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Full Length Research Paper

Carotid intimo-medial thickness [cIMT] and correlation to cardiac risk factors in adolescent type 1 diabetics

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Carotid intimo medial thickness (cIMT) is a sensitive screening tool for cardiac evaluation, but there are limited studies evaluating its role in type 1 diabetes mellitus (T1DM) in developing countries. Thirty diagnosed adolescent type 1 diabetics on conventional insulin regime were included. Their glycated hemoglobin (HbA1C) and lipid profile were measured. Their cardiovascular function (determined by cIMT) was estimated by echocardiography and was evaluated with the clinical and biochemical profile. The mean HbA1C was 8.01%; 18 patients had HbA1C >8%. The mean serum cholesterol, low density lipoprotein (LDL) and triglyceride were normal. The mean cIMT measured was 0.698 ± 0.233 mm. The mean cIMT was higher in patients with higher HbA1C (0.775 ± 0.21 mm) versus those with normal HbA1C (0.583 ± 0.22 mm); P = 0.019. The cIMT correlated significantly to systolic and diastolic blood pressure (P = 0.039 and 0.01). cIMT values were significantly related to serum cholesterol (P = 0.002) and serum LDL (P = 0.017). However, few patients with a normal metabolic profile also had raised cIMT >0.8 mm. cIMT was raised in few patients indicating onset of early cardiovascular changes in adolescence. Cardiovascular screening should be offered to type 1 adolescent diabetics early in the disease, irrespective of the metabolic parameters.

Key words: Type 1 diabetes, carotid intimo-medial thickness (cIMT), cardiovascular screening, lipid profile.

INTRODUCTION

Patients with diabetes have two-four fold risk of death from cardio-vascular disease (CVD) as compared to non-diabetics (Larsen et al., 2002). The metabolic derangements (chiefly glucose and lipid) in diabetes have been implicated as major determinants for CVD (Alemzadah and Wyatt, 1994; Kimball et al., 1994; Jarvisalo et al., 2002; Nathan et al., 2003). However, traditional lipid and non-lipid markers for atherosclerosis do not reflect the atherosclerotic process at arterial level (Bots et al., 2002). Autopsy findings in children with type 1 diabetes mellitus (T1DM) have revealed the presence of early atherosclerosis in the form of coronary plaques (Abdelgaffar et al., 2005; Jarvisalo et al., 2001). Silent coronary atheromatosis was demonstrated in T1DM by Larsen et al. (2002). Early changes of atherosclerosis are arterial vessel wall stiffening and increased carotid artery intimal-medial thickness (cIMT), which are reversible. These are followed by cardiac dysfunction and left ventricular hypertrophy (Bots et al., 2002; Groner et al., 2006). It was seen that cIMT was a powerful indicator for CVD, stroke and cerebro-vascular accidents in adult studies (O'Leary et al., 1999; Hodis et al., 1998; Simon et al., 2002). Ultrasound examination of carotid arteries has emerged as an alternative, noninvasive method to study the evolution of cardiovascular disease (Salonen

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Abbreviations: cIMT, Carotid intimo-medial thickness; **T1DM,** type 1 diabetes mellitus; **HbA1C,** glycated hemoglobin; **TG,** triglyceride; **LDL,** low density lipoprotein; **HDL,** high density lipoprotein; **ADA,** American Diabetes Association; **CVD,** cardio-vascular disease.

and Salonen, 1991; Heiss et al., 1991; Cobble et al., 2010).

The changes in cIMT in adolescents may not be as a result of local atherosclerosis alone, but it may be an adaptive response to altered blood flow and pressure (Sorof et al., 2003). Also, it is important to realize that adolescents experience poorer glycemic control than adults (Couper et al., 1995).

A study was thus undertaken to evaluate the metabolic profile of adolescent type 1 diabetics and identify any risk factors for CVD. These patients were screened for early atherosclerotic changes using echocardiography and the risk factors were correlated using the same method.

MATERIALS AND METHODS

The study was conducted in the Department of Pediatrics of a large tertiary referral hospital.

