppler ultrasonography- for estimation of renal vascular resistance

Estimation of albuminuria:

Urinary albumin concentration was measured from fresh spot urine and was expressed as milligrams creatinine of urine. Normoal buminuria was defined as urinary albumin-to-creatinine ratio < 30 microg/mg. Microalbuminuria was defined as urinary albuminto-creatinine ratio ≥30 –299 microg/mg. Macroal buminuria was defined by albumin-to-creatinine ratio>300 microg/mg.

Duplex Doppler ultrasonography

Both colour coded Doppler and pulsed Doppler modes were used for the study. The Doppler study was carried out in Phillips affinity 50 and a 3.5 MHz convex array probe was used for the study. Kidneys were visualized in longitudinal orientation using oblique position of transducer Intrarenal vascular structures are visualized using colour coded Doppler. Sample volumes were obtained by positioning the cursor of the pulsed Doppler at the mid portion of the interlobar arteries with flow along the renal pyramids. Angle was adjusted to less than 60 degrees. Doppler spectral waveforms were obtained on the lowest pulse repetition frequency possible without aliasing. This maximized the size of the Doppler spectrum and decreased percentage of error in measurements. Lowest possible wall filter for the ultrasound scanner was used. The velocity measurements of peak systolic velocity and end diastolic velocity were automatically calculated from the spectral forms. Intra renal arterial resistive index values from upper, mid and lower poles of each kidney were obtained and the mean of the six values was calculated, the mean resistive index was used for statistical analysis.

$$\text{Resistive index} = \frac{\text{Peak systolic flow velocity - End diastolic flow velocity}}{\text{Peak systolic flow velocity}}$$

3.5 Inclusion criteria

Type 2 diabetes mellitus patients diagnosed at any point of time, and Type 1 DM patients with duration of disease equal to or more than ten years, without hypertension, or with controlled hypertension (SB*P*<130 mmHg and DB*P*<85 mmHg)

Exclusion criteria

a. Patients with hypertension.
b. Patients with cardiac failure
c. Patients on ACE inhibitors, angiotension receptor blockers
d. Patients suffering from acute or chronic urinary tract infections, RAS, renal transplant, malignancies, renal artery and vein thrombosis.
e. Patients with non-diabetic renal disease due to hereditary, metabolic, immunological (excluded by history).

Results

Out of the 100 patients enrolled, 63 were male patients and 37 were female patients. The majority [37%] of patients were in the age group of 41 to 50 years. The mean duration of diabetes in our study was 6.17 ± 5.16 years.

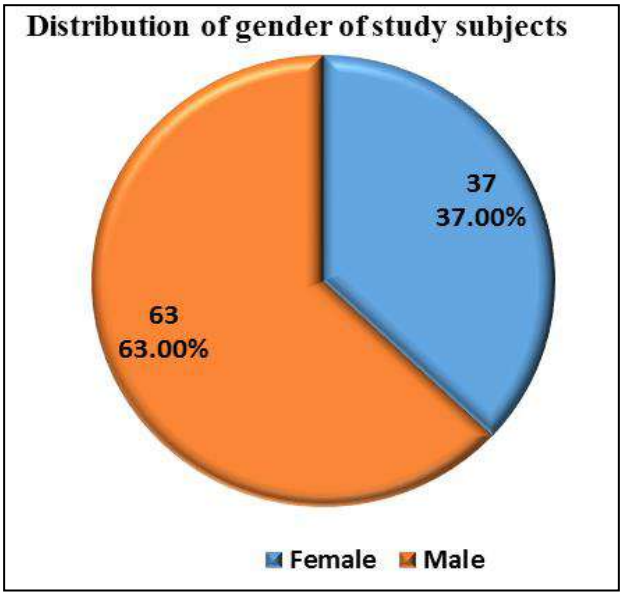

Fig 1: Distribution of gender of study subjects.

