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Original Article

Radiology Section

Role of Ultrasound and Colour Doppler in Diabetic Nephropathy-Correlation with Biochemical Parameters

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ABSTRACT

Introduction: Ultrasound and Doppler are non-invasive modalities for evaluation of renal diseases. Renal sonography has been used fairly routinely in patients with azotemia to exclude possible obstructive uropathy, to measure the size of kidneys and to evaluate the parenchymal echogenicity of the kidney. Doppler is also used in evaluation of renal vascular resistance by using Doppler indices like resistive index in various systemic conditions like Diabetes mellitus, Systemic hypertension. Diabetic nephropathy is a relatively common form of chronic renal disease. It is the most frequent microvascular complication in diabetic patients.

Aim: To evaluate renal sono-morphological characteristics using grey scale ultrasound, renal vascular resistance using Doppler and correlating with biochemical parameters like Fasting Blood Sugar (FBS), Blood urea, Serum creatinine, Total cholesterol, Triglyceride and urine albumin in patients with diabetic renal disease.

Materials and Methods: This cross-sectional study was done in the Department of Radiology, Aarupadai Veedu Medical College, Puducherry, India. Conventional grey scale ultrasound and doppler evaluation of both kidneys were performed in 50 diabetic patients. Renal parameters like renal length, renal parenchymal thickness, renal cortical echogenicity, intra-renal resistive index and biochemical parameters like blood sugar, lipid profile and urine protein were recorded in all the diabetic patients. For purpose of comparison, the patients were subdivided into preclinical, incipient nephropathy, overt nephropathy and renal failure subgroups based on stage of diabetic renal disease. The results were presented in numbers and percentages for categorical data and average and SD for continuous data. Chi-square test of significance, One way Analysis of Variance (ANOVA), Pearson Correlation Coefficient was used (SPSS-version 24).

Results: Renal length and parenchymal thickness showed a progressive decrease with progression of diabetic renal disease. An 81% of patients in the preclinical group had normal renal parenchymal echogenicity. None of the other three subgroups had normal parenchymal echogenicity. A total of 31% and 70% of the patients in overt nephropathy and renal failure subgroups had hyperechogenicity (grade II) changes in renal parenchyma. Renal length and parenchymal thickness showed no correlation with serum creatinine and urine protein. The Slightly increased mean resistive index values (>0.7) were obtained in the subgroups I (preclinical) which suggests doppler ultrasound can detect diabetic renal disease in this early stage. A progressive increase in resistive index values was noted with progression of diabetic nephropathy. Resistive index values showed a positive correlation with blood urea nitrogen and serum creatinine, this correlation was found to be statistically significant.

Conclusion: Renal length and parenchymal thickness are unreliable indicators of the disease severity in diabetic renal disease. The positive correlation of intra-renal resistive index and renal echogenicity with most of the biochemical parameters, though not statistically significant, indicates a complementary role of this doppler index in diabetic renal disease.

Keywords: Conventional gray scale ultrasound, Diabetic renal disease, Intra-renal resistive index, Nephropathy

INTRODUCTION

Renal ultrasonography and doppler studies are being used routinely in patients with azotemia as it is a non-invasive modality and to rule out possible obstructive uropathy, to measure the size of kidneys and to evaluate the renal parenchymal echogenicity [1]. Now-a-days, a lot of work has been directed towards the use of Doppler in evaluation of renal vascular resistance by using Doppler indices like resistive index in various systemic conditions like Diabetes mellitus and Systemic hypertension [2].

Diabetic nephropathy is a relatively common form of chronic renal disease. It is the most frequent microvascular complication in diabetic patients [3,4]. Diabetic nephropathy has become the leading cause of chronic renal failure in developing countries [5]. It is estimated that death due to renal disease is 17 times more common in diabetic than in non-diabetic patients [6-9]. Type I Diabetes mellitus and Type II Diabetes mellitus affects 0.5 and 4% of population, respectively. Nephropathy complicates 30% of cases of Type I Diabetes mellitus and approximately 20% of cases of Type II Diabetes mellitus [2].

Elevated blood pressure, microalbuminuria and proteinuria can be considered as important signs of the progression of glomerular abnormalities in diabetic patients [10,11]. Cholesterol and LDL-cholesterol levels are considered to be good predictors for the development of atherosclerotic changes in diabetes [12,13].

Laboratory tests like urine protein, blood urea and serum creatinine have been traditionally used in clinical diagnosis and follow-up of diabetic nephropathy [2].

