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A CROSS-SECTIONAL STUDY OF ASSOCIATION OF INTRARENAL VASCULAR RESISTANCE WITH BIOCHEMICAL PARAMETERS IN PATIENT WITH TYPE-1 DIABETES MELLITUS

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ABSTRACT

Background: The present study aims at identifying early vascular changes which may help to identify children with early progression of diabetic nephropathy by using non-invasive doppler study and if clinically useful information is obtained it may be useful in follow up for the treatment. **Materials and methods:** This cross-sectional study was done in a tertiary care hospital in India. A total of 120 samples were taken in which 60 were patients with type 1 diabetes mellitus and 60 were age, sex and BMI matched healthy controls. The doppler parameters like renal Resistivity index, Peak systolic velocity and End diastolic velocity and various blood parameters were evaluated and compared between the cases and controls. **Results:** Peak systolic velocity of the cases was significantly higher than the controls (p=0.037). End diastolic velocity of cases was lower than the controls. Resistivity index of cases was significantly higher than the controls (p=0.001). Among the blood parameters, HbA1C, ACR, GFR, triglyceride, LDL and HDL were found to vary significantly between cases and controls (p<0.05). **Conclusion:** The doppler parameters like renal Resistivity index, Peak systolic velocity and End diastolic velocity can be used as potential tools to identify early progression of diabetic nephropathy in children.

KEYWORDS: Diabetic nephropathy, Doppler, Resistivity index, Peak systolic velocity and End diastolic velocity.

INTRODUCTION

Diabetes is one of the most common non communicable disease and most frequent cause of chronic renal failure. We know that ~40% of patients with type I diabetes mellitus are affected by Diabetic nephropathy. It carries a poor prognosis when fully developed in Type 1 diabetic patients where relative mortality is almost 40–100 times that of nondiabetics.[1]

Multiple studies have been conducted in type 2 diabetes mellitus patient to evaluate nephropathy but by far no study has been conducted in type 1 Diabetes Mellitus patients in India to evaluate early stages of nephropathy. Early changes in renal function in diabetes may set the stage for late diabetic nephropathy as evidenced by hemodynamic studies.[2-5] T1DM is thought to be autoimmune or idiopathic in nature and is present in 9% cases of insulin deficiency. T1DM is primarily caused by genetic factors, environmental factors, and disorder of the immune regulatory mechanism. Pre diabetes is the phase before the onset of T1DM which provides a window of opportunity for early treatment.[6,7] All available interventions including steroids, immunosuppressants, and cyclosporine can be possibly applied during the pre-diabetes phase. The treatment goals for T1DM are simple and include maintaining near normal blood glucose levels and avoiding long-term complications.[8-10]

This study aims at identifying early vascular changes which may help to identify children with early progression of diabetic nephropathy by using non-invasive doppler study and if clinically useful information is obtained it may be useful in follow up for the treatment.

MATERIALS AND METHODS

Sampling

This cross-sectional study was done in a tertiary care hospital in India. The ethical approval was obtained from the institutional ethical committee. A total of 120 samples were taken in which 60 were patients with type 1 diabetes mellitus and 60 were age, sex and BMI matched healthy controls. Patients with known Type 1 Diabetic patients with duration of disease equal to or > 2 y with HbA1c below 8.1 were included. Patients with any of the followings were excluded: GFR<60ml/min/1.73m^2, type 2 diabetes mellitus, cardiac

failure or hypertension, on ACE inhibitors, Angiotensin receptor blockers, patients suffering from acute or chronic urinary tract infections, any febrile illness and critically ill patients in ICU, patients with non-diabetic renal disease due to hereditary, metabolic, immunological causes (excluded by history), patients with renal artery stenosis, renal transplant, obstructive kidney disease, malignancies, renal artery and renal vein thrombosis, acute pyelonephritis (excluded by ultrasonography), pregnancy, patients with history of prolonged usage of non-steroidal anti-inflammatory drugs, heavy metals, Ayurvedic or siddha medication, patient having renal bruits, peripheral vascular disease.