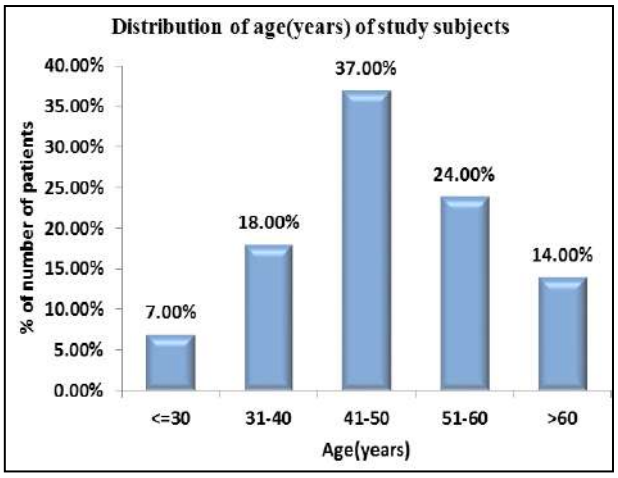

Fig 2: Distribution of age (years) of study subjects.

Out of the 100 patients, 57(57%) patients had elevated resistive index. These patients had a mean duration of diabetes of 7.41 ± 4.9 years and mean HbA1C of 9.15 ± 2.96. On the other hand, the mean duration of diabetes in patients' with normal RI was 4.53 ± 5.07 while the mean HbA1c of these patient's were lower 7.4 ± 3.27. There was a statistically significant correlation between HbA1C and resistive index (p=0.0008- Chi square test, 0.006-t test).

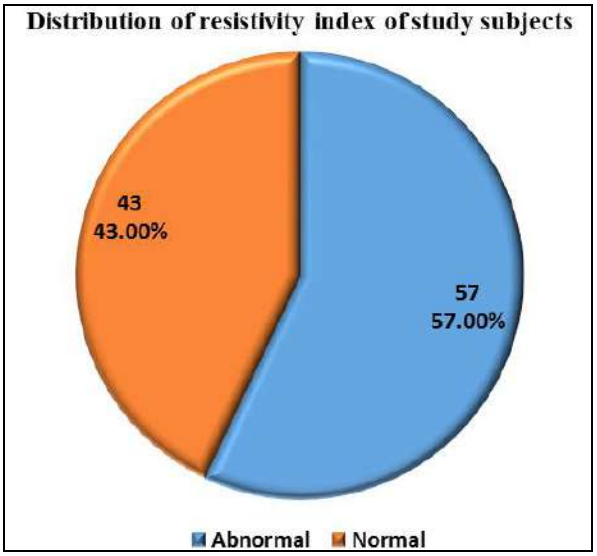

Fig 3: Distribution of resistivity index of study subjects.

Table 1: Association of HbA1C (%) with resistivity index.

HbA1C (%)	Abnormal (n=57)	Normal (n=43)	Total	P value	Test performed
Controlled diabetes	9 (15.79%)	20 (46.51%)	29 (29%)	0.0008	Chi square test,11.235
Uncontrolled diabetes	48 (84.21%)	23 (53.49%)	71 (71%)		
Mean ± SD	9.15 ± 2.96	7.41 ± 3.27	8.4 ± 3.2	0.006	t test;2.788
Median(25th-75th percentile)	8 (7-11.1)	6.7 (5.3-7.9)	7.5 (6.175-10.025)		
Range	4.3-16.2	4-18.5	4-18.5		

The patients were categorised into three groups, namely normoalbuminuric, microalbuminuric and macroalbuminuric, depending on their urinary albumin excretion rate. Out of the 100 patients in the study group, 12(12%) had normoalbuminuria, 62(62%) had microalbuminuria and 26(26%) had macroalbuminuria. Renal vascular resistance was elevated in 98.25% of patients with microalbuminuria, 96% of patients with macroalbuminuria and 2.7% with normoalbuminuria. In our study the mean resistive index in the normoalbuminuric, microalbuminuric, macroalbuminuric groups were 0.62, 0.7, 0.77 respectively. A strong independent statistically significant positive association was seen between resistive index and microalbuminuria (P=<0.0001).

Table 2: Association of microalbuminuria with resistivity index.

Microalbuminuria	Abnormal (n=57)	Normal (n=43)	Total	P value	Test performed
Absent	1 (1.75%)	37 (86.05%)	38 (38%)	<.0001	Fisher Exact test
Present	56 (98.25%)	6 (13.95%)	62 (62%)		
Total	57 (100%)	43 (100%)	100 (100%)		

In our study only 21(21%) of the diabetic patients had raised serum creatinine. Out of the 57(57%) patients who had raised RI values, only 20 patients had a raised serum creatinine and the rest 37 patients had normal serum creatinine level. RI was found to have a positive association with serum creatinine and a negative correlation with eGFR [correlation coefficient=-0.495], which in our study was estimated by Cockroft Gault formula.

