Comparative evaluation of carotid intima media thickness in paediatric type 1 diabetic children and healthy children in Ibadan and Lagos, Nigeria

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Abstract

Patients with type 1 diabetes are at greater risk of cardiovascular disease and atherosclerosis. Carotid intima–media thickness (CIMT) measured by ultrasound is a marker of atherosclerosis and can predict future cardiovascular events. The aim of this study was to measure the CIMT in paediatric type 1 diabetes patients in Ibadan and Lagos and compare results with the CIMT of non-diabetic healthy control children. Carotid ultrasound was performed and CIMT measured in 70 subjects (35 diabetic patients and 35 non-diabetic controls matched for age and sex). Mean age was 12.8±3.2 years. A slightly higher, but non-significant mean CIMT was seen in diabetic cases: mean values in type 1 diabetes patients were 0.475±0.068 and 0.476±0.069 (right and left respectively) while in controls, mean values were 0.467±0.064 and 0.468±0.054 (p=0.618 and 0.575 respectively). The CIMT in both groups correlated positively with age and body mass index (BMI). Significantly higher mean CIMT values were seen in males with type 1 diabetes on both sides. However, there was no significant correlation between CIMT and duration of illness, insulin dosage, or blood pressure. CIMT is a safe and convenient measurement, which may be helpful in predicting an increased risk of future cardiovascular disease in children with type 1 diabetes.

Introduction

Diabetes mellitus is a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both.[1] Type 1 diabetes often occurs in childhood, and potentially reversible atherosclerotic lesions have been demonstrated by autopsy studies and in animal models of paediatric type 1 diabetes.[2] Young adults with type 1 diabetes show a dramatic increase in morbidity and mortality caused by atherosclerotic cardiovascular disease compared with the non-diabetic population.[3,4] Early detection of cardiovascular disease is therefore important so that prompt therapeutic interventions can be instituted.[5]

Carotid ultrasound (CUS) is a non-invasive imaging method for measuring intima–media thickness, a sensitive indicator of cardiovascular risk;[6] it is safe, cheap, and readily available, and does not utilise ionising radiation. This makes it ideal for imaging paediatric and low-resource populations.

The aim of this study was to measure the carotid intima–media thickness (CIMT) in paediatric type 1 diabetes patients, and compare results with the CIMT of non-diabetic healthy children.

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Patients and methods

This was a prospective, case-control study over a period of seven months from August 2013 to February 2014. Thirty-five (35) normotensive children with type 1 diabetes aged up to 18 years were recruited from the endocrinology clinics of the children's outpatient departments of both the University College Hospital (UCH) Ibadan and Lagos University Teaching Hospital (LUTH), Nigeria. Both clinics were used in order to achieve the calculated sample size of 35, since there were only 20 registered paediatric type 1 diabetes patients at UCH at the time the study was conducted. Thirty-five (35) age- and sex-matched, normotensive, non-diabetic controls, aged 0–18 years were either healthy volunteers or recruited from the children's unit of the general outpatient department (GOPD) at UCH.

Two ethical approvals were obtained from the Joint University of Ibadan, UCH and LUTH Health Research Ethical Review Committees. Written informed consent was obtained. Relevant clinical history was obtained

	Type 1 diabetes (n=35)	Controls (n=35)
Male	13	13
Female	22	22
Mean age (years)	12.8±3.2	12.8±3.2
Age group (years)		
0–4	1	1
5–9	1	1
10–14	24	24
15–18	9	9
BMI (kg/m2)	17.9±3.9	17.9±3.9
BMI group		
Underweight	5	5
Normal	24	24
Overweight	4	4
Obese	2	2
Educational status		
Nursery	1	1
Primary	6	6
Secondary	27	27
Tertiary	1	1
Socio-economic class		
Upper	22	24
Lower	13	11
Note: weight classification was according to percentiles of BMI. Underweight <5th centile, normal weight 5th to 85th centile, overweight 85th to 95th centile, and obese >95% centile.		

Table 1: Socio-demographic factors in type 1 diabetes patients and control subjects

from all subjects.

For control subjects, fasting blood glucose (FBG) was measured to screen for diabetes, while fasting serum lipids were also obtained in 20 type 1 diabetes patients and in all controls, to screen for hyperlipidaemia.

Carotid ultrasound was done on all subjects using a 7.5–10.0 MHz linear transducer on a portable SONOSITE ultrasound machine. The near and far walls of the common carotid (CCA), carotid bifurcation, and internal carotid (ICA) arteries were examined for the presence of atherosclerotic plaque. On a longitudinal view, the CIMT at three carotid sites were measured in the far wall of the vessels as the distance between the leading edge of the lumen–intima interface and the leading edge of the media–adventitia interface as described by Touboul et al.[7] The three sites were:

1. the common carotid artery at 1.5 cm proximal to the carotid bulb;
2. the carotid bulb;
3. the proximal internal carotid artery at 1 cm from the carotid bulb.