Methodology

Patients were examined empty stomach after taking a tab Dulcolax a night before. Once patient agrees to participate in the study, informed consent was taken followed by detailed history and brief clinical examination. The procedure begins with the patient lying supine and the head of the bed elevated about 30 degrees procedure will be done in the opposite lateral decubitus position. 3.5 MHz convex array probe was used for the study. Kidneys were visualized in using oblique and flank approach. 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 pyramid. Angle was adjusted to less than 60 degrees and Doppler spectral waveforms were obtained on the lowest pulse repetition frequency possible without aliasing. The velocity measurements of peak systolic velocity and end diastolic velocity were automatically calculated from the spectral forms. Three intra renal arterial resistive index values from upper, mid and lower poles of each kidney were obtained.

Statistical analysis

The data is tabulated in Microsoft excel and analysed with SPSS V.24 software. The continuous variables are presented with mean and standard deviation. The categorical variables are presented with frequency and percentage. Independent t test, chi square test and Pearson's correlation were used for the comparisons. The p value ≤ 0.05 is considered as statistically significant.

RESULTS

The cases consisted of 35 males and 25 females with mean age of 14.2±4.5 years, mean BMI of 22.1±2.1 and mean duration of diabetes of 5.5±2.7 years. The controls consisted of 33 males and 27 females with mean age of 14.1±4.1 years and mean BMI of 20.9±1.6 and there were no statistically significant difference (Table 1).

Table 1: Distribution of demographic parameters.

Parameters	Case	Control	p value
Age (years)	14.2±4.5	14.1±4.1	0.883
Sex (Male:Female)	35:25	33:27	0.854
BMI	22.1±2.1	20.9±1.6	0.505
Duration of diabetes (years)	5.5±2.7	-	-

Table 2 shows the comparison of the laboratory parameters between cases and controls. Mean HbA1C level of cases was 7.7 ±0.4 and control was 4.7+_ 0.3 with a mean difference of 3.0 which is significant (p value=0.001); mean fasting blood glucose (FBG) level of cases was 223.9±51.2 and controls was 85.6±7.8 with a mean difference of 138.3 mg/dl, which was statistically significant; mean post prandial blood glucose (PPBG) level of cases was 233.4±56.2 mg/dl and controls was 102.7±13.5 mg/dl with a mean difference of 130.7 mg/dl which is statistically significant(p value=0.004); mean ACR level amongst cases was 28.8±9.7 and control was 13.2±7.1 with a mean difference of 15.6 which is statistically significant (p value=0.037); mean creatinine level amongst cases was 0.7±0.2 and controls was 0.6±0.1 with mean difference of 0.1 without significant difference; mean GFR among cases was 143.1±17.9 and controls was 133.2±12.6 with mean difference of 10.1 which is significant; mean total cholesterol among the cases was 158.0±25.8 and among the control was 151.3±17.1 with a mean difference of 6.7 which is non-significant; mean Triglyceride among the cases was 142.1±45.5 and among the control was 95.5±13.4 with a mean difference of 46.6 which is significant (p value=0.001); mean LDL among the cases was 98.8±18.9 and among the control was 92±12.6 with a mean difference of 6.8 which is non-significant; mean HDL among the cases was 46.3±6.7 and among the control was 53.1±6.9 with a mean difference of 6.8 which is significant (p value=0.019).

Table 2: Comparison of laboratory parameters.

