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Original Research Article.

A Case Control study of Carotid Artery Intima Media Thickness in Children with Type 1 Diabetes Mellitus at a Tertiary Care Hospital

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ABSTRACT

Background: Diabetes mellitus (DM) is the most prevalent metabolic disease of childhood and adolescence. Individuals with type 1 diabetes have a two- to four-fold increased risk of developing atherosclerotic diseases. Carotid intima–media thickness (CIMT) serves as an early marker of atherosclerosis. The present case control study was conducted to assess thickness of carotid artery intima media in children with Type 1 Diabetes Mellitus at a Tertiary Care Hospital.

Materials and Methods: The present case control study was conducted at Pediatrics and adolescent endocrinology clinic, department of pediatrics, Hindu Rao Hospital over a period of 2 year. A sample size of 40 diabetic children and 40 age and sex matched control were studied. Body weight and Height were measured & Body Mass Index (BMI) was calculated. Baseline Blood Pressure (BP), Fasting and post-prandial blood glucose values, HbA1c, serum creatinine and Urinary albumin/ creatinine ratio, lipid profile were measured. Analysis of the common carotid artery IMT was performed. The results were analyzed using appropriate statistical tests. P value <0.05 was considered as significant.

Results: A total 40 cases of type 1 Diabetes mellitus were compared with 40 age and sex matched control enrolled from Pediatrics and adolescent endocrinology clinic, Hindu Rao Hospital. BMI among the diabetic cases varied from 16.39 ±2.7 kg/mt^2 and in healthy control group BMI varied from was17.23 ± 3.08 kg/mt^2. Among diabetic children systolic BP varied from 102.75 ±10.54 mmHg with maximum of 120 mm hg and minimum of 80 mmHg. Duration of diabetes varied in cases from 4.36 ±3.46 year with maximum of 12 years and minimum of 12 months. Among the cases mean dose of insulin was 38 ±12.5 iu in which maximum was 60 and minimum was 14 iu. Among 40 cases mixtard was used in five case (12.50%), regular + NPH was used in 11 case (27.50%), regular + Glargine was used in 24 cases (60.00%) was used. Amongst cases HbA1C level varied from 9.48 ±2.27% with maximum of 15.18% and minimum of 5.9%. Amongst control mean HbA1C was 3 ± 0.34 % with maximum 4% and minimum 2.4%. Fasting Blood sugar level amongst cases varied from150.02 ±33.24 mg/dl with maximum of 240mg/dl. Amongst control group, fasting blood sugar level varied from 116.95 ± 18.82mg/dl with maximum of 178 mg/dl. Common carotid artery intima media thickness was found to be 0.52±0.29mm with maximum thickness of 1.2 mm and minimum of 0.2 mm. Amongst control thickness vary from 0.29±0.07mm with maximum thickness 0.4mm and minimum of 0.1 mm. According to this study carotid artery intima media thickness is increased in diabetic children with increased duration of diabetes as compared to healthy control.

Conclusion: This study concluded that the common carotid artery intima media thickness increases with increased duration of diabetes in comparison to healthy control.

Keywords: Healthy Control, Common Carotid Artery, Intima Media Thickness, Diabetes.

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INTRODUCTION

Diabetes mellitus (DM) is the most prevalent metabolic disease of childhood and adolescence and is characterized by progressive irreversible autoimmune destruction of pancreatic beta cells via a cytokine-induced apoptosis.[1] The major complication of Type 1 DM is macrovascular namely atherosclerosis and microvascular in form of nephropathy, neuropathy and retinopathy. Individuals with

type 1 diabetes have a two- to four-fold increased risk of developing atherosclerotic diseases. The metabolic derangements (chiefly glucose and lipid) in diabetes have been implicated as major determinants for Cardio vascular disease (CVD).[2] However traditional lipid and non-lipid markers for atherosclerosis do not reflect the atherosclerotic process at arterial level.[3] The atherosclerotic process begins in childhood and develops inconspicuously for many decades before cardiovascular complications, such as myocardial infarction or stroke, occur in middle and late age in the presence of risk factors.[4,5] Early changes of atherosclerosis are arterial vessel wall stiffening and increased carotid artery intima media thickness (cIMT), which are reversible.[3] Carotid artery intima-media thickness is a well-known marker for atherosclerosis in adult and is an independent predictor of atherosclerosis.[6,7] A non-invasive measurement of carotid wall intima media thickness (cIMT) by B mode Ultrasonography is a marker of generalized atherosclerosis that in adults correlates with extent of coronary artery disease[8, 9] and predicts future cardiovascular events.[10] The normal intima-medial thickness of common carotid artery as evaluated by B-mode ultrasound imaging in healthy subjects is 0.74 ± 0.14 mm[11] and a value of cIMT at or above 1 mm is associated with atherosclerosis and a significant increased cardio vascular disease(CVD) risk in any age group[12,13]. Hence, the present case control study was conducted to assess thickness of carotid artery intima media in children with Type 1 Diabetes Mellitus at a Tertiary Care Hospital.

