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Duplex Color Doppler Evaluation of Renal Venous Impedance Index in Patients with Diabetic Nephropathy " Comparison with that of Non-Diabetic Healthy Control Subjects

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Abstract:

Background: *Diabetes mellitus (DM) is the most prevalent metabolic, non-communicable disorder in the world. Diabetic nephropathy(DN) is one of the most serious complications of diabetes leading to end-stage renal failure. Venous impedance index in diabetic nephropathy may predict the early hemodynamic changes in the renal parenchyma of these patients before the clinical onset of nephropathy.* ***Objective:*** *To observe the difference between values of intrarenal venous impedance index measured by duplex color Doppler USG in patients with diabetic nephropathy and in non-diabetic healthy control subjects.* ***Materials and methods:*** *This cross-sectional study was done in the department of Radiology and Imaging, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM). For this purpose, 80 diabetic nephropathy patients were taken as study group and 80 healthy subjects were included as healthy control subjects. Duplex Color Doppler Sonography of intrarenal veins was carried out in both groups to measure the Peak Venous Flow Signal, the Least Venous Flow Signal and Venous Impedance Index.* ***Results:*** *The mean age of the control subjects was 46.93 (± 8.864) years and that of the case patients was 48.39 (±11.994) years. In control group 48 (60%) were male and 32 (40%) were female where as in case group 44 (55%) were male and rest 36 (45%) were female patients. In control subjects the mean value of peak venous flow signals was significantly higher for right kidney but in case group no such difference was observed. The mean venous impedance index of right kidney in control group was 494 ± 0.125 and the mean venous impedance index of right kidney in diabetic nephropathy patients was 2746 ± 0.102. The mean difference of venous impedance index of right kidney in the two groups was statistically highly significant (p<.001). The mean venous impedance index of left kidney in control group was 0.485 ± 0.014 and the mean venous impedance index of left kidney in diabetic nephropathy patients was 0.259 ± 0.101. The mean difference of venous impedance index of left kidney in the two groups was statistically highly significant (p<.001). The mean renal VII of normal controls was 0.4895 (± 0.133) and in DN patients the mean renal VII value was 0.2668 (± 0.101). In reference to VII values in DN patients, it can be suggested that VII would be considered normal if >0.30.* ***Conclusion:*** *It can be concluded that VII remains significantly lower in patients with DN than in controls. The underlying mechanism could be related to interstitial fibrosis in DN kidneys progressively reducing tissue compliance. Lower VII in diabetic nephropathy may predict the early hemodynamic changes in the renal parenchyma of these patients before the clinical onset of nephropathy.*

Key word: *Duplex color Doppler, renal venous, impedance index, diabetic nephropathy, non-diabetic*

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Introduction:

Diabetic nephropathy (DN) is considered the most frequent cause of end-stage renal disease (ESRD) in Africa and developing countries.[1-5] It has been reported that the prevalence of diabetics in Bangladesh is 5.6% and is estimated to rise in near future.[6] Diabetic nephropathy is one of the most serious complications of diabetes leading to end-stage renal failure and leading cause of morbidity and mortality among diabetic patients in Bangladesh.[6] The incidence of end-stage renal disease (ESRD) and type-2 DM as a co-morbid condition has increased continuously during the past decades.[7,8] Presently, there is greater focus on early detection of nephropathy, to help in better patient outcomes.[1]

In the early stage of clinical diabetic nephropathy, renal function remains normal despite the development of proteinuria, where the advanced stage is characterized by clinical renal dysfunction including gradually increased serum creatinine concentration (SCC) and reduced creatinine clearance rate. These advanced stages may progress to end–stage renal disease.[9-13] Renal Doppler sonography has become a useful adjunct to gray scale sonography in the evaluation of renal function in various pathophysiological conditions such as DN.[14-16] The resistance index (RI), which reflects the downstream circulatory impedance, has been advocated as a useful parameter for quantifying alterations in renal blood flow during renal diseases, including DN. Previous studies found that renal artery RI was elevated in advanced DN with increased SCC, but remained normal in early-stage DN.[17,18] Other studies have suggested that intrarenal RI does not offer any advantage over SCC or creatinine clearance rate in patients with early-stage DN and normal renal function.[19] A series of recently performed experiments showed that RI can be considered as the result of complex interactions between numerous factors and concluded that a single isolated RI may not be useful for the differential diagnosis of renal diseases.[14-16,20-22]