The final mean CIMT (in mm) on each side was the average of the values measured at the three sites. To reduce inter-observer variability, one of the authors (NAC) took all CIMT measurements at both study sites, while taking an average of three measurements at each site reduced intra-observer variability.

Using the Statistical Package for Social Sciences (SPSS) version 20 (SPSS Inc. Chicago, IL, USA), data were analysed and presented using frequency tables, percentages, graphs, and means±standard deviation (SD) as appropriate. Associations between categorical and continuous variables were explored using the independent t-test while correlations between continuous variables were explored using Pearson's correlation coefficient. Associations were deemed significant for $p<0.05$ at a 95% confidence interval; p values of 0.000 were denoted as $p<0.001$.

Results

Of the 35 type 1 diabetes cases, 24 (68%) were recruited from Lagos, and 11 (32%) from Ibadan; the 35 controls were all recruited from Ibadan. The socio-demographic data of study subjects are summarised in Table 1. Age range for both groups was 2–18 years with a median age of 12 years and a mean age of 12.8±3.2 years. There were 26 (37%) males and 44 (63%) females, with a male:female ratio of 1.0:1.7. Most (94%) of the participants were above nine years old with the largest proportion 48 (68%) seen within the 10–14 year age group. A total of 54 (72%) of the participants were in secondary school while two (3%) were either in nursery school or at university. FBG levels were significantly higher in individuals with type 1 diabetes compared with controls (8.4±0.5 vs 4.4±1.6 mmol/l, p=0.021). Ten (34%) of the

	Minimum CIMT (mm)	Maximum CIMT (mm)	Mean CIMT + SD (mm)	Significance
Type 1 diabetes group				
Right side	0.29	0.60	0.476+0.069	p=0.618
Left side	0.29	0.59	0.475+0.068	
Control group				
Right side	0.29	0.61	0.468+0.054	
Left side	0.29	0.59	0.467+0.064	p=0.575
CIMT, carotid intima–media thickness				

Table 2 CIMT values in type 1 diabetes patients and non-diabetic controls

Variables	Sex	Mean CIMT+SD (mm)	Significance
Type 1 diabetes group Right side	Male Female	0.49+0.07 0.46+0.06	p<0.001
Left side	Male Female	0.49+0.07 0.46+0.06	p<0.001
Control group Right side	Male Female	0.48+0.06 0.45+0.06	p<0.002
Left side	Male Female	0.48+0.06 0.45+0.06	p<0.001

Table 3: Comparison between right and left mean CIMT by gender

diabetic patients had a positive family history of diabetes, while none of the controls had such a history. Most of the type 1 diabetes subjects had had the disease for more than one year, with about two-thirds having had the disease for 1–6 years. The mean duration of diabetes was 2.7±2.8 years.

CIMT measurements: correlation with gender, age, duration of diabetes, insulin dosage, and blood pressure

The mean CIMT was higher in those with type 1 diabetes (0.47±0.06mm on each side) when compared with controls (0.46±0.06mm and 0.46±0.05mm on the right and left side respectively). However, this difference in CIMT was not statistically significant (right, p=0.618; left, p=0.575). Side-to-side comparison shows no statistically significant difference between the right and left CIMT in both study groups. The data are shown in Table 2. Bilaterally, in both groups, males had higher mean CIMT than females (Table 3) and this observed gender difference was statistically significant. There was a positive and significant correlation between CIMT and age bilaterally for both groups. Pearson correlation coefficients were 0.493 and 0.491 for right and left CIMT respectively in type 1 diabetes patients, and 0.484 bilaterally for controls (p=0.003 for both sides, in both groups). This correlation was seen in both genders with p<0.001 for females bilaterally, and in males, p values were 0.005 and 0.004 on the right and left sides respectively. There was a weak positive non-significant correlation between duration of diabetes and CIMT bilaterally. The correlation between CIMT and insulin dosage was also weak and not statistically significant. Mean systolic and diastolic blood pressures were higher in the type 1 diabetes group (99±10 mmHg and 71±11 mmHg respectively) when compared with controls (98±10 mmHg and 67±10 mmHg), but the difference was also not statistically significant.

CIMT, BMI, and serum lipids

The mean CIMT values (right and left side) were higher in patients with type 1 diabetes (0.51±0.07 mm and 0.50±0.07 mm) and controls (0.50±0.08 mm and 0.50±0.06 mm) who were overweight and obese when compared with mean CIMT of patients with type 1 diabetes (0.47±0.05 mm and 0.47±0.05 mm) and controls (0.46±0.06 mm and 0.46±0.07 mm) with a normal BMI. These differences were statistically significant in both the type 1 diabetes group (p=0.041 and p=0.031 on the right and left sides respectively) and controls (p=0.044 and p=0.038 on the right and left sides respectively). Bilaterally, there was a positive correlation between CIMT and BMI in the diabetic and non-diabetic groups, but this positive correlation was higher in controls than in type 1 diabetes patients. In patients with type 1 diabetes (r =0.392) and controls (r =0.414), the correlation was noted to be significantly higher on the right side when compared with the left (p<0.05). Serum lipid profiles for type 1 diabetes patients and the control group showed no significant differences.