MATERIALS AND METHODS

The present case control study was conducted at Pediatrics and adolescent endocrinology clinic, Department of Pediatrics, Hindu Rao Hospital over a period of 2 year (July 2016 to June 2018). Ethical clearance was taken from the Institutional Ethical Committee. Patients included in the study were Type 1 diabetic children aged 2 to 18 years, diabetes duration >1 year, regularly attending Pediatrics and adolescent endocrinology clinic at Hindu Rao hospital. Patients excluded from the study were children with chronic disease such as hypertension, cardiovascular disorder, other metabolic condition, children with BMI more than 95% of age, sex specific and diabetic children taking regular medication other than insulin. A convenient sample size of at least 40 diabetic children was taken and 40 age matched control children were also studied. Parents of these children were explained about the purpose of the study and written consent was taken from parents. Body weight was recorded using an electronic/digital weighing machine to the nearest 0.01 Kg. Height was measured using a stadiometer with the participant at same time of day, standing on a firm/level surface to the precision of 0.1 cm. Each measurement was done twice and mean of the two readings were recorded. The same measuring equipment's were used throughout the study. The Body Mass Index (BMI) was calculated as weight (kg)/height (m^2). The BMI readings were interpreted using World Health Organisation (WHO) charts and recorded to nearest percentile.[14] Baseline Blood Pressure (BP) was recorded using a standard oscillatory sphygmomanometer using appropriate size cuff in the supine position after 10 min rest period. An average of two readings were recorded. The BP readings were interpreted against height and age and sex adjusted BP centiles as per recommendations by American Academy of Pediatrics and a value of >95th centile was considered as raised.[15] The patients were subjected to metabolic screening. 5 ml of fasting blood sample was collected by venipuncture under sterile conditions. Blood was collected in plain vial for lipids, potassium ethylene - diaminetetraacetic acid (EDTA) vial for glycated haemoglobin (HbA1C) and sodium fluoride/potassium oxalate vial for glucose estimation. Fasting and post-prandial blood glucose values were measured by the glucose oxidase method. HbA1C was measured using immunoturbidimetric method which measured the absorbance of the HbA1C fraction and total haemoglobin fraction at 415 nm. The normal value for HBA1C in our laboratory in a non-diabetic population is <6.5 percent[16]. Serum creatinine and Urinary albumin/creatinine ratio were measured to exclude renal involvement. Urine analysis for the presence of microalbuminuria was done by spot urine albumin/creatinine ratio. Cut off levels were considered as equal or more than 30mg/mmol.[17] Measure fasting blood sugar and cut off value-126 mg/dL. Cut off values of lipid profile: Serum triglycerides (TG), cholesterol (C), Low density lipoprotein-cholesterol (LDL-C) and High-density lipoprotein-cholesterol (HDL-C)[18] as follow: Hypertriglyceridemia was considered as serum triglycerides >160mg/dl, High LDL as >130mg/dl, Hypercholesterolemia as >200mg/dl, While low HDL cholesterol as <50mg/dl. Analysis of the common carotid artery IMT was performed with B- mode ultrasound 7 to 12 MZH phased array scanner used. Patients were examined in a supine position. The common carotid artery (below the carotid bulb and 1 cm proximal to bifurcation) was scanned with the neck in hyper-extension, on B mode (real time) ultrasound [19,20]. The longitudinal section of carotid artery was scanned, and its wall was assessed for intimal thickness. The first line was the luminal-intimal interface, while the second was collagen containing upper layer of adventitia. cIMT was measured as the difference between two echogenic lines of the vessel wall.[21] Both right and left common carotid arteries were scanned and mean of both sides (recorded thrice and average of three) was taken as common final value. The normal limit for cIMT is arbitrary and is influenced by age, gender and population. The definition of abnormal cIMT is less clearly defined in children[22]. It is thus interpreted in terms of increased risk rather than statistical distribution; however, a value of >1 mm is definitely abnormal[23,24]. The data for normative cut-off of cIMT in Indian population was not available; in one study a value of >0.8 mm was taken as abnormal[25]. All parameters were evaluated by a single experienced vascular sonographer who was blinded to the clinical and metabolic profile of the patients. The results were analyzed using appropriate statistical tests on Statistical Package for Social Sciences (SPSS) software. Quantitative data was expressed as mean ± 2 standard deviation (SD). A P value <0.05 was considered as significant. P value <0.001 was taken as highly significant.