Unlike the arterial side, the vascular resistance on the venous side is normally negligible because veins act as capacitance vessels, so that their impedance to blood flow is directly related to compliance. Because the pulsatility of the renal venous signal reflects the compliance of kidney tissue, flow pattern in intrarenal veins depends on surrounding renal parenchymal histology as much as on right atrial function. Therefore, intrarenal venous impedance indices (VII) obtained by Doppler USG are related to venous wall and renal parenchyma compliance and may be helpful in assessing renal parenchymal alterations that may occur with renal disease.[21]

Diabetes causes specific changes in renal vascular structure. Classic glomerulosclerosis is characterized by increased glomerular basement membrane width, diffuse mesengial sclerosis, hyalinosis, microaneurysm and hyaline arteriosclerosis.[23] Tubular and interstitial changes are also present. Areas of extreme mesengial expansion called Kimmelsuel-Wilson nodules or nodular mesengial expansion are observed in 40-50% of patients developing proteinuria.[24-26] Micro and macroalbuminuric patients with type-2 diabetes have more structural heterogenecity than patients with type-1 diabetes. [27, 28]

The incidence of diabetes mellitus (DM) and diabetic nephropathy (DN) have risen rapidly in the past few decades and have become an economic burden to the healthcare system.[29] Therefore, in patients with DN, the increased cardiovascular risk associated with diabetes and with CKD are additive and increase as DN progresses.[30] The risk of cardiovascular events was significantly increased in those with either CKD or diabetes alone, but cardiovascular risk was greatest when both conditions are present.[31] In this condition, monitoring Type-2 DM patients for nephropathy becomes vital to avoid ESRD. The regular monitoring of these patients should delay the onset of this comorbidity.[32] Interestingly, many patients with CKD, particularly elderly patients, may be several times more likely to die of CVD before progression to ESRD.[33]

In view of all these, one realizes that early detection of patients at high risk is crucial.[34] In this study we have focused on the impedance index values obtained from the venous side of the renal vasculature and tried to determine whether VII could help evaluating renal function in DN. To the best of our knowledge, no prior study has so far been available in Bangladesh regarding this topic.

Materials and methods:

It was a cross-sectional study carried out Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka. Type-2 diabetic subjects with nephropathy and age and sex matched healthy control volunteers were selected for the study. Patients with diabetic nephropathy diagnosed by bedside albuminuric status referred to radiology and imaging department of BIRDEM from department of Nephrology, BIRDEM, Dhaka, for USG. Total 160 patients were enrolled in the study. Appropriate data were collected by using a preformed data sheet.

Type 2 diabetic subjects with and without nephropathy was selected for the study. Then both subjects were undergoing US examination of both kidneys including renal veins for the evaluation of venous impedance index (VII). The examinations were done by the researcher at first and then confirm by a consultant radiologist of the Department of Radiology and Imaging. Each measurement was taken 3 times and the mean value was used in the analysis. For measuring VII of renal vein, no previous preparation of the patient is required. Doppler USG of intrarenal vein was performed by using Medison Sonoace 800 live Machine with a multifrequency linear transducer of 6-10 MHz. Patients were lie on supine position, then kidney was identified. From that position patient was turned lateral on the side of examination. First, gray scale USG was confirming proper anatomic position of kidney. Then color flow was given and flow velocity was measured. As venous signal is very dependent on respiratory phase, Doppler spectra was obtained at the end of expiration of suspended respiration. Doppler waveforms of interlobar and segmental renal veins were taken by keeping the angle at a minimum (≤60°) by selecting midpole vessel as parallel to the beam as possible. VII was calculated as v_1-v_2/v_1, where v_1=peak venous flow signal and v_2=least venous flow signal. Result of the study was calculated and analyzed by standard statistical method. Data were expressed as Mean ±SD. A value of $P < 0.05$ was considered statistically significant. Difference between two groups (the diabetic with nephropathy and without nephropathy) was analyzed by the unpaired student "t" test. Differences in the same patient (right and left kidney of the same person) were calculated by paired "t" test. For analysis of data SPSS for Windows (IBM SPSS Statistics for Windows, version 19.0, Armonk, NY: IBM Corp.) software was used.