There are studies which has shown the role of conventional ultrasound and Doppler evaluation of kidneys in the early detection of diabetic renal disease [14,15]. One of these studies didn't compare with the biochemical parameters [14] and other study didn't have study population who were exclusively diabetics [15].

Hence, we decided to study the role of grey scale ultrasound, doppler in evaluation of diabetic renal disease and its correlation with biochemical parameters like Fasting Blood Sugar (FBS), blood urea, serum creatinine, total cholesterol, triglyceride and urine albumin in patients with diabetic renal disease [16-18].

MATERIALS AND METHODS

This was a cross-sectional study done in the Department of Radiology between September 1st 2014 to August 31st 2016 (two

years) where patients who were diagnosed as diabetes mellitus (both males and females) above the age of 20 years and above were selected. The study was approved by the ethical committee and all patients gave informed consent to participate in the study. Patients with findings of obstructive uropathy, cardiac failure, severe uncontrolled systemic hypertension, unilateral or bilateral contracted kidneys on sonography due to any cause other than diabetic nephropathy, urinary tract infection were excluded from the study. Overall 50 patients were evaluated.

The study group was divided into four broad sub-groups based on the clinical stage of diabetic renal disease.

Subgroup I (Preclinical): Diabetic patients without any clinical or biochemical indicators of diabetic renal disease.

Subgroup II (Incipient nephropathy): Diabetic patients with incipient diabetic nephropathy as reflected by presence of micro albuminuria (urine albumin excretion in the range of 30-300 mg/dl which is not detected by normal method).

Subgroup III (Overt nephropathy): Diabetic patients who had overt proteinuria (nephropathy) without features of renal failure like raised serum creatinine and blood urea nitrogen.

Subgroup IV (Renal failure): Diabetic patients in renal failure secondary to diabetic nephropathy [19-21].

Both kidneys were evaluated with Voluson S6 colour doppler ultrasound unit using a 3.5 MHz convex array probe. Patient was placed in supine position with sonologist sitting on right side of patient. Ultrasound probe was positioned on the flank in an oblique projection and the kidney visualised in longitudinal axis [22]. The right kidney was examined in supine position through the liver. The transducer was angled obliquely if liver was small. If bowel gas obscured visualisation of the lower pole, the right side up decubitus position was used and scan performed by lateral approach [22]. With the patient in the left side up position, his/her arm was extended over the head and using a coronal approach the left kidney was visualised through the spleen. Suspended inspiration was usually necessary to measure bipolar length of the kidney. Renal cortical echogenicity of both the kidneys were assessed by comparing with that of non-diseased liver and renal sinus.

The renal cortical echogenicity was also evaluated and classified into one of the four groups:

Grade 0: Normal- The echogenicity of the cortex of the right kidney is less than that of liver.

Grade I: The echogenicity of cortex of right kidney equal to that of liver.

Grade II: The echogenicity of the cortex of right kidney is greater than that of liver, but less than that of the renal sinus.

Grade III: The echogenicity of renal cortex is equal to that of the renal sinus [19,20].

Both colour coded doppler and pulsed doppler were used with same ultrasound probe. Intrarenal vascular structures were visualised using colour coded doppler and diameter of vascular structures was observed. The colour box was as small and as superficial as possible. Sample volumes were obtained by positioning the cursor of the pulsed doppler mode at the mid portion of the interlobar arteries with flow along the renal pyramid [23]. Doppler sample volume was set at 2-4 mm. Angle was adjusted to less than 60 degrees. Doppler spectral wave forms were obtained on the lowest pulse repetition frequency possible without aliasing. The velocity measurements of the peak systolic velocity and end diastolic velocity were calculated from the spectral wave forms [23]. Time required for completion of doppler study for each patient was approximately 15 to 20 minutes.

Doppler ultrasound indices measured [23]:

Resistive index (Pourcelot index) =

Peak systolic flow velocity-End diastolic flow velocity/Peak systolic flow velocity {RI = PSV-EDV/PSV}

A detailed medical history, duration of diabetes, family history of diabetes mellitus was elicited from the patients. Biochemical parameters like FBS, serum creatinine, blood urea nitrogen, total cholesterol and triglycerides were taken as a part of diagnostic work up of the patients. Urine analysis parameters like microalbuminuria, urine protein (albumin), urine sugar, and microscopic findings were recorded in all patients. Biochemical parameters of all patients was done by using MINDRAY AUTOANALYSER BS-330E.