Table 3: Association of serum creatinine (mg/dL) with resistivity index.

Serum creatinine(mg/dL)	Abnormal (n=57)	Normal (n=43)	Total	P value	Test performed
Abnormal	18 (31.58%)	3 (6.98%)	21 (21%)	0.003	Fisher Exact test
Normal	39 (68.42%)	40 (93.02%)	79 (79%)		
Mean ± SD	1.15 ± 0.6	0.82 ± 0.3	1.01 ± 0.52	0.0005	t test;3.62
Median(25th-75th percentile)	1 (0.8-1.5)	0.8 (0.6-1)	0.9 (0.7-1.125)		
Range	0.5-3.8	0.36-2	0.36-3.8		

Table 4: Association of eGFR (mL/min/1.73m²) with resistivity index.

eGFR(mL/min/1.73m²)	Abnormal (n=57)	Normal (n=43)	Total	P value	Test performed
Abnormal	13 (22.81%)	1 (2.33%)	14 (14%)	0.003	Fisher Exact test
Normal	44 (77.19%)	42 (97.67%)	86 (86%)		
Mean ± SD	93.63 ± 12.86	103.47 ± 9.63	97.86 ± 12.53	0.0001	t test;4.201
Median(25th-75th percentile)	95 (91-99)	102 (96-111)	98 (92-108)		
Range	62-120	85-122	62-122		

Figure 4: 70 year old male with duration of diabetes of 16 years, with macro albuminuria.

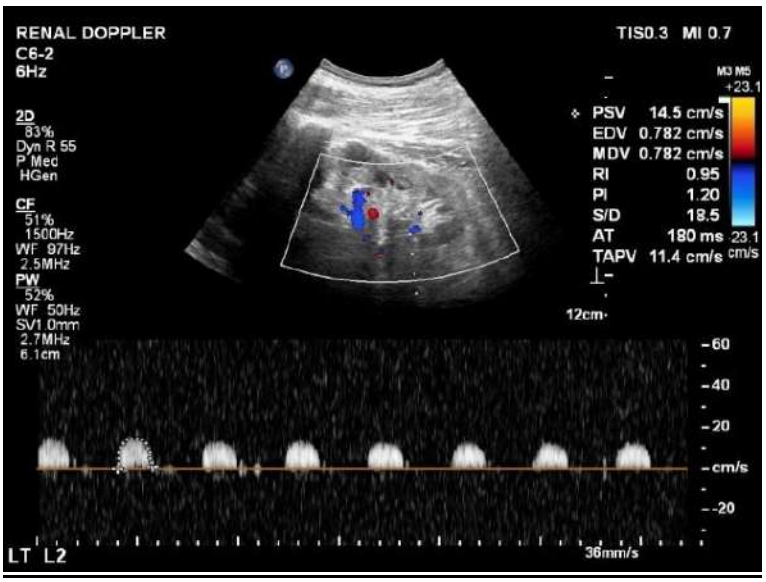

Fig 4a: Left kidney showing RI value of 0.95

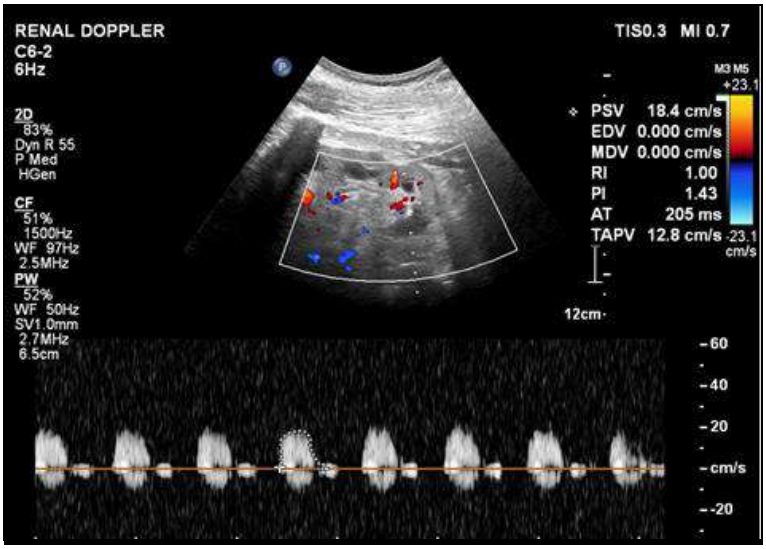

Fig 4b: Right kidney showing RI value of 1.0

Figure 5: 42 year old male with duration of diabetes of 1 year, with micro albuminuria.

