

Carotid Duplex Study in Correlation with High Sensitivity C-Reactive Protein and Lipid Profile in Children with Type-1 Diabetes Mellitus

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Abstract

Background: Chronic diabetic hyperglycemia is well known to be associated with long-term damage of various organs, including heart and blood vessels. Even if manifestation is seen in the adult diabetic patient, the process of vascular changes starts much earlier in childhood. Carotid Intima-Media Thickness (CIMT), a pre-atherosclerosis marker, and its relation to different risk factors in Diabetic children is not fully investigated.

Aim of the work: To evaluate serum hs-CRP levels in type-I diabetic T1DM children and its relation with CIMT.

Methods: This study included group I: 60 T1DM children and group II: 40 apparently healthy age, sex and BMI matched control. Both were subjected to; full history taking, thorough clinical examination (BP, anthropometry, lab studies, including oral glucose tolerance test, Lipid Profile (serum cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglyceride), high sensitive CRP (HS-CRP) and 24 h microalbuminuria). Carotid duplex study B-mode and color-coded duplex sonography of extra cranial carotid.

Results: The CIMT of both RCCA and LCCA in diabetic children was significantly increased. CIMT positively correlated with age, duration of diabetes, BMI, DBP, LDL, TG, HbA1c, as well as daily insulin dose and negatively with HDL. On the other hand, there were insignificant correlations with other risk factors.

Conclusion: Regular monitoring of the high-risk children may help to identify the development and progression of atherosclerotic changes and cardiovascular disease.

Keywords: High sensitive C-reactive protein (hs-CRP); Carotid intima-media thickness (CIMT); Type-1 Diabetes Mellitus (T1DM); Cholesterol; High density lipoprotein cholesterol (HDL); Triglycerides

Background

T1DM is an autoimmune disease that causes destruction of Beta cells of the pancreas leading to a dangerous state of hyperglycemia. Chronic diabetic hyperglycemia is well known to be associated with long-term damage, of various organs, including heart and blood vessels. It is considered a strong risk factor for atherosclerotic vascular disease.

Even though macrovascular disease is not seen in T1DM in the childhood or adolescent years, risk factors that predispose to it are frequently present earlier, and adolescents and their families should be aware of these [1].

Increased aortic and carotid intima-media thickness (CIMT) has been detected by ultrasensitive ultrasound in adolescents with type-1 diabetes [2].

However CIMT, a pre-atherosclerosis marker, and its relation to different risk factors in Diabetic children are not fully investigated.

Aim of the Work

The aim of this study was to evaluate serum HS-CRP levels in T1D children and its relation with carotid atherosclerotic changes.

Methods

This study included 50 children and adolescents who were classified into 2 groups; Group I: 30 patients who were diagnosed as diabetic patients, according to ADA criteria [3] and had regular follow up at the Diabetes outpatient clinic, Minia university children's hospital, Egypt; and 20 apparently healthy, age, sex, and BMI matched control group, classified as Group II. They were collected in the period between March 2015 and October 2015.

The inclusion criteria of patients' group: age ranged from 9 to 16 yrs, diabetes duration >1 yr, normotensive, non-smoker, no chronic diseases other than type-1 diabetes, and none of the children were taking regular medications other than daily insulin. The exclusion criteria: diabetes less than 1 yr duration, diabetics with other chronic diseases, obese children (body mass index-for-age >95th percentile), children with physical challenges that may limit the results of carotid US examination such as: short muscular neck, high carotid bifurcation, tortuous vessels, calcified shadowing plaques, tracheostomy tubes,

surgical sutures, postoperative hematoma or bandages, central lines, inability to lie flat in respiratory or cardiac disease or to rotate the head in patients with arthritis and uncooperative patients.