Discussion

This study has shown a higher mean CIMT in the diabetic group compared with the non-diabetic controls, although the difference was not statistically significant. Several case control studies have been conducted on CIMT in paediatric patients with type 1 diabetes, and these studies show contradictory findings, with the CIMT values in both diabetic and non-diabetic healthy controls varying significantly.[8-15] The CIMT values in our study are closest to those of Rodriguez et al8 in Mexico who studied children with a similar age and recorded a mean CIMT of 0.463±0.04 mm and 0.441±0.04 mm in diabetic and non-diabetic Hispanic children respectively. The CIMT values are also close to those of Babar et al[13] who reported a mean CIMT of 0.48±0.02 mm and 0.46±0.04 in 21 American paediatric type 1 diabetes patients and 15 non-diabetic children with an age of 8.3±0.3 years. However, our values of CIMT were less than those recorded by Tołwińska et al[15] (0.52 mm and 0.43 mm in diabetic and non-diabetic patients respectively) in subjects with a higher mean age of 15.5±4.3 years. In agreement with their findings, we also showed a positive correlation between the mean CIMT and age in both diabetic patients and non-diabetic controls (p=0.003). Other authors have reported similar age correlations in both children and adults.[9,10,16] Age-related physiologic carotid wall thickening occurs both in adults and children but the mechanism is poorly understood in children.[17] In adults, it has been suggested that an increase in blood pressure with age is related to an increase in CIMT.[18] The finding of an age correlation with CIMT is however at variance with studies by Babar et al[13] in the USA and Margeirsdottir et al[12] in Norway.

We have showed gender variation in the CIMT values with males having significantly higher values than females. Similar findings have been reported by some workers,[9,19] but not by others. It is also known that the eventual macrovascular complications of diabetes are more common in males

than in females, and this may be evident from childhood.[20]

The mean duration of diabetes in this study was 2.7±2.8 years and no correlation was found between CIMT and duration of diabetes, in agreement Gunczler et al.[14] However, other studies in subjects with longer duration of diabetes have found a positive and significant correlation between CIMT and disease duration.[9,10] Other factors such as level of glycaemic control may also contribute to the difference in study findings.

It is estimated that the mean CIMT progression in the general population ranges from 0.001 to 0.030 mm per year,[21] and in type 1 diabetes its progression to atherosclerosis begins in childhood.[22] As such, intensive insulin therapy may slow the progression of CIMT.[23]

Ten of our diabetic patients had a positive family history of diabetes. The presence of a positive family history of diabetes and hypertension in childhood type 1 diabetes are important risk factors for cerebrovascular disease (CVD).[24,25]

Even though the majority (60%) of our subjects had a normal BMI, a positive and significant correlation was found between CIMT and BMI, but no correlation was found between CIMT and serum lipids. This may suggest that the rate of progression of atherosclerosis may be determined by risk factors such as BMI which is also implicated in adult coronary heart disease.[22] Reduction in BMI has been shown to slow the yearly rate of increase in CIMT in adults,[26] and maintenance of a normal BMI in paediatric type 1 diabetes may therefore be beneficial. In support of this finding, Järvisalo et al[27] suggested that the diffusely increased CIMT in paediatric type 1 diabetes reflects intimal changes related to early atherogenesis. Rodriguez et al[8] in Mexico documented no correlation between CIMT and BMI in their study, while Abdelghaffar et al[28] in Egypt also found no correlation between CIMT and serum lipids, in agreement with this study.

Autopsy studies have shown that atherosclerosis begins in childhood and is accelerated in the presence of risk factors such as raised total and low density lipoprotein (LDL) cholesterol levels.[19] Thus, an increase in CIMT has been reported in children with familial hypercholesterolemia.[29] We found no plaques in our patients' carotid arteries, which may not be surprising as the study population was less than 20 years of age, and plaques are uncommon below this age.30 However, histological atherosclerotic vascular changes in the form of fatty streaks may be found in the walls of the arteries even below the age of two years.[30]

We have confirmed the feasibility of measuring CIMT in paediatric patients with type 1 diabetes using ultrasound. In our clinical practice, CIMT is not yet routinely measured in children, but it has been found to be a suitable surrogate end point in clinical studies and correlates well with cardiovascular risk factors and coronary atherosclerosis.[22] Routine CIMT measurement at presentation with annual follow-up may in future be included as part of the management of paediatric type 1 diabetes in order to identify patients who may be at risk of future cardiovascular disease. Long-term prospective studies are needed to evaluate the progression of CIMT and vascular changes in relation to duration of diabetes, glycaemic control, and progression through the stages of puberty into adulthood.

Author declaration

Competing interests: none.

Any ethical issues involving humans or animals: none.

Was informed consent required: yes - documentation on file.

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