Sample characteristics

Type 1 diabetics who were attending the Pediatric Endocrinology Clinic at Lok Nayak Hospital were evaluated. Patients were included if they fulfilled the following inclusion criteria: age 10 to 18 years, regular and compliant visits at follow up clinic. Patients were excluded if they had any evidence of neuropathy or retinopathy on clinical examination, any history of hypertension or intake of antihypertensive or lipid lowering medication, any history of substance abuse or any family history of life threatening cardiac event which occurred before 55 years age. All patients were on pre-meal insulin bolus regimen (short and long acting insulin) administered thrice a day. Informed consent was taken from the parents/guardians. Out of the 45 patients attending the Endocrinology Clinic, 30 fulfilled our study criteria and were included in the study. The study design was cross-sectional and the study was approved by the Institutional Ethical Committee.

Experimental

All pertinent clinical information was obtained through a questionnaire which was completed after reviewing medical records and information provided by the patient and their guardian. The weight was measured on standard weighing scale and height was recorded on stadiometer. 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 (WHO, 2005). Baseline blood pressure (BP) was recorded using a standard mercury sphygmomanometer using appropriate size cuff in the supine position after a 10 min rest period. An average of two readings was recorded. The BP readings were interpreted against height and age adjusted BP centiles as per recommendations by American Academy of Pediatrics and a value of >95th centile was considered as raised (AAP, 2004). Then, patients were subjected to metabolic screening. Five milliliter of fasting blood sample was collected by venipuncture under sterile conditions. Blood was collected in plain vial for lipids, potassium ethylenediaminetetraacetic acid (EDTA) vial for glycated hemoglobin (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 hemoglobin fraction at 415 nm. Total cholesterol and serum triglyceride were measured using enzymatic colorimetric estimation. Serum high density lipoprotein-cholesterol (HDL-C) was estimated by an automated direct assay method on an auto-analyzer. Serum LDL-C was calculated by Friedewald's formula (Warnick et al., 1990).

cIMT was assessed using trans-thoracic echocardiography (7 to 12 MHz phased array scanner which was interfaced to an AGILENT SONOS 4500 ULTRASOUND MACHINE). 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) and Doppler imaging (Paucillo et al., 1994; Larsen, 2002). 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 (Xiao et al., 2007). Both right and left common carotid arteries were scanned and mean of both sides (recorded thrice) was taken as common final value (Figure 1). 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 (Sorof et al., 2003). It is thus interpreted in terms of increased risk rather than statistical distribution; however, a value of >1 mm is definitely abnormal (Bots et al., 2002; Simon, 2002). The data for normative cut-off of cIMT in Indian population was not available; a value of >0.8 mm was taken as abnormal (O'Leary, 1999; Sorof et al., 2003).

All parameters were evaluated by a single experienced vascular sonographer who was blinded to the clinical and metabolic profile of the patients.

Statistical analysis

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). Statistical significance of quantitative variables between different categories was analysed using t test. Pearson's correlation coefficient/Spearman's rank coefficient (r) was used to indicate significant linear relationship among quantitative variables and regression analysis was done. A P value <0.05 was considered as significant. Any P value <0.001 was taken as highly significant.

RESULTS

The baseline clinical features of the patients are depicted in Table 1. Equal number of males and females were recruited (15 each). The mean BMI was at 25th percentile as per WHO growth charts for both girls and boys and no patient was found to be overweight or obese. Two patients had increased BP as adjusted to age and height. Both systolic blood pressure (SBP) and diastolic (DBP) were directly associated to duration of diabetes (P = 0.002; r = 0.51 and P = 0.016; r = 0.39 respectively). The mean fasting blood glucose was 223.8 mg/dl and post

Table 1. Baseline clinical characteristics of study population.