All the studied subjects were subjected to the following: thorough history taking, clinical examination and laboratory investigations. Clinical examination include anthropometric measurements by using a scale and a wall-mounted stadiometer to the nearest 0.5 Kg and 1.0 cm, respectively, BMI was calculated as weight (in kilograms) divided by the square of the height in meters, blood pressure's measurement by using a standard mercury sphygmomanometer and appropriate size cuff on both arms, twice at 2 min intervals, after resting for 5 min; and proper systematic examination: including neurological, cardiac, chest and abdominal examination.

Laboratory work-up was done with the assessment of fasting blood glucose (FBG) and 2 h post-prandial (2 hpp), and glycosylated hemoglobin (HbA1c) using Noycard reader-Oslo Norway column chromatography. HbA1c reflects levels of glycaemia over the preceding 4-12 weeks (ADA, 2011a). Lipid Profile including: serum total cholesterol, high density lipoprotein cholesterol (HDL) and triglyceride concentrations were measured using standard enzymatic methods. Low density lipoprotein cholesterol (LDL) concentration was calculated using Friedewald's equation. High sensitivity (Hs-CRP) using hs-CRP ELISA Kits supplied by IBL international GMBC, using HUMA READER plus Model: 3700, Germany normal hs-CRP references range in pediatrics is 0.8-2.5 mg/l and 5-24 h microalbuminuria was done for children with diabetes duration 5 yrs or more. Finally, a carotid duplex study was done for all patients and controls by using B-mode and color-coded duplex Sonography of extracranial carotid and vertebral arteries.

Carotid Duplex Study

Finally, a carotid duplex study was done for all patients and controls by using B-mode and color-coded duplex Sonography of extracranial carotid and vertebral arteries.

Apparatus and examiner

All studies were performed using a LOGIC 5 PRO and a 12.0 MHz linear array transducer. All ultrasound scans were performed by an experienced vascular operator who was unaware of children's clinical details.

The patient lies supine with his neck exposed, the neck is extended and the head is slightly rotated away from the examiner so as to make the vessel more perpendicular to the transducer.

B-mode scan

Scanning was done through anterior, lateral and posterior approaches till we had good images of all vessels. We tried to demonstrate the bulb, ICA, ECA in one view; however, it was difficult in many patients. Differentiation of both internal and external carotid was then done. The internal is larger, with no neck branches, usually more posterior and has an ampullary region of mild dilatation of its origin. The vessels were evaluated meticulously for the presence of subintimal lucency, atherosclerotic plaques that bulge into the lumen, and measuring the intima plus media thickness (IMT).

IMT was measured in 1 cm segment proximal to the dilation of the carotid bulb, referred as CCA, and always in plaque-free segments. For each subject, three measurements on both sides were performed, on

the anterior, lateral, and posterior projection of the far wall. Values for the different projections and for right and left arteries were then averaged.

All scans were digitally stored on the ultrasound system internal hard disk for subsequent off-line analysis. Two end-diastolic frames were selected and analyzed for mean IMT, and the average reading from these two frames was calculated for both right and left carotid arteries.

Statistical methods

All data were recorded, reviewed and subjected to statistical analysis and the work was done by the help of the Statistical Unit of the General health and Community Department of Minia University. All statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 11. 0.1. Results are expressed as mean $\pm$ SD. Comparisons between the groups were conducted by Student's t test. Univariate associations between the study variables were analyzed by calculating the Pearson's correlation coefficients. Multivariate analyses were done using linear regression techniques.

Result

As regard to the risk factors included in this study are classified as follows:

Relative risk factors

As sex, age, duration, BMI, daily insulin dose, Systolic blood pressure, Diastolic blood pressure; there were insignificant differences between group I and group II regarding age ($P=0.29$), sex ($P=0.56$), systolic blood pressure ($P=0.853$), diastolic blood pressure ($P=0.109$), and BMI ($P=0.74$) (Figure 1).