Parameters	Case	Control	p value
HbA1C	7.7±0.4	4.7±0.3	0.001
FBG (mg/dl)	223.9±51.2	85.6±7.8	0.001
PPBS (mg/dl)	233.4±56.2	102.7±13.5	0.004
ACR	28.8±9.7	13.2±7.1	0.037
Creatinine	0.7±0.2	0.6±0.1	0.060
GFR	143.1±17.9	133.2±12.6	0.004
Total Cholesterol	158.0±25.8	151.3±17.1	0.116
Triglyceride	142.1±45.5	95.5±13.4	0.001
LDL	98.8±18.9	92.0±12.6	0.058
HDL	46.3±6.7	53.1±6..9	0.019

Table 3 shows the comparison of the radiological parameters between cases and controls. Mean peak systolic velocity of the cases was 35.9 ±11.2 and control was 30.5 ±8.9 with difference of 5.4 which is significant

(p value=0.037); Mean end diastolic velocity of cases is 12.7±3.9 and controls is 13.5±4.1 with mean difference of 0.8 without significant difference; Mean resistivity index of cases is 0.6± 0.04 and controls is 0.5± 0.05 with mean difference of 0.1 having significant difference (P value=0.001). Among the Type 1 diabetic cases having ACR >30 the mean RI was 0.63±0.14 and those having ACR >30 the mean RI was 0.61±0.12 with mean difference of 0.02 which is significant (p value=0.013). Among the Type 1 diabetic cases having ACR <30 the mean RI was 0.61±0.12 and among the healthy controls the mean RI was 0.50±0.02 with mean difference of 0.11 which is significant (p value=0.037).

Table 3: Comparison of radiological parameters.

Parameters	Groups		p value
Peak systolic velocity (cm/sec)	Case	35.9±11.2	0.037
	Control	30.5±8.9	
End diastolic velocity (cm/sec)	Case	13.8±3.9	0.480
	Control	13.6±4.1	
Resistivity index	Case	0.6±0.04	0.001
	Control	0.5±0.02	
Resistivity index	ACR>30	0.63±0.14	0.013
	ACR<30	0.61±0.12	
Resistivity index	ACR<30	0.6±0.12	0.037
	Control	0.5±0.02	

Table 4 shows the correlations between laboratory and radiological parameters. Moderate Positive correlation was noted between resistivity index and HbA1c with a (r value =0.529) and ACR with RI (r value=0.173) which were also statistically significant (p value=0.001, 0.037 respectively). Weakly positive correlation was noted between resistivity index and fasting blood sugar with a (r value=0.173) which was statistically significant (p value=0.011) and moderate positive correlation between FBG with PSV (r value=-0.008) which was also significant (p value=0.955). Weakly positive correlation was noted between resistivity index and creatinine with a (r value=0.237) which was not statistically significant (p value=0.068). Weakly negative correlation was noted between resistivity index and glomerular filtration rate, PSV with GFR, EDV with GFR which were significant (p value=-0.026, -0.010, -0.002 respectively). Nearly negligible correlation was noted between PPBS with RI, PPBS with PSV, ACR with PSV, PPBS with EDV, ACR with EDV which were non-significant. Very Weak Positive correlation was noted between resistivity index and Total cholesterol (r value=0.118) which was also significant (p value=0.022), PSV with total cholesterol (r value=0.042) which is also significant (p value=0.018). Very Weak Positive correlation was noted between PSV and Triglyceride (r value=0.011) which was also significant (p value=0.004), EDV with triglyceride (r value=0.057) which is also significant (p value=0.020). Very Weak Positive correlation was noted between resistivity index and LDL (r value=0.051) which was also significant (p value=0.008), PSV with LDL (r value=0.212) which is also significant (p value=0.043), EDV with LDL (r value=0.230) which is also significant (p value=0.033). Very Weak negative correlation was noted between resistivity index and HDL (r value=-0.067) which was also significant (p value=0.015).

Table 4: Correlation between laboratory and radiological parameters.