RESULTS

A Total of 40 cases of type I diabetes mellitus were compared with 40 age & sex matched enrolled from the Pediatrics and Adolescent Endocrinology clinic, Hindu Rao Hospital. Among the total 40 cases of diabetes 5 (12.5%) were in the age group of < 5 years, 12(30%) were in the age group of 6-10 years, 18(45%) were in the age group of 11-15 years and 5(12.5%) were in the age group of > 15 years. Among the 40 controls 13(32.50%) were in the age group of <5 years, 12(30%) were in the age group of 6-10 years, 11 (27.50%) were in the age group of 11-15 years and 4

(10.00%) were in age of >15 years. However, this difference in distribution was statistically not significant [p value=0.147]. The mean age among cases was 10.63±3.91 and among control mean age was 8.75 ± 4.38 years. Among the diabetic cases 25(62.5%) were females & 15(37.5%) were males. Among the controls 17(42.5%) were females & 23(57.5%) were males. however, this difference in distribution was not statistically significant. [p value=0.073] Among cases mean weight was 30.58±11.02 kg. Among control mean weight was29.68 ± 14.64 kg. However, this difference in distribution was not statistically significant. [p value=0.756] Among the cases mean height was 133.61±18.82 cm. Among the controls mean height was 125.82 ± 22.79 cm. However, this difference in distribution was statistically not significant [p value=0.1]. Among the cases mean BMI was 16.39±2.7 kg/m^2. Among the controls mean BMI was17.23 ± 3.08 kg/m^2. However, this difference in distribution was not statistically significant [p value=0.19]. There was no family history of diabetes mellitus. Among the case mean duration of diabetes was 4.76±3.46 years. Among the case mean dose of insulin was 35.38±12.5 IU. Among the 5 case mixtard [12.50%], regular and NPH 11[27.50%], regular and glargin 24 case [60.00%].

Among the case mean systolic BP was 102.75±10.54 mmHg. Among the controls mean systolic BP was 97.92 ± 14.28 mmHg. However, this difference in distribution was not statistically significant. [p value=0.099]

Among the cases mean diastolic BP was 65.55±12.97 mmHg. Among the controls mean diastolic BP was 62.3 ± 9.66 mmHg. However, this difference in distribution was not statistically significant. [p value=0.052].

Among the cases mean HbA1c was 9.48±2.27% with max of 15.1% and min of 5.9%. Among the controls mean HbA1c was 3±0.34% with max of 4% and min of 2.4%. However, this difference in distribution was statistically significant. [p value= <0.0001].

Among the cases mean FBS was 150.02±33.24 mg/dl. Among the controls mean FBS was 116.95±18.82 mg/dl. However, this difference in distribution was statistically significant. [p value=<0.0001]

Among the cases the mean creatinine levels was 0.74 ± 0.11 mg/dl. Among the controls the mean level was 0.69 ± 0.16 mg/dl. However, this difference in distribution was not statistically significant. [p value=0.379]

Among the cases the mean cholesterol levels was found to be 170.42 ± 18.84 mg/dl. Among the controls the mean levels were 140.88 ± 16.27 mg/dl. However, this difference in distribution was statistically significant. [p value<0.0001]. But total cholesterol was within normal range. Among the cases the mean LDL level was found to be 78.2 ± 18.4 mg/dl. Among the controls the mean level was 52.75 ± 11.18 mg/dl. However, this difference in distribution was statistically significant. [p value<0.0001]. But LDL level was within normal range. Among the cases the mean HDL level was found to be 74.7 ± 16.46 mg/dl. Among the controls the mean HDL level was 70.85 ± 8.68 mg/dl with max level of 98 mg/dl and min level of 55 mg/dl. However, this difference in distribution was not statistically significant. [p value=0.157]. Among the cases the mean TG level was 119.25 ± 22.71 mg/dl. Among the control group mean TG level was 91.52 ± 14.16 mg/dl with max level of 135 mg/dl. However, this difference in distribution was statistically significant. [p value<0.0001].

Among the cases mean thickness was found to be 0.54 ± 0.27 mm. Among the controls the mean thickness was found to be 0.29 ± 0.07 mm. However, this difference in distribution was statistically significant. [p value<0.0001].