Absolute risk factors

As hs-CRP, Total-cholesterol, LDL, HDL, TG, HbA1c, Microalbuminuria, where there were highly significant differences were found as regard hs-CRP ($P=0.001$), TG ($P=0.001$), HbA1c ($P=0.002$) and significant differences as regard total cholesterol ($P=0.026$) and LDL ($P=0.015$) between diabetic group and control group (Table 1). But there was no significant difference as regards HDL where ($P=0.232$).

Risk Factor	Diabetic group (n=30)	Control group (n=20)	P value
Sex	1.5 $\pm$ 0.5	1.5 $\pm$ 0.5	0.56
Age (years)	13.1 $\pm$ 3.2	12.05 $\pm$ 2.5	0.293NS
BMI (kg/m ²)	18.7 $\pm$ 2.80	18.5 $\pm$ 2.00	0.74
Systolic blood pressure (mmHg)	116.77 $\pm$ 5.1	112.3 $\pm$ 6.8	0.853
Diastolic blood pressure (mmHg)	76.4 $\pm$ 7.82	72.75 $\pm$ 4.4	0.109
hs-CRP	49.1 $\pm$ 36.9	1.89 $\pm$ 1.18	0.001*
Total-cholesterol (mg/dl)	155.8 $\pm$ 39.6	126 $\pm$ 37.9	0.026*
LDL (mg/dl)	105.5 $\pm$ 33.4	79.3 $\pm$ 24.4	0.015*

HDL (mg/dl)	42 ± 3.3	43.5 ± 3.8	0.232
TG (mg/dl)	91.6 ± 32.2	55.9 ± 28.8	0.001*
HbA1c (%)	7.6 ± 1.40	6.4 ± 0.40	0.002*
RCCA-IMT (CM)	0.79 ± 0.12	0.52 ± 0.007	0.0001*
LCCA-IMT (CM)	0.79 ± 0.13	0.52 ± 0.06	0.003*

Table 1: Comparison between diabetic and control as regard the studied parameters; BMI: Body mass index; HbA1c: Glycosylated hemoglobin; HDL: High density lipoproteins; Hs-CRP: High sensitivity CRP; LCCA: Left common carotid artery; LDL: Low density lipoproteins; RCCA: Right common carotid artery; TG: Triglyceride. *P-value<0.05 is significant; **P-value<0.01 is highly significant; P>0.05 insignificant; References range of hs-CRP is 0.8-2.5 mg/l.

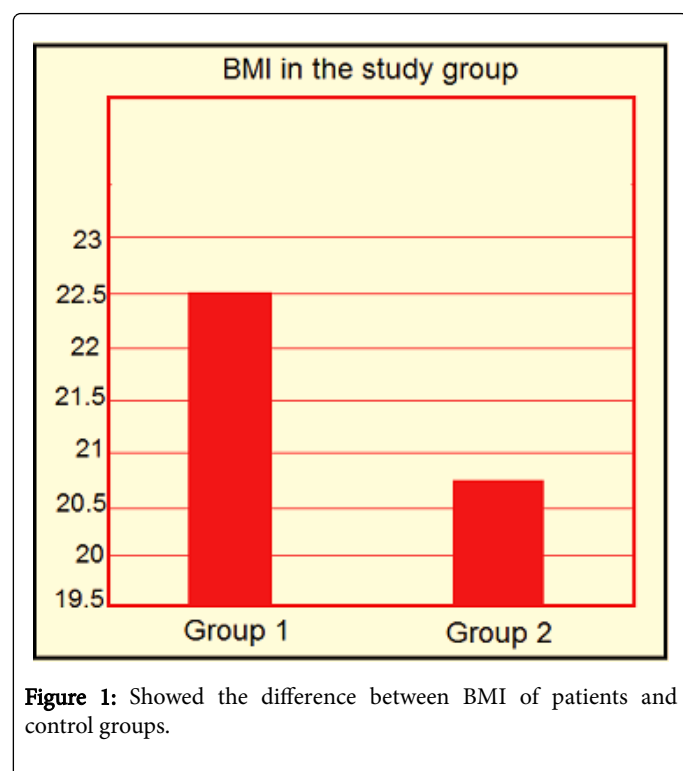


Figure 1: Showed the difference between BMI of patients and control groups.