STATISTICAL ANALYSIS

Data analysis was carried out using Statistical Package for Social Science (SPSS-version 24).

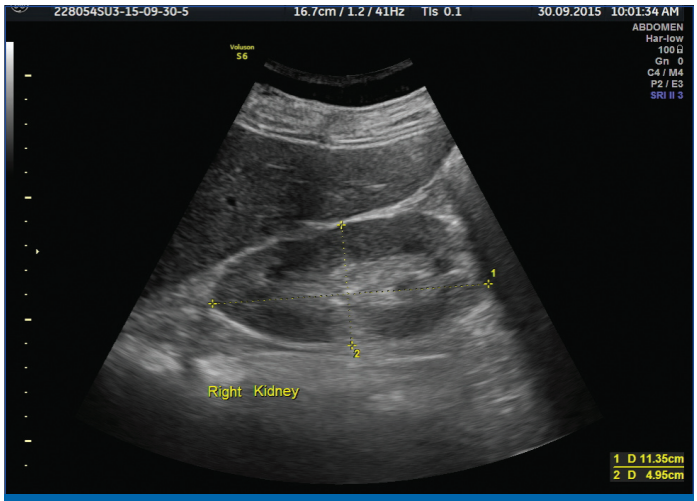
The proportions were compared using Chi-square test of significance, One-way Analysis of Variance (ANOVA), Pearson Correlation Coefficient: In all the above tests the p-value of less than 0.05 was accepted as indicating statistical significance.

RESULTS

The number of patients in each clinical subgroups were:

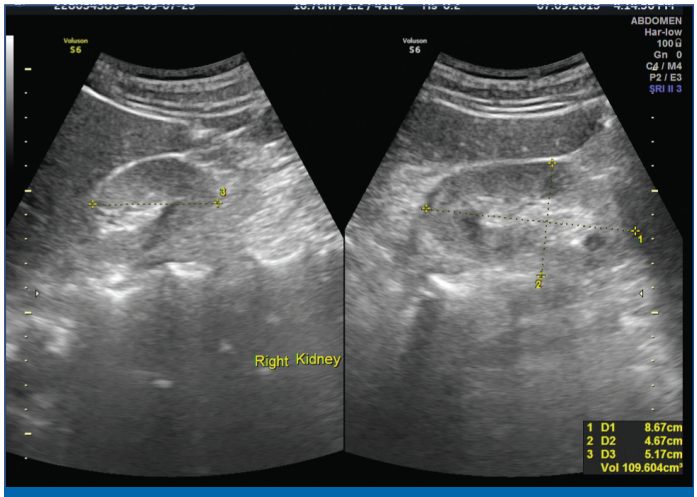
Subgroup I (Preclinical) subgroup: 22 patients, Subgroup II (Incipient Nephropathy): 05 patients, Subgroup III (Overt Nephropathy): 13 patients, Subgroup IV (Renal Failure): 10 patients.

Renal length and parenchymal thickness showed a progressive decrease with progression of diabetic renal disease. An 81% of patients in the preclinical had normal renal parenchymal echogenicity [Table/Fig-1].



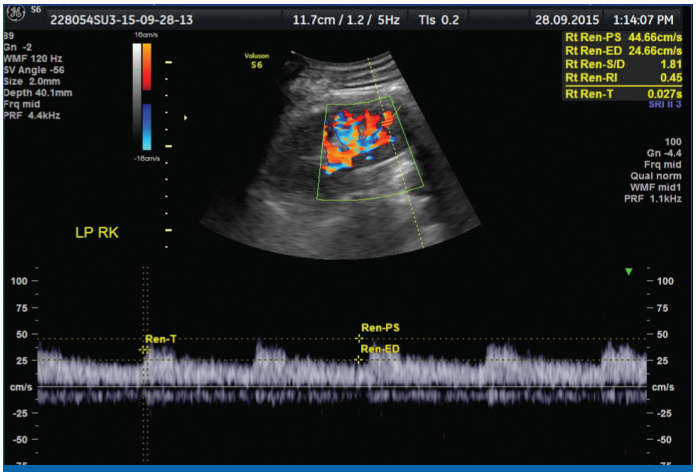
[Table/Fig-1]: Normal renal parenchymal echogenicity-right kidney.