Parameter	Mean ± SD
Age (years)]	14.30 ± 3.09
Weight (kg)	34.40 ± 11.14
Height (cm)	140.03 ± 15.4
BMI (kg/m^2)	17.1 ± 2.91
SBP (mmHg)	111.46 ± 12.52
DBP (mmHg)	70.48 ± 9.16
Disease duration (years)	5.35 ± 2.94
Insulin dose (U/kg/day)	1.102 ± 0.303

Table 2. Comparison of clinical and laboratory values of patients with good and poor glycemic control.

Parameter	Good glycemic control (n = 12; HbA1C <8%)	Poor glycemic control (n = 18; HbA1C ≥8%)	P value (Correlation coefficient = r)
SBP (mmHg)	107.66 ± 11.36	114.0 ± 12.27	0.17 (0.25)
DBP (mmHg)	67.33 ± 10.43	73.11 ± 7.66	0.047* (0.36)
Disease duration (years)	3.96 ± 2.92	6.28 ± 2.70	0.009* (0.44)
Insulin dose (U/kg/day)	0.98 ± 0.30	1.18 ± 0.28	0.038* (0.49)
FBG (mg/dl)	155.33 ± 112.33	269.50 ± 80.72	0.001† (0.46)
PPBG (mg/dl)	191.25 ± 112.8	319.0 ± 85.6	0.001† (0.48)
Serum cholesterol (mg/dl)	142.0 ± 35.39	159.83 ± 31.26	0.07 (0.33)
Serum triglyceride (mg/dl)	99.17 ± 46.78	120.22 ± 50.93	0.21 (0.23)
Serum HDL (mg/dl)	36.28 ± 11.17	39.67 ± 11.63	0.48 (0.13)
Serum LDL (mg/dl)	86.30 ± 29.34	96.4 ± 30.12	0.19 (0.24)
c-IMT (mm)	0.583 ± 0.22	0.775 ± 0.21	0.019* (0.43)

Values are mean ± SD. *P < 0.05 significant, †P < 0.01 highly significant. SBP: Systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; PPBG: post prandial blood glucose.

prandial was 267.9 mg/dl. The observed HbA1C range was 4-13.1% (mean = 8.01%). The mean values of lipid profile-cholesterol, triglyceride and LDL were 152.70 ± 33.5, 111.8 ± 49.61 and 92.39 ± 29.73 mg/dl, respectively; all within normal range. The mean HDL was 38.31 ± 11.38 mg/dl, less than the reference of 40 to 60 mg/dl.

The mean cIMT measured was 0.698 ± 0.233 mm (range 0.36 to 1.27 mm). There was no difference in cIMT when compared with age (P = 0.16) or gender (equal male and female subjects). Patients with a longer disease duration had higher cIMT; though, result was statistically insignificant (P = 0.282; r = 0.16). The cIMT did not correlate with BMI (P > 0.05). The cIMT correlated positively with SBP and DBP (P = 0.02; r = 0.38 and P = 0.005; r = 0.46, respectively) (Figure 2) after adjusting for age. The patients were further divided into two groups based on their HbA1C values (below and above 8%), as shown in Table 2. The DBP was significantly higher in those with poor glycemic control as compared to good glycemic control (P = 0.047; r = 0.36). Patients with longer disease duration had higher HbA1C (P = 0.009; r = 0.44). The mean daily insulin dose was significantly higher in those with poor glycemic control (P = 0.038). Patients with higher HbA1C had higher serum lipids; (p > 0.05). The correlation of HbA1C with cIMT was significant (P = 0.019; r = 0.51; Figure 3). There were 8 patients with high cIMT >0.8 mm; 5 of them (62.5%) had HbA1C ≥ 9%. Two variables among lipid profile had a significant association with cIMT-serum cholesterol (P = 0.002; r = 0.48) and LDL (p = 0.017; r = 0.44) (Figure 4). Serum triglyceride and HDL failed to show any correlation with cIMT. However, 4 (50%) of the 8 patients with increased cIMT (>0.8 mm) had normal lipid profile.