Comparison between the two groups as regard measurement of IMT

IMT of the RCCA in diabetic children ranged from 0.5 cm to 0.9 cm with a mean value of (0.79 ± 0.12) cm, while in the control group the IMT of the same artery ranged from 0.2 cm to 0.4 cm with a mean value of (0.52 ± 0.07) cm with highly significant increase in the thickness of intima-media of the RCCA of diabetic group (P=0.001). The IMT of the LCCA in diabetic children ranged from 0.4 cm to 0.9 cm with the mean value of (0.79 ± 0.012) cm while in the control group the IMT of the same artery ranged from 0.2 cm to 0.4 cm with the mean value of (0.52 ± 0.006) cm indicating a highly significant increase in the IMT of LCCA (P=0.003) as in Table 1.

Correlations between the risk factors of T1DM and RCCA-IMT

In diabetic group, RCCA-IMT get fair correlation with the values of age (P=0.028) (R=0.33), duration of diabetes (P=0.001) (R=0.62), hs-CRP (P=0.001) (R=0.588), total cholesterol (P=0.001) (R=0.637), TG (p=0.025) (R=0.481) and LDL (P=0.017) (R=0.434), insignificant correlation were found between the CCA-IMT and the values of the Sex, BMI, SBP, DBP, HDL, Microalbuminuria and HbA1c (Figure 2). In the control group RCCA-IMT did not correlate with any of the risk factors (Table 2).

Risk Factor	Diabetic group (n=30)		Control group (n=20)			
	Mean ± SD	P	R	Mean ± SD	P	R
Sex	1.5 ± 0.5	0.969	0.08	1.5 ± 0.5	0.506	0.16
Age (years)	11.3 ± 3.10	0.028*	0.33	10.2 ± 3.3	0.209	0.01
Duration of diabetes (years)	3.9 ± 2.5	0.001*	0.62	-	-	-
BMI (kg/m²)	18.7 ± 2.80	0.058	0.14	18.5 ± 2.0	0.654	0.11
Daily insulin dose (IU/Kg/day)	1.0 ± 0.3	0.467	0.15	-	-	-
Systolic blood pressure (mmHg)	116.77 ± 0.1	0.853	0.035	112.3 ± 6.3	0.283	0.1
Diastolic blood pressure (mmHg)	76.4 ± 7.82	0.865	0.023	72.75 ± 4.4	0.207	0.2
hs-CRP (0.8 mg/dl)	49.1 ± 36.9	0.001*	0.588	2.4 ± 2.1	0.737	0.08
Total-cholesterol (mg/dl)	155.8 ± 39.6	0.001*	0.637	126 ± 37.9	0.416	-0.19
LDL (mg/dl)	105.5 ± 33.4	0.017*	0.434	79.3 ± 24.4	0.001*	-0.01
HDL (mg/dl)	42 ± 3.3	0.247	0.18	43.6 ± 3.8	0.016*	-0.01
TG (mg/dl)	91.6 ± 32.2	0.025*	0.481	55.9 ± 28.8	0.317	-0.23
HbA1c (%)	7.42 ± 1.8	0.064	0.1	5.1 ± 0.38	0.084	-0.12
Microalbuminuria® (mg/dl)	19.9 ± 5.70	0.596	0.1	-	-	-

Table 2: Correlations between the risk factors of type-1 Diabetes and RCCA-IMT; HbA1c: Glycosylated hemoglobin; HDL: High density lipoproteins; Hs-CRP: High sensitivity CRP; TG: Triglyceride; SD=Standard Deviation. *P-value <0.05 significant; **P-value <0.01 highly significant; P>0.05 insignificant.