None of the other three subgroups had normal parenchymal echogenicity. A 31% and 70% of the patients in overt nephropathy and renal failure subgroups had hyperechogenicity changes in renal parenchyma [Table/Fig-2]. Fifty diagnosed patients with diabetes mellitus underwent sonographic and doppler evaluation of kidneys

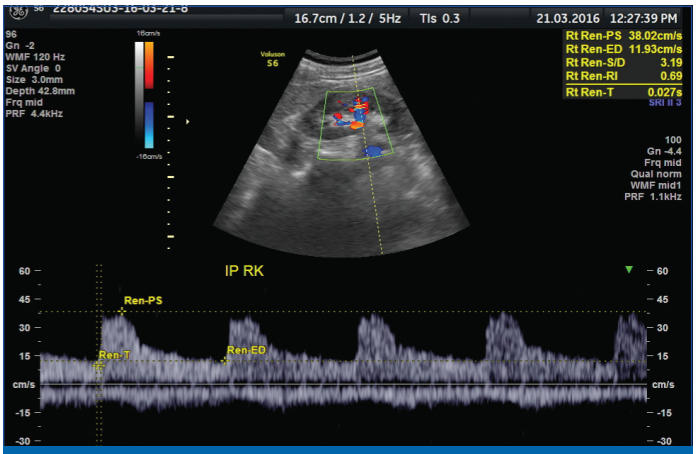


[Table/Fig-2]: Increased parenchymal echogenicity – Grade I in right kidney.

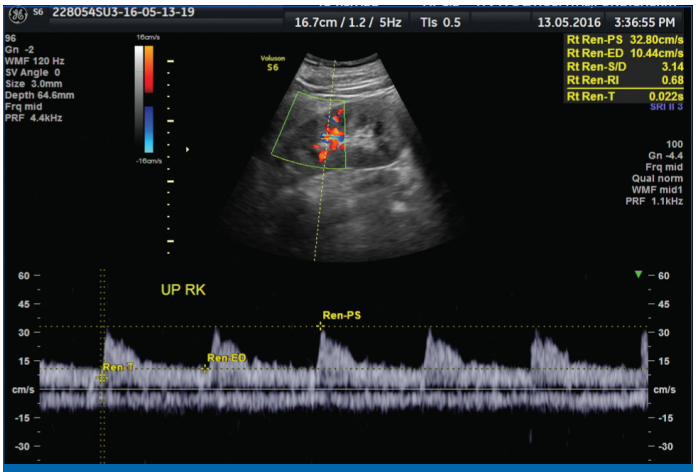
[Table/Fig-3-5]. Renal length and parenchymal thickness showed no correlation with serum creatinine and urine protein.



[Table/Fig-3]: Spectral waveform and resistive index recorded from right lower pole interlobar artery.



[Table/Fig-4]: Spectral waveform and resistive index recorded from right Inter polar interlobar artery.



[Table/Fig-5]: Spectral waveform and resistive index recorded from right upper pole interlobar artery.

The slightly increased mean resistive index values (> 0.7) obtained in the subgroup I (preclinical) suggests doppler ultrasound can detect diabetic renal disease in this early stage. A progressive increase in renal echogenicity and resistive index values was noted with progression of diabetic nephropathy as shown in [Table/Fig-6,7] respectively. Resistive index values and renal echogenicity showed a positive correlation with blood urea nitrogen and serum creatinine, this correlation was found to be statistically significant [Table/Fig-8].

Fasting blood sugar, total cholesterol and triglyceride showed no significant correlation with any of the ultrasound or Doppler parameters [Table/Fig-9]. Blood urea nitrogen, serum creatinine and urine protein showed a fair positive correlation with renal echogenicity grading and resistive index while showing no correlation with rest of ultrasound parameters [Table/Fig-9].

Final Diagnosis	Echogenicity (Grade)			Total
	Normal	Grade I	Grade II	
Preclinical	18 81%	3 14%	1 5%	22 100%
Incipient Nephropathy	0 0%	4 80%	1 20%	5 100%
Stage of Nephropathy	0 0%	9 69%	4 31%	13 100%
Renal failure	0 0%	3 30%	7 70%	10 100%
Total	18	19	13	50

[Table/Fig-6]: Distribution of echogenic grading of renal parenchyma among the various subgroups.