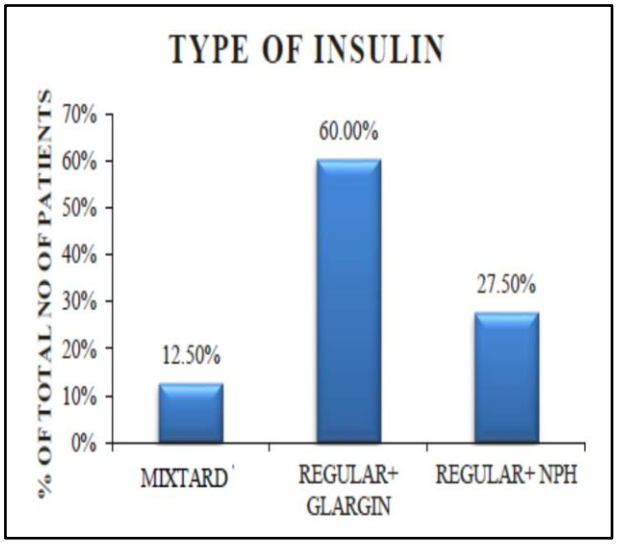

Fig 1: Type of Insulin

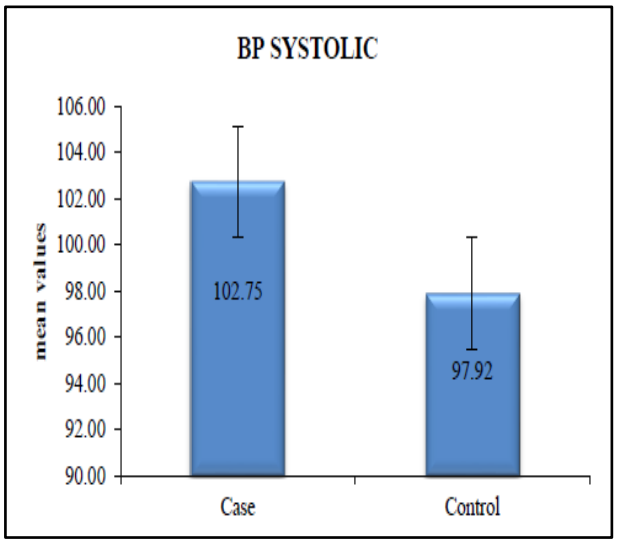

Fig 2: BP Systolic

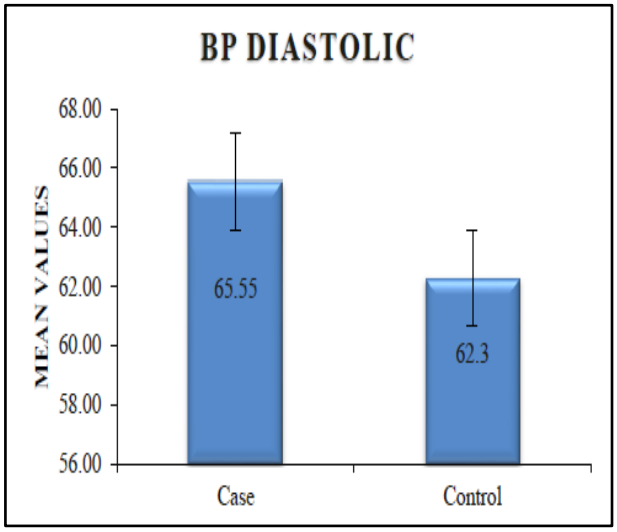

Fig 3: BP Diastolic

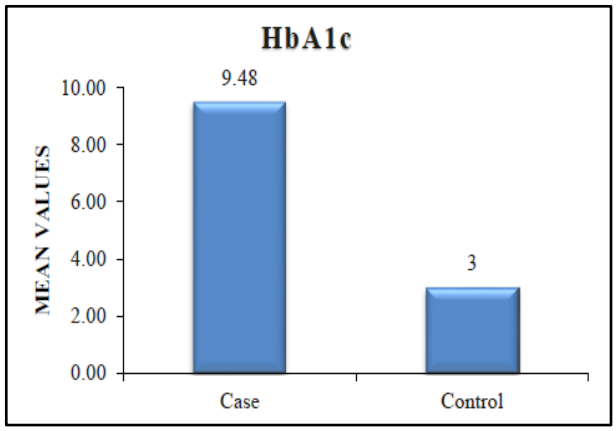

Fig 4: HbA1c

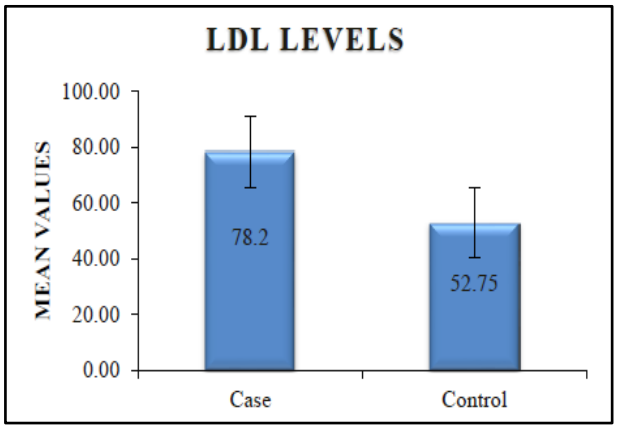

Fig 7: LDL Levels

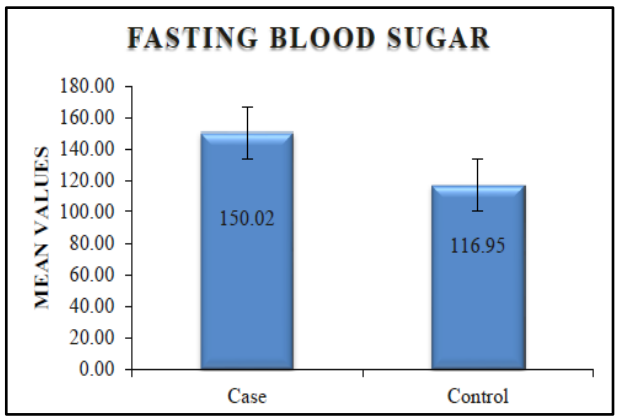

Fig 5: Fasting Blood Sugar

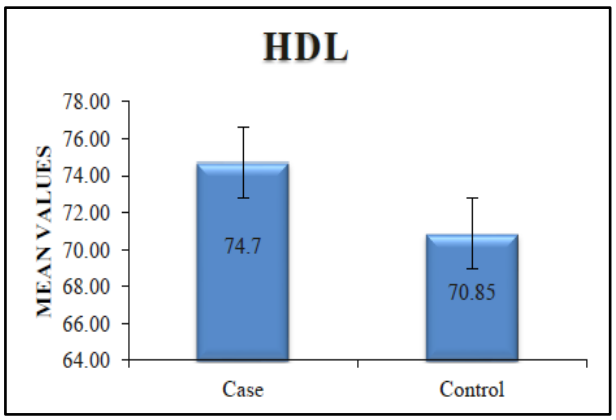

Fig 8: HDL Levels

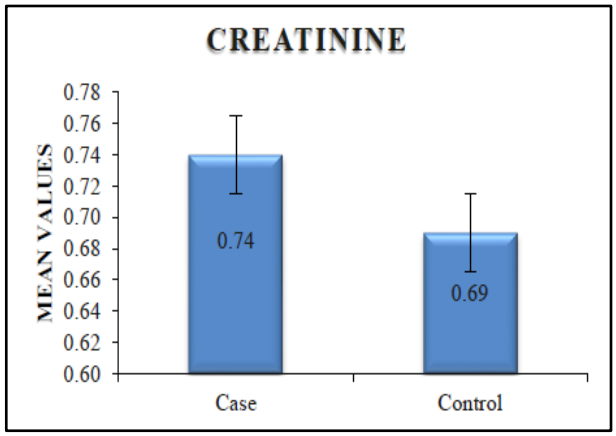