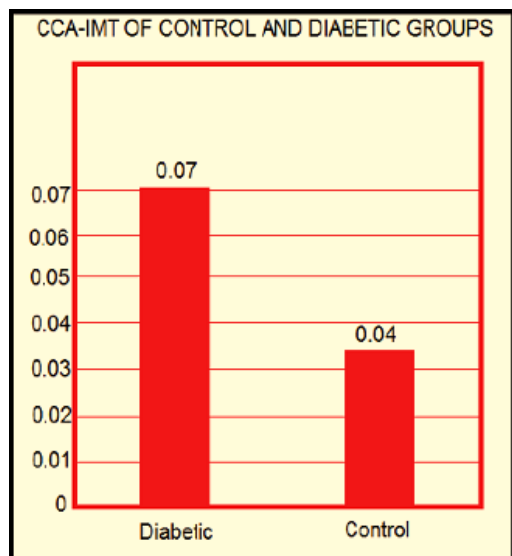


Figure 2: Showed the difference between CCA-IMT of patients and controls.

Correlations between the risk factors of T1DM and LCCA-IMT

LCCA-IMT get moderate correlation with the values of age ($P=0.001$) ($R=0.51$), duration of diabetes ($P=0.003$) ($R=0.57$), hs-CRP ($P=0.001$) ($R=0.588$) and fair correlation with BMI ($P=0.007$) ($R=0.40$), DBP ($P=0.019$) ($R=0.40$), LDL ($P=0.04$) ($R=0.30$), HbA1C ($P=0.02$) ($R=0.34$) and TG ($P=0.01$) ($R=0.38$). On the other hand, there were insignificant correlations were found between the LCCA-IMT and the values of the sex, SBP, HDL, total cholesterol and microalbuminuria (Figures 3-5) while in the control group LCCA-IMT get moderate correlation with age ($P=0.001$) ($R=0.73$), BMI ($P=0.006$) ($R=0.59$), while there were insignificant correlations regarding the other risk factors (Table 3).

Risk Factor	Diabetic group			Control group		
	Mean $\pm$ SD	P	R	Mean $\pm$ SD	P	R
Sex	1.5 $\pm$ 0.5	0.902	0.003	1.5 $\pm$ 0.5	0.535	0.4
Age (years)	11.3 $\pm$ 3.10	0.001*	0.51	10.2 $\pm$ 3.3	0.001*	0.73
Duration of diabetes (years)	3.9 $\pm$ 2.5	0.003*	0.57	-	-	-
BMI (kg/m ²)	18.7 $\pm$ 2.80	0.007*	0.40	18.5 $\pm$ 2.0	0.006*	0.59
Daily insulin dose (I.U/Kg/day)	1.0 $\pm$ 0.3	0.052	0.39	-	-	-
Systolic blood pressure (mmHg)	100.4 $\pm$ 16.70	0.248	0.18	99.7 $\pm$ 10.5	0.114	0.36
Diastolic blood pressure (mmHg)	65.6 $\pm$ 10.70	0.019*	0.40	63.2 $\pm$ 10.2	0.066	0.41

hs-CRP (mg/dl)	(0.8) 49.1 $\pm$ 36.9	0.001*	0.588	0.60 $\pm$ 0.35	0.799	0.06
Total-cholesterol (mg/dl)	210.3 $\pm$ 36.20	0.065	0.27	156 $\pm$ 16.6	0.214	-0.29
LDL (mg/dl)	105.3 $\pm$ 36.2	0.040*	0.30	94.2 $\pm$ 16.9	0.560	-0.14
HDL (mg/dl)	46.4 $\pm$ 11.8	0.062	-0.28	50.7	0.134	-0.34
TG (mg/dl)	94.7 $\pm$ 33.6	0.010*	0.38	78.9 $\pm$ 5.90	0.085	0.39
HbA1c (%)	7.6 $\pm$ 1.40	0.023*	0.34	6.4 $\pm$ 0.40	0.860	0.04
Microalbuminuria (mg/dl)	19.9 $\pm$ 5.70	0.052	0.62	-	-	-

Table 3: Correlations between the risk factors of Type-1 diabetes and LCCA-IMT; HbA1c: Glycosylated hemoglobin; HDL: High density lipoproteins; Hs-CRP: High sensitivity CRP; TG: Triglyceride. *P-value<0.05 is significant; **P-value<0.01 is highly significant; P>0.05 is insignificant.