DISCUSSION

cIMT has been correlated to cardiac risk factors and established as a cardiac screening tool in studies on high risk adults. Both age and gender are identified as non- modifiable

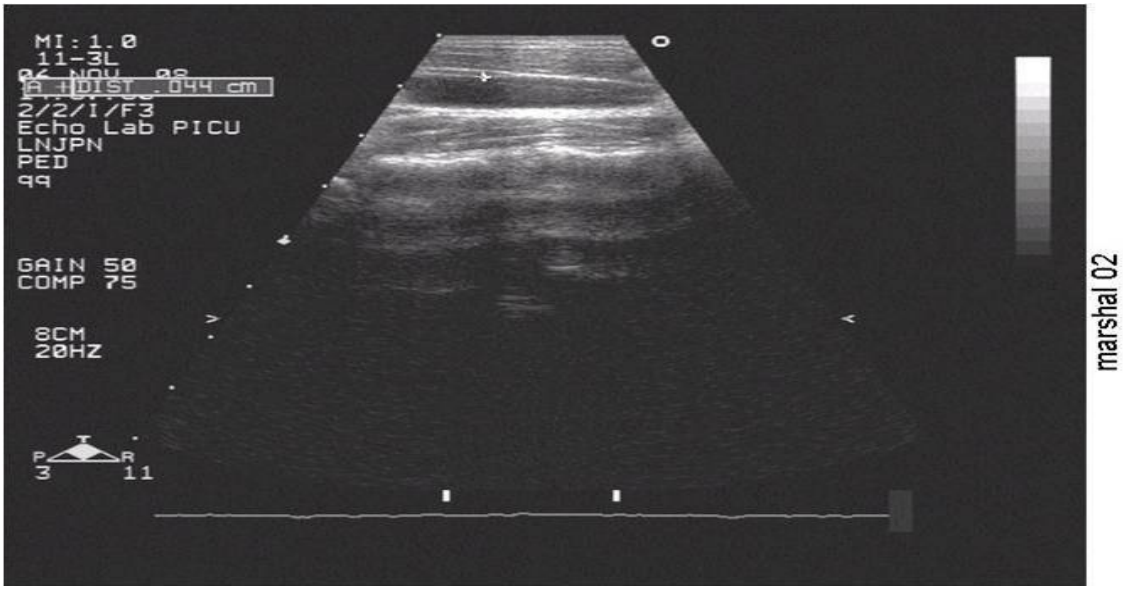

Figure 1. Measurement of carotid intimo-medial thickness on B-mode echocardiography.

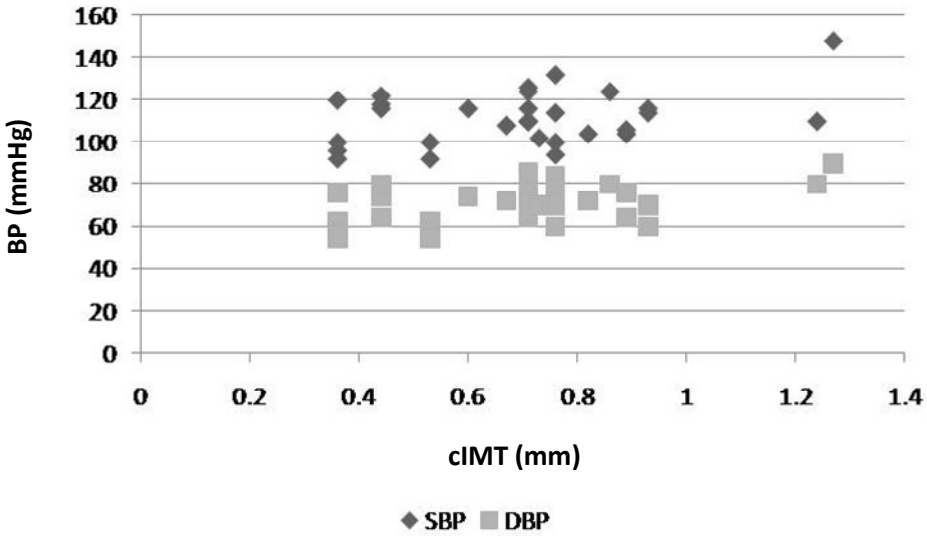

Figure 2. Correlation of cIMT and blood pressure (BP).

atherosclerotic risk factors in adults. However, cIMT is not influenced by age or gender in the pediatric age group (Koivisto et al, 1996; Saas et al., 1998); which is similar to results from our study.