Fig 5: Creatinine

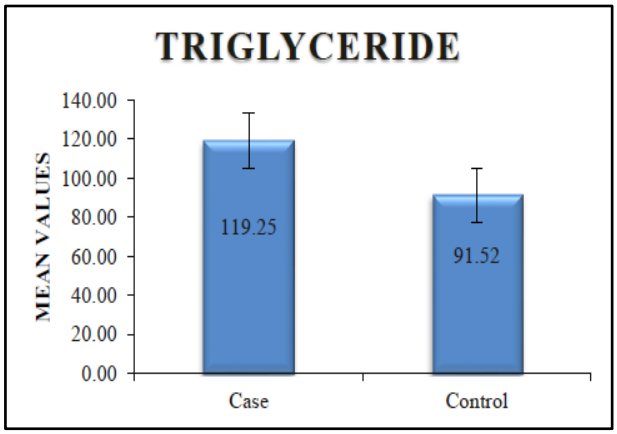

Fig 9: Triglyceride Levels

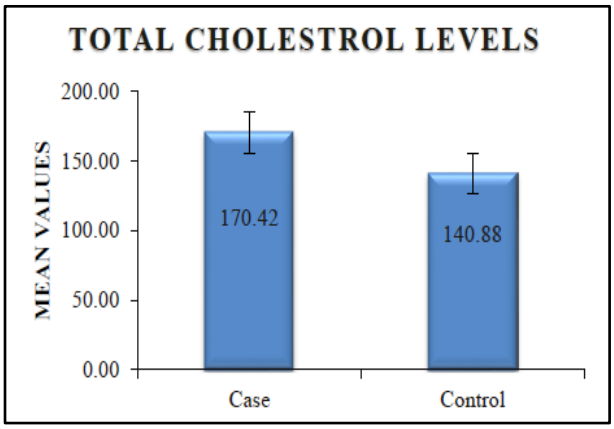

Fig 6: Total Cholesterol Levels

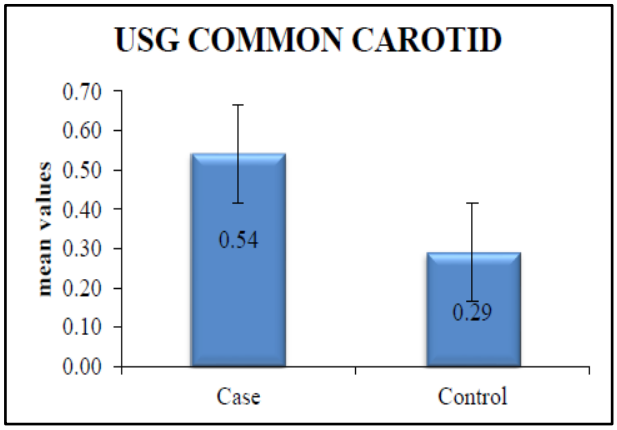

Fig 10: USG Common Carotid

DISCUSSION

In this study total 40 Diabetic children were enrolled which were compared with 40 normal healthy control. The mean chronological age of cases was 10.63 ± 3.91 years and among control was 8.75 ±4.38 years.