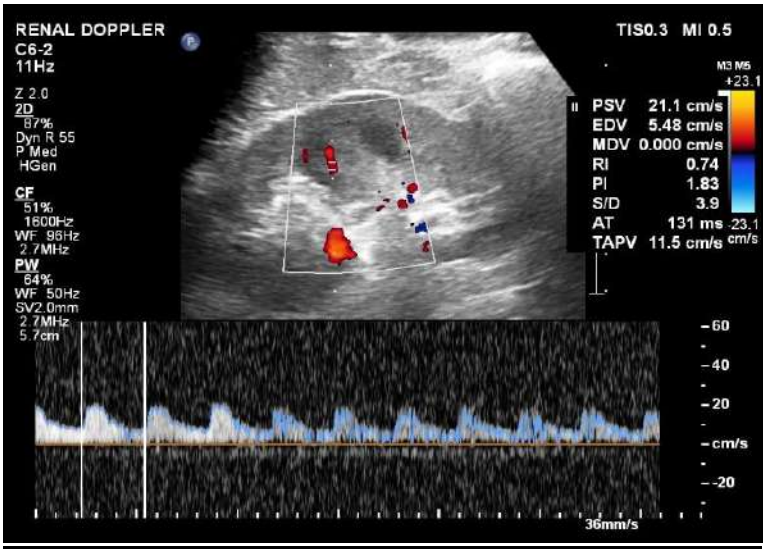

Fig 5a: Left kidney showing RI value of 0.74

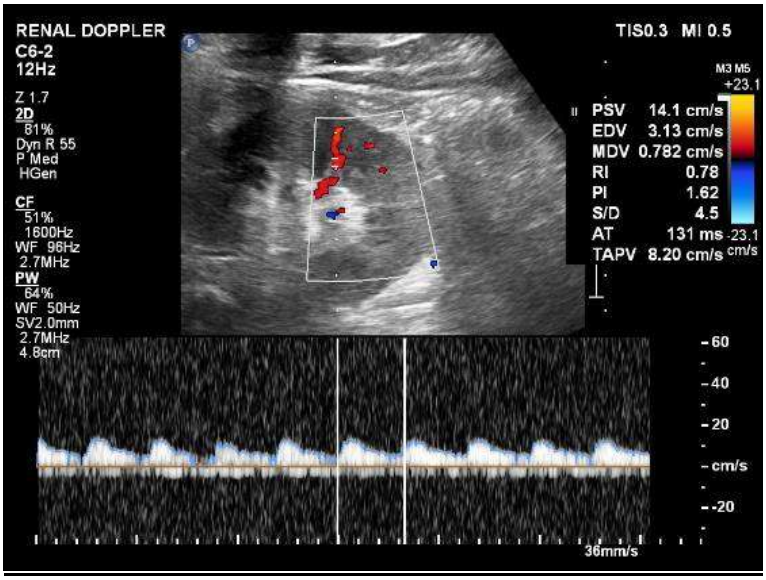

Fig 5b: Right kidney showing RI value of 0.78

Figure 6:- 46 year old male with duration of diabetes of 5 years, with micro albuminuria.