The risk factors predicting cIMT are not well established in pediatric diabetic patients (Paucillo et al., 1994; Hodis et al., 1998; Parikh et al., 2000; Jarvisalo et al., 2002; Rathsman et al., 2012). Few follow up studies indicate that progression of cIMT is influenced by factors like HbA1C, BMI, disease duration and serum LDL (Kawamori et al., 1992; Pozza et al., 2011). Our study established the following as cardiac risk factors affecting cIMT in diabetic adolescents-duration of disease, blood pressure, HbA1C, serum cholesterol and LDL.

The probability of acquiring CVD is increased with prolonged duration of T1DM; more so if HbA1C values remain deranged (Yamasaki et al., 1994; Abdelgaffar, 2005). As the disease progresses, additional bio-chemical pathways (other than hyperglycemia) contribute and exacerbate disease pathology (Nickerson and Dutta,

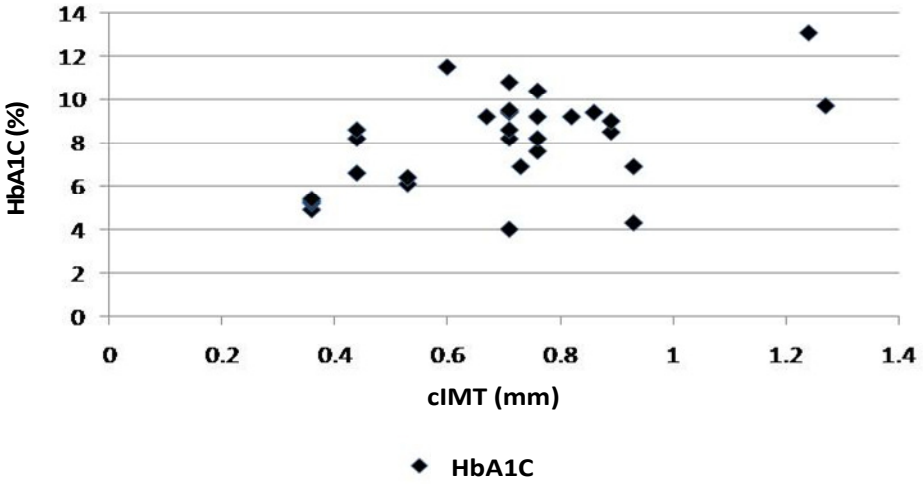

Figure 3. Correlation of cIMT and HbA1C.

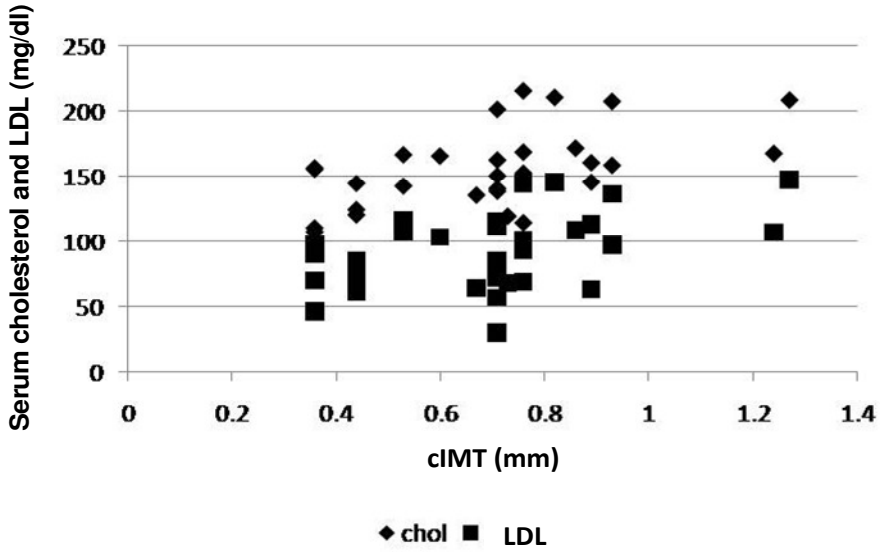

Figure 4. Correlation of cIMT and serum cholesterol and LDL.