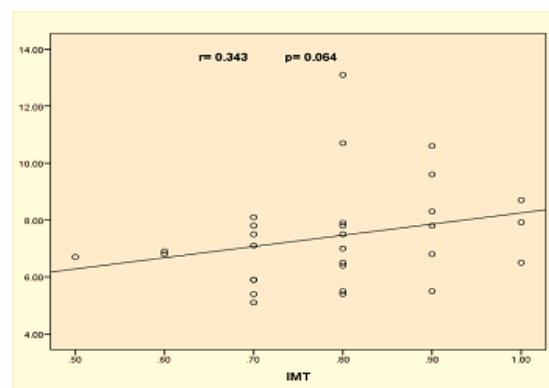


Figure 3: Showed the correlation HbA1c and LCCA-IMT.

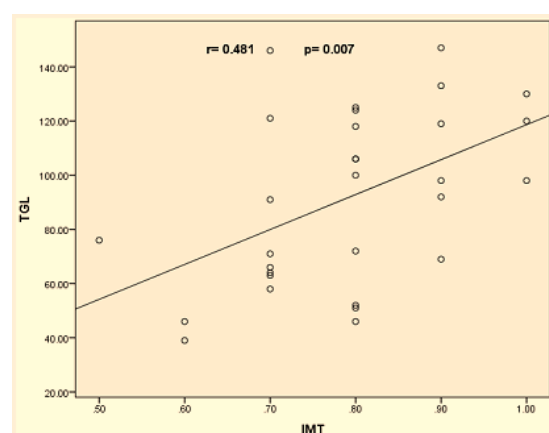
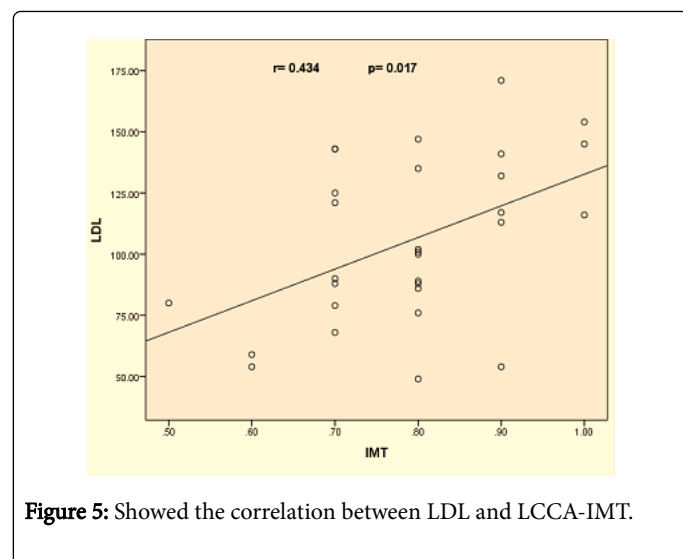


Figure 4: Showed the correlation between TGL and LCCA-IMT.



Multiple regression analysis of risk factors affecting RCCA-IMT and LCCA-IMT among all the studied diabetic children

It showed that the duration of diabetes was the only most important and statistically significant factor that affects the RCCA-IMT, ($\beta=0.997$) ($P=0.020$). The other risk factors were insignificant (Table 4), while that of LCCA-IMT: the duration of diabetes ($\beta=1.287$) ($P=0.001$) and the DBP ($\beta=0.539$) ($P=0.042$) were the most important and statistically significant factors affecting the LCCA-IMT, while the other risk factors were statistically insignificant (Table 4).