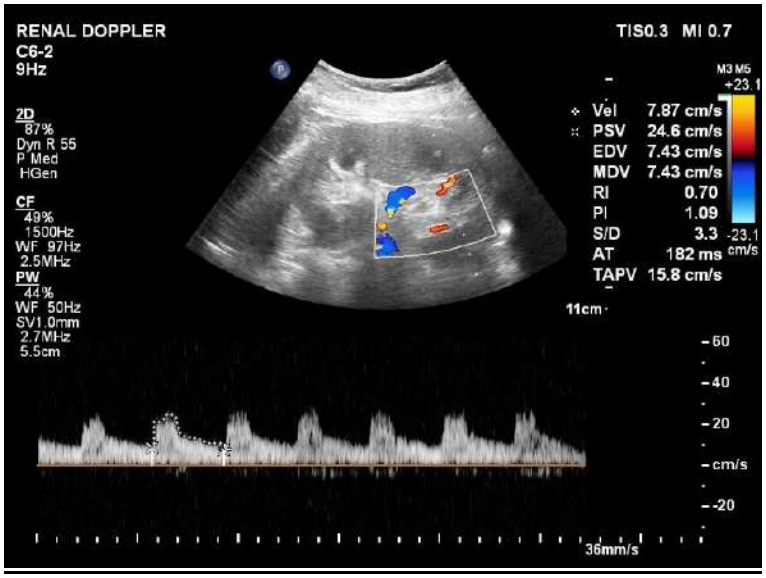

Fig 6a: Left kidney showing RI value of 0.70

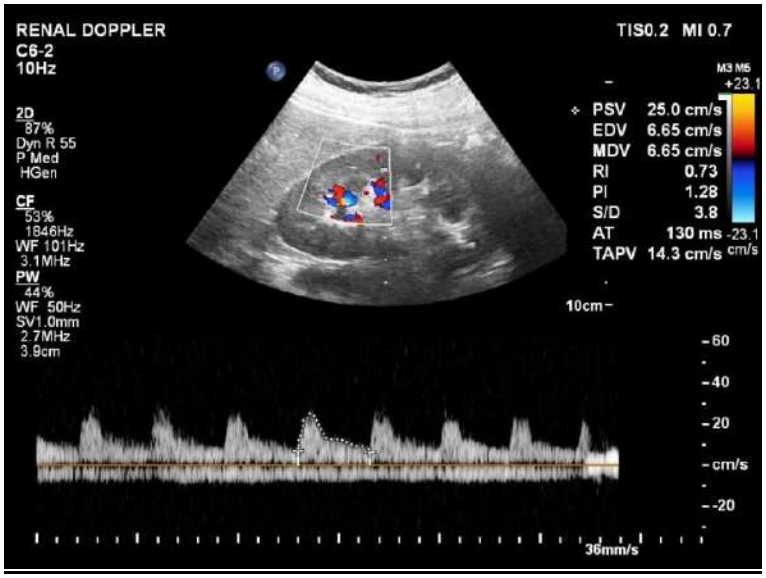

Fig 6b: Right kidney showing RI value of 0.73

Figure 7: 44 year old male with duration of diabetes of 4 years, with micro albuminuria.