Parameters	Resistivity Index		PSV		EDV	
	r	p value	r	p value	r	p value
HbA1C	0.529	0.001	0.222	0.088	0.020	0.878
FBG	0.173	0.011	0.419	0.044	0.211	0.106
PPBS	0.077	0.281	-0.008	0.955	0.093	0.346
ACR	0.134	0.020	0.022	0.865	0.093	0.273
Creatinine	0.237	0.068	0.060	0.651	0.059	0.118
GFR	-0.318	0.026	-0.227	0.010	-0.461	0.002
Total Cholesterol	0.118	0.022	0.042	0.018	0.066	0.055
Triglyceride	0.177	0.057	0.011	0.004	0.057	0.020
LDL	0.051	0.008	0.212	0.043	0.230	0.033
HDL	-0.067	0.015	-0.021	0.052	-0.041	0.059

DISCUSSION

The diagnosis of diabetic nephropathy is done on the basis of proteinuria and declining GFR. Intra renal arteriosclerosis can be estimated by invasive techniques like arteriography or biopsy. But arteriography visualizes only most advanced lesions in the renal arteries, and biopsy identifies very initial lesions in a limited area which cannot represent the whole organ. RI values are useful markers to determine the degree of intra renal arteriosclerosis and interstitial lesions. RI obtained by

DDU is most consistent and reproducible. The availability of Duplex Doppler ultrasonography has provided a rapid non-invasive method to study the characteristics of intrarenal blood flow.[11,12]

In our study there was an increase in GFR in the patient group in comparison with control 143.1±17.9 vs133.2±12.6) which is significant (p value=0.04). This is in accordance with the study by Magee et al[13] which suggest there is hyperfiltration state which finally progress into declining GFR. Intrarenal mean RI was significantly increased in Type 1 DM cases over age, sex and BMI matched controls (0.6± 0.04 vs 0.5± 0.05), P value=0.001.This is accordance with the findings of Youssef et al.[14], Saif et al.[15], Pelliccia et al.[16] There was significant difference in PSV between type 1 diabetes patients than their age, sex and BMI matched healthy controls. EDV was non-significantly raised among type 1 DM cases compared to healthy controls.

Mean HbA1C level of T1DM cases was more than controls (7.7 ±0.4 vs 4.7±0.3) with a mean difference of 3.0 which is significant (p value=0.001). Moderate Positive correlation was noted between resistivity index and HbA1c with a (r value=0.529). This is accordance with the findings of Pelliccia et al.[16] Mean ACR value was increased among T1DM cases over age, sex and BMI matched controls (28.8±9.7 vs 13.2±7.1 with a mean difference of 15.6 which is statistically significant with p value=0.037). Weak positive correlation was noted between ACR with RI (r value=0.173). This is accordance with the findings of Hamano, Kumiko et al.[17] We could not find any significant difference in Mean creatinine level amongst cases was (0.7±0.2 vs 0.6±0.1) with mean difference of 0.1 without significant difference. This finding is not in accordance with Sari et al.[18]

Amongst the type 1 DM cases when correlation was tried between biochemical parameters (glycaemic profile) and doppler parameters (renal RI, PSV AND EDV)-Weakly positive correlation was observed between resistivity index (RI) with HbA1c, RI with FB, PSV with FBG which were also statistically significant. Amongst the type1 DM cases when correlation was tried between biochemical parameters (lipid profile) and doppler parameters (renal RI, PSV AND EDV)-Weakly positive correlation was observed between resistivity index (RI) with Total cholesterol, RI with LDL, RI with HDL, PSV with Total cholesterol, PSV with triglyceride, PSV with LDL, EDV with triglyceride, EDV with LDL which were also statistically significant. It is in accordance with findings of Tolonen N et al.[19] Gray scale ultrasonography and colour doppler is a very efficient, low cost and easily available tool to assess early haemodynamic changes in renal artery amongst type 1 DM patients.[20]

CONCLUSION

From the results of the study we can conclude that renal blood flow and vascular indices in children with type 1 diabetes mellitus markedly vary from healthy individuals. The doppler parameters like renal Resistivity index, Peak systolic velocity and End diastolic velocity can be used as potential tools to identify early progression of diabetic nephropathy in children with type 1 diabetes mellitus. Further research in larger population is recommended in order to explore various other biochemical and radiological aspects in type 1 diabetes mellitus.

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