2012). However, few authors did not find any correlation between duration of diabetes and cIMT (Yavuz et al., 2002).

Hypertension induces smooth muscle proliferation and exacerbates cardiac structural changes mediated through calcium pathways, predispose to atherosclerosis (Barbagallo et al., 1996). Previously conducted studies have reported a highly significant difference in blood pressure of type 1 diabetics versus controls in respective cohorts (Kimball et al., 1994; Abdelgaffar, 2005; Schwab et al., 2006; Pozza et al., 2011). However, few authors did not find any substantial relation of blood pressure with HbA1C (Peppa-Patrikiou et al., 1998; Parikh et al., 2000). These variable results can be accounted for by variations in measurement techniques and confounders like race, genetics and environmental factors. A strong association between BMI and cIMT has been established in obese children (Simsek, 2010; Gökçe, 2012) and in T1DM (EDIC, 1999; Pozza et al., 2011). Our cohort belonged to a developing country and mean BMI was influenced by socio-economic factors; thus, was normal and did not correlate with cIMT.

Hyperglycemia is a postulated marker for atherosclerosis and causal factor for macrovascular complications in T1DM (DCCT, 1991; Kimball et al., 1994; Jarvisalo et al., 2002; Danielson, 2013). Conversely, few authors found

no difference in cIMT values of T1DM against controls studied (EDIC, 1999; Parikh et al., 2000; Gunczler et al., 2002). It may be argued that most of the adverse effect of hyperglycemia in atherosclerosis is due to a chronic process and poor glycemic status should not be considered as an unconditional marker for atherosclerosis (EDIC, 1999).

The DCCT research group had found lipid abnormallities more frequently in younger T1DM with relatively higher HbA1C and attributed this occurrence to poor dietary patterns (DCCT, 1991). Loh et al. (1996) reported dyslipidemia in 34 to 60% diabetics (most common aberration found as hypercholesterolemia followed by a mixed pattern and hypertriglyceridemia). Both cholesterol and LDL adversely affected cIMT in the children of this study ($P < 0.05$) similar to results reported earlier by separate authors (Jarvisalo et al., 2002; Pozza et al., 2011). Peppa-Patrikiou et al. (1998) and Yamasaki et al. (1994) did not detect any abnormality between cIMT and lipids in their study on T1DM. The variability in the aforementioned outcomes can be a consequence of various confounding factors which were present in each study like diet, gender, HbA1C level and disease duration.

Though both hyperglycemia and dyslipidemia were established as risk factors in our study; few patients with increased cIMT had a normal metabolic profile. This increases the possible role of other inflammatory markers in the occurrence of CVD and further research is needed to confirm the occurrence.

To summarize, deranged metabolic factors predicted increased cIMT in type 1 diabetics. However, an increase in cIMT was recorded in few others who had relatively normal sugars/lipids, suggesting the role of additional inflammatory factors which contribute to cardiovascular morbidity. Both long disease duration and high blood pressure were identified as adverse factors for increased cIMT. Thus, our study recommends that cIMT should be offered to adolescent T1DM as a screening tool for CVD after minimum of five years disease duration, especially in the presence of deranged metabolic parameters. A healthy lifestyle with good metabolic control is recommended to minimize progression of subclinical atherosclerosis to overt disease.

STUDY LIMITATIONS

The sample size was small and age matched controls were not evaluated. Thus, results from this study cannot be generalized. Also, data for normal range of cIMT in our population was not available. However, our study is one of the first studies which address the role of cIMT and cardiac risk factors from this part of the developing world and results are noteworthy.

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