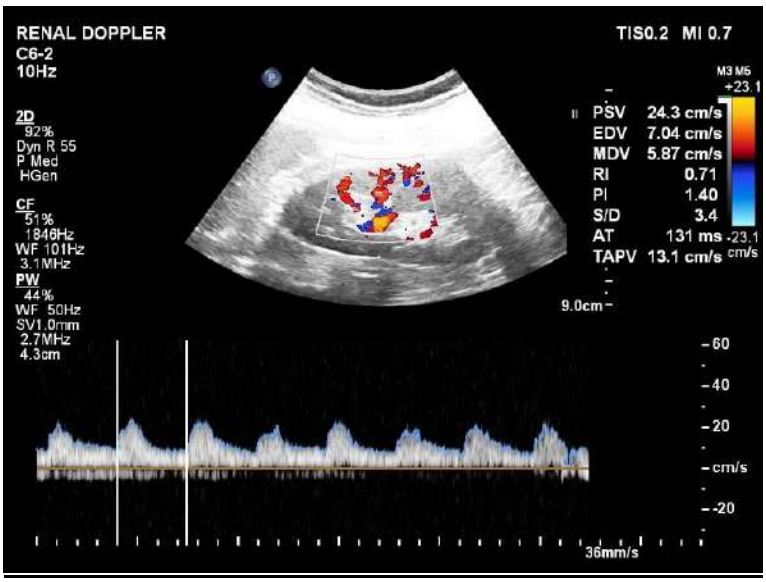

Fig 7a: Left kidney showing RI value of 0.71

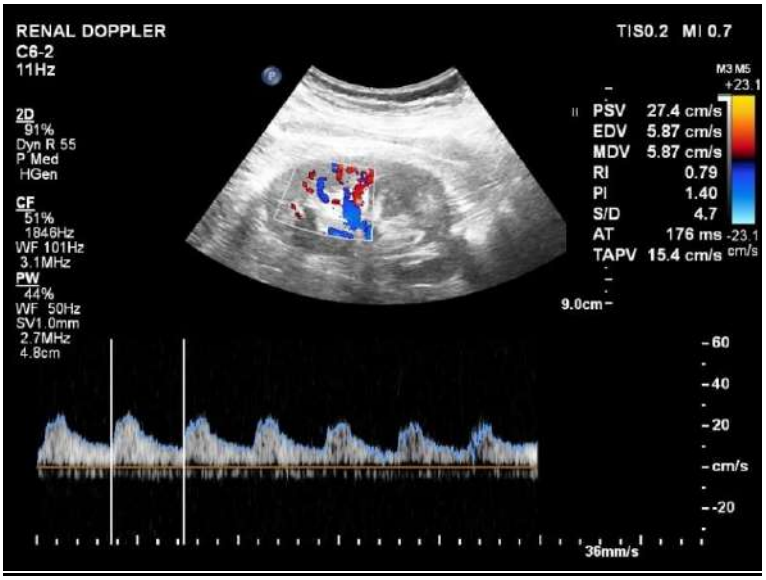

Fig 7b: Right kidney showing RI value of 0.79

5. Discussion

Diabetic nephropathy is often diagnosed only at later stages, when there is onset of overt proteinuria, rise in serum creatinine, and symptoms of end stage renal disease. Early detection of diabetic nephropathy in the incipient stages is of importance in clinical practice. Early diagnosis of diabetic nephropathy is also useful in instituting preventive measures like strict glycemic and blood pressure control, frequent monitoring for assessing the progression, to start ACE inhibitors and ARB when indicated. Identifying patients with incipient nephropathy has a role in therapeutic decision making like cautious use of nephrotoxic drugs, avoiding conditions which can rapidly deteriorate the already affected kidneys like urinary tract infection, hypotension, dehydration. Our study was designed to find out the association between biochemical markers and renal resistive index in diabetic patients. The biochemical markers assessed were HbA1C, e GFR, serum creatinine and BMI. Renal resistive index was estimated by Duplex Doppler ultrasonography.

Out of the 100 patients, 57(57%) patients had elevated resistive index. The mean duration of diabetes in these patients' was 7.41 ± 4.9 years, while the mean HbA1C of these patient's was 9.15 ± 2.96. In comparison, the mean duration of diabetes in patients' with normal RI was 4.53 ± 5.07 and mean HbA1c was lower 7.4 ± 3.27. This indicates that elevated resistive index was probably due to uncontrolled diabetes and also that longer duration of diabetes leads to increased resistive index.

In our study, the mean resistive index in the normoalbuminuric, microalbuminuric, macroalbuminuric groups were 0.62, 0.7, 0.77 respectively. Our results are comparable with similar study by Kumiko *et al.*, where the mean RI was significantly higher in macroalbuminuric group (0.745+/-0.077) compared to patients with normoalbuminuria (0.68+/-0.06) [2]. This shows that there is a significant progressive increase in the resistive index with the progression of diabetic renal disease.

We found a positive association with serum creatinine (P=0.003- Fisher exact test, 0.0005 – t test) and a negative

correlation with eGFR [correlation coefficient=-0.495]. The above results were similar when compared to the study by Yuko *et al.*, who found resistive index had a positive association with albuminuria, serum creatinine and negative correlation with creatinine clearance. A similar study by sari *et al.*, revealed Serum creatinine and creatinine clearance had statistically significant correlation with intrarenal RI values [4].

In our study only 21(21%) of the diabetic patients had raised serum creatinine. Out of the 57(57%) patients who had raised RI values, only 20 patients had a raised serum creatinine and the rest 37 patients had normal serum creatinine level. Therefore, it appears that resistive index seems to be elevated even before a rise in serum creatinine. Hence an estimation of RI may be an early indicator of diabetic nephropathy.

Ishimura E *et al.* found that RI was significantly higher in type 2 Diabetic patients who had micro and macroalbuminuria compared to patients with normal albumin excretion. Resistive index in diabetic patients was significantly affected by creatinine clearance, age and duration of diabetics [5]. The above results matched with our study.

Our results were comparable to a study done by Boeri *et al.* who showed that in diabetic patients, resistive index correlated with BMI, creatinine clearance and HbA1c [6]. In our study, 81 out of 100 patients were either overweight, pre-obese or obese; and it was found that BMI had a statistically significant correlation with RI (P=0.001).