Results:

A total of 80 healthy normal subjects were included in the study. The mean age was 46.93 years with standard deviation (SD) ± 8.864 years and their age ranged from 29 to 65 years in control group. The mean age was 48.24 years with standard deviation (SD) ± 11.998 years in case group. Out of which 48 (60%) were male and rest 32 (40%) were female in control group and out of which 44 (55%) were male and rest 36 (45%) were female patients in case group (Table I). A total of 80 diabetic nephropathy patients were included in the study. They were divided into three groups on the basis of duration of diabetes. The mean duration was 7.44 years with standard deviation (SD) ± 4.5172.1 years. Maximum patients were suffering from diabetes mellitus for 5-9 years (Table II). The mean peak venous flow signal (PVFS) in right kidney was 24.83+6.64 (mean + SD), ranged 14.8-42.3 and the mean peak venous flow signal (PVFS) in left kidney was 23.56±5.062 (mean±SD), ranged 13.7-33.1 in control group. The mean peak venous flow signal (PVFS) in right kidney was 17.11±3.82 (mean ±SD), ranged 10.8-29.1and the mean peak venous flow signal (PVFS) in left kidney was 17.72±4.07 (mean ± SD), ranged 12.8-27.8 in case group (Table III). The mean least venous flow signal (PVFS) in right kidney was 11.86±1.21 (mean ± SD), ranged 9.3-14.6and the mean least venous flow signal (PVFS) in left kidney was 11.84±1.87 (mean ± SD), ranged 9.5-14.6 in control group. The mean least venous flow signal (PVFS) in right kidney was 12.03±1.21 (mean ±SD), ranged 8.3-15.0 and the mean least venous flow signal (PVFS) in left kidney was 12.74±1.45 (mean ±SD), ranged 9.95-17.1 in case group (Table IV). The mean venous impedance index of right kidney in control group was 494±.125 (mean ±SD), ranged .19-.89 and the mean venous impedance index of right kidney in diabetic nephropathy patients was 2746±.102 (mean + SD), ranged .14-.5 in control group. The mean venous impedance index of left kidney in control group was 0.485±.014 (mean + SD), ranged 0.18-0.93 and the mean venous impedance index of left kidney in diabetic nephropathy patients was 0.259 ± 0.101 (mean + SD), ranged 0.259 ± 0.101 in case group (Table V).

Table I

Age distribution of the subjects (n=80)

Age group	Case (n=40)		Control (n=40	
	Frequency	Percent	Frequency	Percent
<=30	04	5.1	03	3.8
31-40	21	26.6	20	25
41-50	23	29.1	31	38.8
51-60	17	21.5	18	22.5
>60	14	17.7	08	10
Total	04	5.1	80	100
Mean ± SD	48.24(±11.998)		46.93 (±8.864)	
Sex				
Male	44	55	48	60
Female	36	45	32	40

Table II

Distribution of mean duration of DM (N=80)

Duration of DM	Frequency	Percent	Mean (±SD)	Range (yrs)
<5	24	30	7.44 (4.517)	2-20
5-9	35	43.8		
≥10	21	26.3		
Total	80	100		

Table III

Comparison between peak venous flow signal between two groups subjects (n=80)

Peak venous flow signal	Case		Control		P
	Mean ± SD	Range	Mean ± SD	Range	value
Right kidney (n=80)	17.11±3.82	10.8-29.1	24.83+6.64	14.8-42.3	0.001
Left kidney (n=80)	17.72±4.07	12.8-27.8	23.56+5.06	13.7-33.1	0.001

Table IV

Comparison between least venous flow signal between two (n=80)

Least venous flow signal	Case		Control		P
	Mean ± SD	Range	Mean ± SD	Range	value
Right kidney (n=80)	12.03±1.21	8.3-15	11.86±1.21	9.3-14.6	0.381
Left kidney(n=80)	12.74±1.45	9.95-17.1	11.84±1.87	9.5-14.6	0.367

Table V

Comparison of venous impedance index between case and control groups (n=160)

Venous impedance	Case		Control		P
index of right kidney	Mean ± SD	Range	Mean ± SD	Range	value
Right kidney (n=80)	0.275±0.10	0.14-0.50	0.494 ±.125	0.19-.89	0.001
Left kidney (n=80)	0.259±0.10	0.12-0.46	0.485±0.14	0.18-0.93	0.001

Discussion:

Doppler ultrasonography (DUS) can improve the sonographic assessment of renal dysfunction. Changes in Doppler waveforms of intrarenal vessels are associated with numerous renal pathologies. DUS is primarily used for the evaluation of renal arteries, but has not been widely investigated in venous renal diseases. Recent studies have shown that intrarenal venous flow was affected to a greater extent than arterial flow in ureteral obstruction, exhibiting a reduced VII on the obstructed side. Moreover, VII was found to be more sensitive than arterial RI to physiological changes in acute renal obstruction.[16, 20, 21] Other reports stated that the mean VII of pregnant women in the second or third trimester of gestation was significantly lower than that of nonpregnant subjects; VII was reported to be higher in patients with preeclampsia than in controls.[35,36, 37] However, no report has been issued on the Doppler analysis of intrarenal veins in DN, and no normal reference values have been published. In the present study, we focused on the impedance index values obtained from the venous side of the renal vasculature and tried to determine whether VII could help evaluating renal function in DN.