Risk Factor	RCCA-IMT		LCCA-IMT	
	β	P	B	P
Duration of diabetes (year)	0.997	0.020*	1.287	0.001**
Diastolic blood pressure (mmHg)	0.368	0.277	0.539	0.042*

Table 4: Multiple regression analysis of significant risk factors affecting RCCA-IMT and LCCA-IMT among the studied diabetic children; *P-value<0.05 is significant; **P-value<0.01 is highly significant; P>0.05 is insignificant.

Multiple regression analysis of risk factors affecting IMT among the diabetic children with increased IMT

Showed that the daily insulin dose was the only most important and significant factor that affects the RCCA-IMT ($\beta=0.511$) ($P=0.044$). Whereas, the total cholesterol ($\beta=6.345$) ($P=0.031$) and the HDL ($\beta=-2.445$) ($P=0.019$) are the significant factors affecting LCCA-IMT (Table 5).

Risk Factor	RCCA-IMT		LCCA-IMT	
	β	P	B	P
Total-cholesterol (mg/dl)	3.283	0.416	6.345	0.031*
HDL (mg/dl)	-2.058	0.182	-2.445	0.019*

Daily insulin dose (IU/Kg/day)	0.511	0.044*	0.729	0.066
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Table 5: Multiple regression analysis of significant risk factors affecting RCCA-IMT and LCCA-IMT among the diabetic children with increased IMT; HDL: High density lipoprotein. *P-value<0.05 is significant; **P-value<0.01 is highly significant; P>0.05 is insignificant.

Multiple regression analysis of significant risk factors affecting RCCA-IMT and LCCA-IMT among the diabetic children with microalbuminuria

It showed 24 h microalbuminuria was a significant factor affecting the LCCA-IMT ($\beta=0.839$) ($P=0.040$) but not a significant factor for the RCCA-IMT ($\beta=0.259$) ($P=0.580$) as shown in Table 6.

Risk Factor	RCCA-IMT		LCCA-IMT	
	B	P	β	P
Microalbuminuria (mg/dl)	0.259	0.580	0.839	0.040*

Table 6: Multiple regression analysis of significant risk factors affecting RCCA-IMT and LCCA-IMT among the diabetic children studied for microalbuminuria. *P-value<0.05 is significant; **P-value<0.01 is highly significant; P>0.05 is insignificant.

Discussion

As a valuable guide for detection of early stages of atherosclerosis, and as an index of progression of atherosclerotic lesions and its correlation with traditional risk factors, ultrasonographic evaluation of CIMT was conducted in 2 groups of subjects: sixty diabetic children with type-1 diabetes and forty healthy children, age, sex and BMI matched as a control group.

We found that CIMT of both right and left common carotid arteries are significantly increased in children with type-1 diabetes compared with normal, non-diabetic children (Table 1), which may indicate early vascular structural atherosclerotic changes of the carotid arteries in patients with type-1 diabetes in this group compared to healthy controls.

In our study, a direct correlation was found between IMT and risk factors for cardiovascular disease including: age, duration of diabetes, DBP, hs-CRP, HbA1c, LDL, BMI (Tables 2 and 3) and mean daily insulin dosage (Table 5).

The present study revealed that there was significant elevation of hs-CRP levels in type-1 diabetic children at an early age. C-reactive protein is known as a marker of low grade inflammation, which characterizes an atherosclerotic process in its early stages. Another study supporting the positive relation between CRP and cardiovascular diseases obtained by Cao et al. [4] who found that elevated CRP was associated with increased risk for CVD and all-cause mortality only in those with detectable atherosclerosis based on carotid ultrasound.

In contrary to our results, other studies had been unable to demonstrate this relation where Lorenz et al. [5] stated that hs-CRP is not an independent casual factor for the initiation and progression of early atherosclerotic changes of carotid arteries, this association was not significant after controlling age, gender and cardiovascular risk factors.