The sex distribution showed predominantly females in cases and no particular dominance in controls. Among the cases 25 (62.50%) were females and 15 (37.50%) were males and amongst control 17(42.50 %) were females and 23 were male (57.50%). This data differed from other studies like Gupta A et. al.[26] Where the mean age of study population was 14.3 ±3.09 years and Abdelghaffar shereen et al.[27] where the mean age of diabetic children was 15.2 ±8 years and Rodriguez, Rocio Rabago, et al[28] the mean age of diabetic cases was 11.8 ±3.1years. This suggests that age of presentation of diabetic child in this study was found to be younger than other literature.

In this study Body Mass Index (BMI) of diabetic cases was 16.39 ±2.7 kg/m2 and control healthy cases BMI 17.23 ±3.08 kg/m2. And within normal range.

In other studies, Gupta A et. Al[26] 17.1±2.91 mg/m2. Rodriguez, Rocio Rabago, et al[28] BMI of diabetic children 19.3 ±1.3mg/m2 and control 19.9 ±4.3mg/m2 and Jarvisalo et. al.[29] 19.1 ± 2.4 mg/m^2 and on control 19.4 ±4.1 mg/m^2.

This suggests that BMI of case and control are similar as compared to other literature. The correlation between BMI and USG common carotid artery thickness is as per figure 11.

In this study, systolic blood pressure of cases varying 102.75 ±10.54mm Hg with a maximum of 120 mmHg as compared to control 97.92 ± 14.28mmHg. These value within normal range.

In other study, Rodriguez, Rocio Rabago, et al.[28] 99 ±9.9mmHg cases and control 99.6 ±8.9 mm Hg. In this study, systolic BP of the children was similar to other study. Correlation between BP systolic & usg common carotid artery thickness is as per figure 12.

Diastolic BP of children in this study is found to 65.55 ±17mmHg of the diabetic children and control group was found to be 62.3 ±9.66mmHg.

Mean diastolic BP of cases in this study is similar to other studies like Urbina, Elaine M., et al.[30] 70.3 ±5.6 mm Hg., Rodriguez, Rocio Rabago, et al.[28] 62.9 ±6 mm Hg. and Gupta A et. al [26] 67.33 ±10.4 mm Hg. These value within normal range.

In study diastolic blood pressure similar to other study. The correlation between diastlolic BP and common carotid artery thickness is as per figure 13.

Duration of diabetes in this study group varies from 4.37 ±3.46 years with minimum 12 months to maximum 12 years.

Other studies like Rad, Masoud Pezeshki, et al.[31] duration of diabetes was 4.34 ±3.2 years, Jarvisalo et. al.[29] mean duration was 4.4 ±3.0 years and Gupta A et. al.[26] duration was 3.96 ±2.92 years.

In this study duration of diabetic children is similar to other studies. The correlation between duration in years and common carotid artery thickness is as per figure 14.

In this study group mean fasting blood glucose was varying from 150 ±33.24mg/dl as in other studies like Gupta A et. al.[2 6] 155 ±112.33 mg/dl, Urbina, Elaine M., et al.[30] 210 ±40 mg/dl, Rad, Masoud Pezeshki, et al.[31] 179 ±34 mg/dl.

The difference of the FBS in our study comparable to other literature because diabetic children visiting to OPD were well controlled on insulin.

In this study, HbA1C diabetic children were varying from 9.48 ±2.27% as compared to healthy control 3 ±0.34%.

In other studies, like Abdelghaffar shereen et al[27] HbA1C level of diabetic children was 9.5 ±1.0%, Urbina, Elaine M., et al[82] 8.9 ±1.1% and Jarvisalo et. al.[29] 8.9 ±1.4%.

There is no difference in HbA1C level in this study as compared to other studies. The correlation between HbA1C and common carotid artery thickness is as per figure 15.

In this study total cholesterol level found to be 170 ±18.84 mg/dl of diabetic children among healthy control cholesterol level was 140.88 ±16.27 mg/dl.

In other studies, Abdelghaffar shereen et al.[27] total cholesterol level of diabetic cases varied from 192.5 ±34.5 mg/dl and control group 128.5 ±3.5 mg/dl and Urbina, Elaine M., et al[30] total cholesterol of diabetic cases170 ±34.3 mg/dl and control 162.4.