Final Diagnosis	No. of Patients		Total
	Normal Doppler RI (<0.7)	High Doppler RI (>0.7)	
Preclinical	13 (59%)	9 (41%)	22 (100%)
Incipient Nephropathy	5 (100%)	0 (0%)	05 (100%)
Overt Nephropathy	3 (23%)	10 (77%)	13 (100%)
Renal Failure	1 (10%)	9 (90%)	10 (100%)
Total	22	28	50

[Table/Fig-7]: Relative percentages of Doppler (RI) in various clinical subgroups.

	r	p-value
RI vs. serum creatinine	+0.491	0.0001
RI vs. blood urea nitrogen	+0.570	0.0001
RI vs. fasting blood sugar	-0.087	0.2046
RI vs. urine protein	+0.450	0.0005
RI vs. total cholesterol	-0.042	0.6966

[Table/Fig-8]: Correlation of resistive index with biochemical parameters (r-Pearson coefficient value).

	Renal length (RK)	Renal length (LK)	Parenchymal thickness (RK)	Parenchymal thickness (LK)	Echogenicity (Grade)	RI value (Doppler)
Fasting blood sugar (mg/dL)	-0.2009	-0.1404	-0.0902	-0.02365	-0.25360	-0.0871
Blood urea nitrogen (mg/dL)	-0.1331	-0.3545	-0.3256	-0.3792	+0.54585	+0.5708
Creatinine (mg/dL)	-0.0769	-0.2741	-0.3704	-0.3916	+0.4327	+0.49119
Total cholesterol (mg/dL)	-0.1874	-0.0602	-0.1853	-0.2072	-0.28368	-0.0424
Triglyceride (mg/dL)	-0.2218	-0.1035	-0.0943	-0.0377	-0.06817	-0.1761
Urine protein (Alb)	-0.1213	-0.1303	-0.0093	-0.0929	+0.4116	+0.4503

[Table/Fig-9]: Correlation between ultrasound doppler and biochemical parameters.
The value in each unit of tabular column represents r-value. A positive r-value represents a positive correlation while a negative value represents a negative correlation between the parameters; Very good positive correlation being represented by an r-value of >0.75

DISCUSSION

In our study, bilateral renal length and renal parenchymal thickness were normal in the preclinical stage and showed a progressive decrease as the stages of diabetic renal disease progressed, but this decrease was not found to be statistically significant (p-0.52 and p-0.67, respectively).

According to our results, it is not particularly useful to consider renal length and parenchymal thickness as an indicator for the severity/progression of diabetic nephropathy. Ultrasound measurements are subject to considerable intra and inter observer variation, and it is a known fact that renal volume is influenced by the degree of hydration at the time of scan. Apart from that, renal length can be physiologically short by upto 10% with increasing age of the subjects undergoing scan [24].

In a similar study done by Shaw M et al., the renal length did not show linear variation with progression in severity of diabetic nephropathy, but the biggest kidneys were found in preclinical subgroup [25]. The study done by Soldo D et al., showed that in asymptomatic diabetic nephropathy, renal length and parenchymal thickness were significantly increased ($p < 0.01$ and $p < 0.03$, respectively). The higher mean renal length and parenchymal thickness in the preclinical subgroup in their study probably represented hyper filtration-induced nephromegaly as was noted in the previous studies. In their study only advanced stages showed significant reduction internal length and parenchymal thickness [16].

In our study, 59% of the patients in the preclinical subgroup and all patients in the incipient nephropathy subgroup had a normal resistive index value (< 0.70). This may be due to the less number of people in the incipient nephropathy subgroup, while most of the patients in the overt nephropathy group (77%) and in the renal failure group (90%) had a raised resistive index value probably indicating a raised peripheral vascular resistance due to arteriosclerosis in the peripheral intra-renal vasculature and tubulo-interstitial nephropathy is advancing stage of diabetic renal disease.

Renal cortical echogenicity, which is considered to be a reliable sign of renal impairment at grey scale imaging was found to be a good indicator of diabetic nephropathy as the disease progressed (p-value< 0.01). In our study, 81% of patients in the preclinical had normal renal parenchymal echogenicity. None of the other three subgroups had normal parenchymal echogenicity.

The study done by Soldo D et al., demonstrated that there was no significant renal echogenicity changes for groups 1 and 2 and in 2/3rd of patients with advanced renal disease (group 3). Only 22% of patients in azotemia group were found to have renal parenchymal hyperechogenicity [16]. In another study done by Shaw M et al., out of 60 patients, only 14 (23.3%) patients had abnormal renal parenchymal echogenicity [25].