Our study was a onetime prospective cross-sectional study to evaluate the resistive index in diabetic patients. Studies have shown that patients with elevated resistive index at base line have a rapid progression of diabetic nephropathy, increase in the albumin excretion rate and a decline in the renal function on follow up. Follow up studies done by Milovanceva *et al.*, Masulli M *et al.*, Romano *et al.*, showed that elevated RI at baseline strongly predicts the worse outcome of renal disease in type 2 diabetic patients even before there is rise in serum creatinine or fall in GFR [7, 8, 9].

The final conclusion of our study was that renal resistive index has a strong association with biochemical markers routinely used to assess diabetic nephropathy. Renal duplex sonography can be used as a screening modality for early detection of diabetic nephropathy and hence treatment of the same can be started early.

The limitation of our study was the lack of follow up of the patients.

6. Conclusion

a. Out of 100 patients, resistive index was elevated in 57(57%) patients.
b. Resistive index has a statistically significant association with microalbuminuria.
c. A statistically significant association between resistive index and
- Serum creatinine
- eGFR
- BMI
- Duration of diabetes
- HbA1c

d. Resistive index which is a measurement of tubulointerstitial lesions and intra renal arteriosclerosis, is found to be elevated in 96% patients with macroalbuminuria and 98.2% with microalbuminuria.
e. Baseline estimation of resistive index a marker of intra renal vascular resistance, can be an additional diagnostic tool for diabetic nephropathy.

Resistive index has a statistically significant association with microalbuminuria. A statistically significant correlation between resistive index and serum creatinine, Uncontrolled Diabetes (HbA1C), eGFR and duration of diabetes was found. Baseline estimation of resistive index a marker of intra renal vascular resistance, is an additional diagnostic tool for diabetic nephropathy.

7. References

1. Vedaraju KS, Deepa Benegal S. Correlation of renal artery resistive index with albuminuria and other risk factors in type 2 diabetes mellitus patients. International Journal of Contemporary Medicine Surgery and Radiology 2019;4(1):A65-A68.
2. Kumiko H, Takayasu O, Ai Nitta, Shuzo K. Association of renal vascular resistance with albuminuria and other macroangiopathy in type 2 Diabetic patients. Diabetes care 2008;31(9):1853-1857.
3. Dr. Manzura R Mulani, Dr. Pandharinath S Gawali, Dr. Veena S Hatolkar. Study of biochemical markers in patients of ischemic heart disease and hypertension in IIMSR Hospital, Warudi. Int J Adv Biochem Res 2019;3(2):05-08.
DOI: 10.33545/26174693.2019.v3.i2a.33
4. Sari A, Dinc H, Zibandeh A, Telatar M, Gumele HR. Value of resistive index in patients with clinical diabetic nephropathy. Invest Radiol 1999;34:718-721.
5. Ishimura E, Nishizawa Y, Kawagishi T, Okuno Y, Kogawa K, Fukumoto S *et al.* Intrarenal hemodynamic abnormalities in diabetic nephropathy measured by duplex Doppler sonography. Kidney Int 1997;51(6):1920-1927.
6. Boeri D, Derchi LE, Martinolli C, Simoni G, Sampierto L, Storace D. Intrarenal arteriosclerosis and impairment of kidney function in NIDDM subjects. Diabetologia 1998;41:121-124.
7. Milovanceva-Popovska M, Dzikova S. The value of intrarenal resistive index in Diabetic nephropathy. BANTAO Journal 2009;7(1):38-44.
8. Masulli M, Mancini M, Liuzzi R, Daniele S, Mainenti PP, Vergara E *et al.* Measurement of the intrarenal arterial resistance index for the identification and prediction of diabetic nephropathy. Nutr Metab Cardiovas Dis 2009;19(5):358-364.
9. Romano N, Mario V, Enrico B, Cataldo A, Andrea C, Francesco P *et al.* Increased renal arterial resistance predicts the course of renal function in type 2 diabetes with Microalbuminuria. Diabetes 2006;55(1):234-239.
10. Yuko Ohta, Koji Fujii, Hisatomi Arima, Kiyoshi Matsumura, Takuya Tsuchihashi *et al.* Increased renal resistive index in atherosclerosis and diabetic nephropathy assessed by Doppler sonography. Journal of Hypertension 2005;23:1905-1911.