In this study, total cholesterol level was increased in cases but within normal range as compared to control. Cholesterol level of cases is similar to other studies.

In this study, LDL level of case was found 78.2 ±18.4mg/dl and control group 52.74±11.18 mg/dl.

In other studies, Gupta A et. al.[26] 86.3 ±29.3mg/dl. Jarvisalo et. al.[77] 42 ±10mg/dl and Urbina, Elaine M., et al.[30] 117 ±34.4 mg/dl. There is difference between LDL levels in this study as compared to other studies. But LDL level within normal range. The correlation between LDL and common carotid artery thickness is as per figure 16. In this study, HDL level of cases was 74.7±16.46 mg/dl and control group were 17.85±8.68 mg/dl.

In other studies, Abdelghaffar shereen et al[27] 30.4 ±6 mg/dl., Urbina, Elaine M., et al[30] 54 ±13.5 mg/dl.

HDL level in this study was slightly higher than other studies but HDL level of cases was similar to control group.

In this study group, triglyceride level (TG) of diabetic children was found to be 119.25 ±22.27mg/dl and control group 91.51 ±14.16 mg/dl.

In other study, Gupta A et. al.[26] Triglyceride level of diabetic children varies from 102.22 ±50.93, Abdelghaffar shereen et al[27] 154 ±24.4 and Urbina, Elaine M., et al[30] 95 ±58 mg/dl.

There is no difference in TG level in this study compared to Gupta A et. Al[26] and Urbina, Elaine M., et al.[30] But there is slight difference between Abdelghaffar shereen et al.[27] and in this study group. There is a difference in TG level in this study between diabetic cases and healthy controlled group. These triglyceride level within normal range.

In this study group, common carotid artery thickness varied in cases 0.54 mm ± 0.27 mm with a minimum of 0.2 mm and maximum of 1.2 mm as compared to control group, which was 0.29 ±.07 mm.

In other studies, like Gupta A et. al.[26] Mean carotid artery thickness was 0.583 ±0.22 mm., Urbina, Elaine M., et al.[30] it was 0.49 ± 0.073 mm and Abdelghaffar shereen et al.[27] it was 0.8±0.1 mm.

In 5 Diabetes cases carotid artery intima media thickness was greater than 1mm. In these cases, blood pressure, BMI, lipid profile, LFT, KFT and urinary albumin/ creatinine ratio were in normal range but duration of diabetes >5 years and HbA1c level increased. In this study thickness of common carotid artery intima media is similar to other studies but there is significant difference of carotid artery intima media thickness of cases as compared to control group.