In some systemic diseases (including diabetes mellitus) with secondary renal parenchymal changes, hyperechogenicity of the cortex has been reported as an indicator of renal functional impairment [16].

Previous studies done by Soldo D et al., Brkljacic B et al., and Ishimura E, et al., Platt JF et al., have revealed that doppler indices like intra-renal resistive index correlated well with renal function. Intra-renal resistive index was elevated in most patients with advanced diabetic nephropathy but was within normal limits (RI < 0.7) in most patients with asymptomatic diabetic renal disease [16-18,26].

In a similar study done by Shaw M et al., a total of 68.3% of patients had increase RI values (>0.7). Major percentage of patients belonging to preclinical subgroup (70.5%) had normal RI value (<0.7) while most of the patients belonging to incipient nephropathy (72.7%), overt nephropathy (80%) and renal failure subgroups (90.9%) had increased renal resistive index indicating increased renal vascular resistance as the disease progressed [25].

The mean RI values in the preclinical group, incipient nephropathy, overt nephropathy and renal failure were 0.71±0.023, 0.72±0.020 SD, 0.74±0.069 and 0.79±0.072, respectively showing a progressive increase with progression of diabetic renal disease and this was found to be statistically significant (p-value <0.0001). The mean resistive index value of 0.71+0.023 in the preclinical subgroup shows a marginal increase in the mean resistive index (normal range <0.70) and suggests the ability of intra-renal resistive index to detect patients in this early stage of diabetic renal disease.

The study done by Soldo D et al., have shown that 27% patients showed normal renal vascular resistance (0.642±0.05) and had microalbuminuria. Therefore, they concluded that the sub-clinical phase of diabetic renal disease-even the presence of microalbuminuria-is not necessarily accompanied by an increase in renal vascular resistance [16]. Hamano K et al., also found that resistive index values were higher in diabetic patients with albuminuria than in patients without albuminuria [27].

Blood urea nitrogen showed a fair positive correlation with renal cortical echogenicity grading and resistive index while showing no correlation with other ultrasound parameters. Serum creatinine showed a positive correlation with renal cortical echogenicity grading and resistivity index values. A similar strong positive correlation between resistive index and serum creatinine has been noted in previous studies done by Kim SH et al., Soldo D et al., Platt JF et al., [1,16,26]. According to the study done by Shaw M et al., blood urea nitrogen showed fair positive correlation with renal parenchymal echogenicity ($r= 0.53$; $p<0.001$) and with renal resistive index ($r=0.50$; $p<0.001$), Serum creatinine also showed fair positive correlation with renal parenchymal echogenicity ($r= 0.47$; $p<0.001$) and renal resistive index ($r=0.47$; $p<0.001$) [25].

No statistically significant correlation was noted between the FBS and renal ultrasound parameters or resistive index values. Serum cholesterol and triglyceride levels also showed no correlation with renal ultrasound parameters or with resistive index. Similar lack of statistically significant correlation was observed between FBS, total cholesterol, triglycerides and restive index in a study done by Ishimura E et al., involving 112 diabetic patients [18].

LIMITATION

The major limitation in our study was that our study method was a cross-sectional study. Therefore, follow-up of the cases was not possible and variations of the parameters over time could not be measured. So, a prospective study with follow-up is needed to know and understand about better relationship with biochemical parameters and progression of disease.

CONCLUSION

The present study demonstrated that pathologic resistive indices (>0.70) were detected in most of the diabetic patients in the overt nephropathy and renal failure subgroups indicating its role as a doppler parameter, which can be used as complementary to biochemical parameters. Most of the patients in the preclinical subgroup had mild increase in intra-renal resistive index values indicating the ability of this parameter to detect patients with early diabetic renal disease even before the biochemical and the grey scale imaging features of diabetic nephropathy sets in.

Measurements of RI values in addition to conventional ultrasound imaging may also add an information on such renal lesions. One of the best non-invasive techniques that could be used to find association with biochemical parameters and diabetic changes in kidneys is renal doppler. An increasing intra-renal resistive index value could prompt the physician to a more rigid attempt to control the blood sugar levels and hypertension in diabetic patients and delay the progression to end stage renal failure.

Although further studies are required, RI values may be used as a useful tool to evaluate the arteriosclerotic changes of small

infrarenal arteries in patients without renal insufficiency, since only few useful options are there to assess the small artery lesions other than biopsy with histopathological correlation or post-mortem examination.

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