Vein blood flow depends on many factors, such as inflow, fasting and level of hydration, local and systemic factors, atrial function, drug effects, etc. A simplified hemodynamic model of renal vein blood flow modulation would take into account the pressure gradient (from arterial microvessels to the vena cava), the elasticity or compliance of the venous wall (transmural pressure), and the vein length. Phantom studies demonstrated that the arterial RI is actually an impedance index that depends on both vascular resistance and compliance.[20] On the venous side of blood circulation, resistance to flow is negligible because veins are high capacitance vessels, and compliance becomes the main determinant of flow pulsatility. The flow pattern in intrarenal veins depends on renal parenchymal histology and atrial function. Therefore, intrarenal VII depends largely on compliance, which may be affected by the renal parenchymal changes produced by renal disease or systemic renovascular disease.[21] Our present study rationale was based on this simplified model of renal blood flow.

The right atrium pressure changes along the cardiac cycle are responsible for the triphasic modulation of venous blood flow in the inferior vena cava and hepatic veins, with a transient flow decrease or reversal during atrial systole (A wave).[39] Because the pulsatility of the hepatic venous signal reflects the compliance of liver parenchyma, most pathologies that reduce compliance also dampen the hepatic vein blood flow modulation.[39-41] Such a mechanism can occur in the kidney and decrease waveform pulsatility whenever there is a loss of compliance of renal parenchyma and/or venous wall.

The peak and least venous flow signals of the both kidneys were measured in control and case groups. In control subjects the mean value of peak venous flow signals was significantly higher for right kidney but in case group no such difference was observed. The long renal vein in right side could be the cause of such difference. These findings are consistent with the findings of an international study.[35] In control group the least venous flow signal was slightly higher in right kidney but without statistical significance. In DN patients this value was significantly higher in left kidney.

Jeong SH et al. reported the mean VII was lower in interlobar veins, which are surrounded by renal parenchyma, than in segmental veins whose environment is in part formed by calyces. The main renal vein is almost three times shorter on the right than on the left side. Besides, the left renal vein passes through a crook formed by the abdominal aorta dorsally and the superior mesenteric artery anteriorly.[42,43] As per our expectation the mean VII was found to be higher in the right than in the left kidney because of this anatomic difference.

DN patients showed decreased waveform modulation, resulting in lower VII. The pathologic features of DN depend on the severity of renal involvement. At an early stage, the glomeruli are primarily affected, with glomerulosclerosis, whereas cortical tubule-interstitial changes are more prevalent and lead to tubular atrophy and interstitial fibrosis at end stage.[44] In the present study, VII was significantly lower in patients with DN than in controls. The underlying mechanism could be related to interstitial fibrosis in DN kidneys progressively reducing tissue compliance.

Although there is no clear theoretical background supporting the hypothesis that renal VII measurements could be of any value in patients with diabetic nephropathy, we thought that it was more affected by adjacent parenchymal alteration than by the anatomic difference between the right and left renal vein, in our DN patients.

The mean renal VII in our normal controls was 0.4895 (±0.133) and in DN patients the mean renal VII value was 0.2668 (±0.101). In reference to VII values in DN patients, Jeong SH et al suggested that VII would be considered normal if >0.32.[35] From our study findings we can go for >0.30 value as normal. Because of the cross-sectional design of our study, we are unable to comment on the value of possible changes of VII with time, and its predictive value as regards renal function deterioration in diabetic patients.

Conclusion:

From the findings of present study, it can be concluded that VII remains significantly lower in patients with DN than in controls. The underlying mechanism could be related to interstitial fibrosis in DN kidneys progressively reducing tissue compliance. Lower VII in diabetic nephropathy may predict the early haemodynamic changes in the renal parenchyma of these patients before the clinical onset of nephropathy. However, further study can be undertaken by including large number of study subjects, comparing haemodynamic changes in different stages of diabetic nephropathy, finding out the correlation of haemodynamic changes and levels of glycaemic control.

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