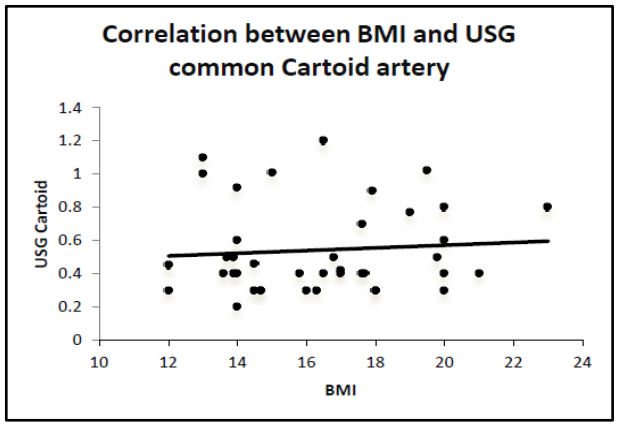

Fig 11: Correlation Between BMI and USG

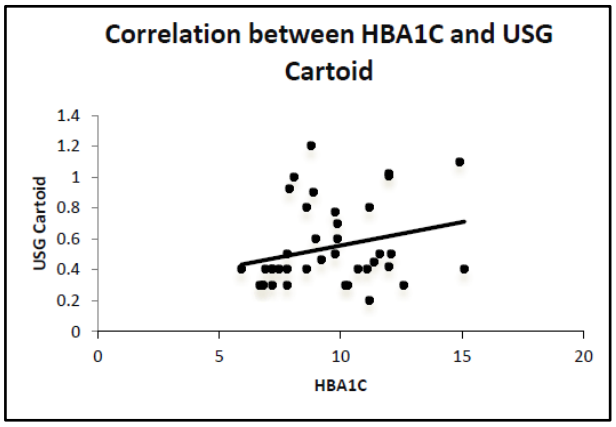

Fig 15: Correlation Between HbA1c and USG

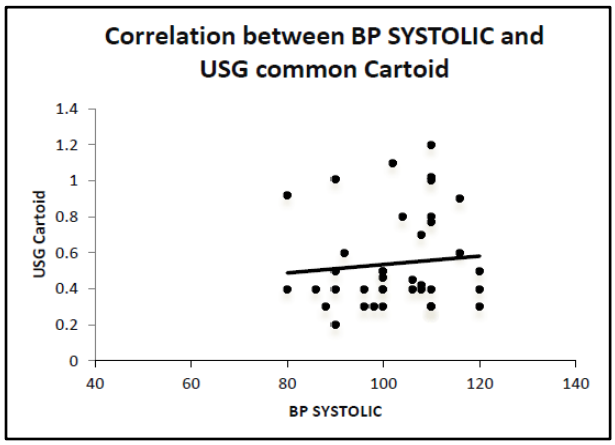

Fig 12: Correlation Between BP Systolic and USG

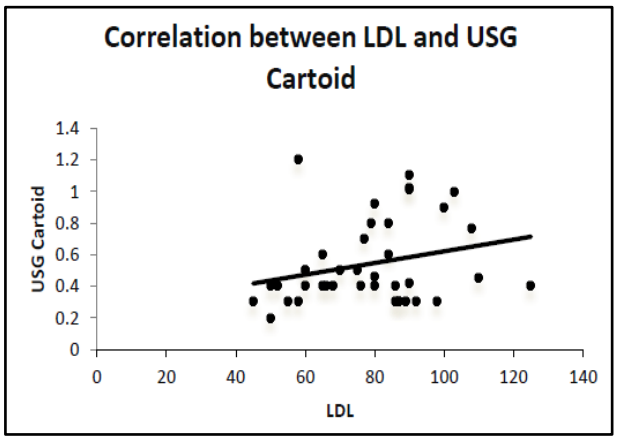

Fig 16: Correlation Between LDL and USG

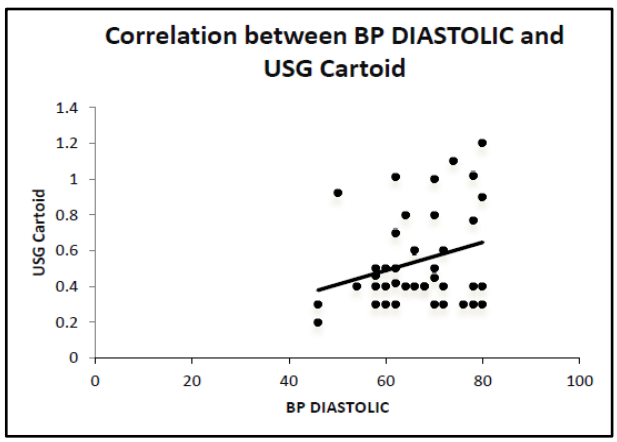

Fig 13: Correlation Between BP Diastolic and USG

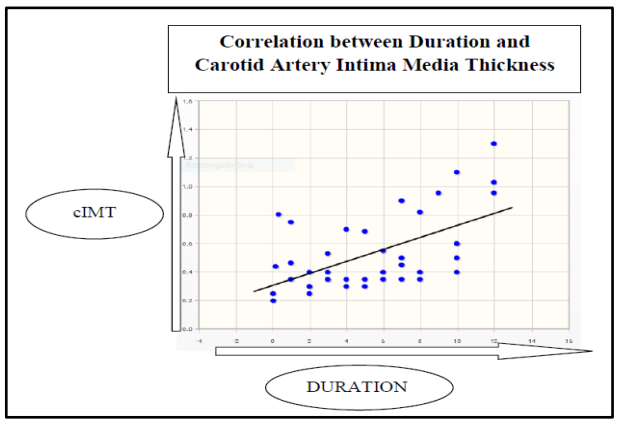

Fig 14: Correlation B/w Duration & Intima Media Thickness

LIMITATIONS

1. Sample size was small.
2. Normal carotid artery intima media thickness in Indian population not available.

RECOMMENDATIONS

1. Yearly monitoring of cIMT by Ultrasonography to detect early atherosclerosis (duration of diabetes more than 5 years or prepubertal age) and along with it a healthy life style with good metabolic control in the form of rigorous glycaemic, lipid, and blood pressure control to minimise the progression of sub clinical atherosclerosis to overt disease.
2. cIMT can be measured more reliably with greater reproducibility and have better predictable value and less missing data as compared to other metabolic profile such as lipid, blood sugar, HbA1c which vary from lab to lab and fasting & post prandial, hence more preferable.

CONCLUSION

The cIMT is easily, safely, reliably and inexpensively measured with B-mode ultrasound. USG is more accurate than conventional lipid and non-lipid marker of early atherosclerosis without any hazard for needle prick and radiation.

Ultrasound studies using measurement of intimal-medial thickness (cIMT) have been used to detect the atherosclerotic process before the development of vessel stenosis. There is strongly positive correlation between duration of type 1 DM and cIMT. If prevention is to begin early in life, it would be useful to have a noninvasive method to detect premature atherosclerosis so that

interventions could be targeted early at those at the highest risk. In this study common carotid artery intima media thickness increases in comparison to healthy control with increasing duration of diabetes.

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