Our results coincide with the results obtained by Tołwińska et al. [6] and Abd elghafar et al. [7] who stated that children with type-1 diabetes have mean IMT values greater than non-diabetic children and CIMT was found to be positively correlate with age, BMI, duration of diabetes, SBP, DBP, hs-CRP as well as HbA1c and correlates negatively with HDL-cholesterol, and considered CIMT as a useful marker for early diagnosis of subclinical atherosclerosis in diabetic children.

Another study supporting the positive relation between IMT and atherosclerosis was the result obtained by Distiller et al. [8], who found that the major factors influencing the CIMT in patients with long surviving type-1 diabetes were the age, duration of diabetes, HS-HS-CRP, existing hypertension and HDL (protective).

Daminiano et al. [9] established a strong correlation between CIMT measured by B-mode as a simple reading technique and possible risk factors in patients at high risk of vascular disease.

Chan et al. [10] revealed that the CIMT is a useful surrogate marker for cardiovascular risk and correlates better than the flow-mediated vasodilatation of the brachial artery. This was supported by the results of Kazuo et al. [11] who reported that CIMT evaluated by B-mode ultrasonography independently predicts vascular events in high risk children with type-1 diabetes and was of value for clinical stratification of patients at high risk of vascular events.

Reduced production of nitric oxide by endothelial cell due to the effect of diabetes mellitus itself impairs endothelial function [12]. Endothelial dysfunction has been found to be well correlated with the HbA1c level that reflects the metabolic control of the disease [13].

Nevertheless, some other studies disagreed with our results and didn't find early atherosclerotic changes in the 1st few years of the disease or alteration of the cardiac mass or function [14].

Also Parikh et al. [15] stated that the earliest changes in macrovascular function may precede abnormalities in cardiac function or in arterial IMT in adolescents with short duration T1DM and also supports a relationship between hyperglycemia and carotid artery dysfunction. This may be explained in the way that the atherosclerotic arterial anatomical changes need a longer duration to be detected than the physiological dysfunction of the arteries.

In the present study, we found that the Diastolic blood pressure was an independent predictor of IMT in diabetic patients (Table 4). Jonathan et al. [16] supported the relation between blood pressure and IMT as a marker of early arterial wall changes for predicting other cardiovascular sequelae in hypertensive children.

Moreover, Yang et al. [17] found DPB to be a risk factor in pre-clinical atherosclerosis with no statistically differences found between left and right carotid arteries. This relationship between increased IMT and blood pressure suggests that smooth muscle proliferation also plays a role in the early diffuse thickening of the arterial wall. In the present study, diabetic children with increased IMT had higher LDL cholesterol concentration than controls (Tables 1-3). This might be explained in the way that excess body fat in childhood may potentiate early atherosclerosis through its adverse effect on atherogenic mediators such as hyperinsulinemia, insulin resistance and proinflammatory cytokines.

These results are consistent partly with the results obtained by Mikko et al. [18] who found the LDL and blood pressure together with the diabetic state are independent predictors of IMT in diabetic children.

These also were obtained by Shengxu et al. [19] who concluded that the LDL and BMI measured either in childhood or adulthood are significant childhood predictors of carotid IMT and coronary events, and stated that among childhood lipoprotein variables, LDL level was the most predictive of adulthood dyslipidemia, with prevalence more among those individuals who had higher BMI in childhood.

Patricia et al. [20] stated that carotid IMT in young and middle-aged adults correlates with LDL-cholesterol in both sexes, HDL-cholesterol and DBP in males, and triglycerides and BMI in females and added that risk factors measured as early as ages 8 to 11 are predictive of adult carotid IMT. This was also supported by Robert et al. [21] who found the age of onset of diabetes, mean daily insulin dose, SBP and the total cholesterol were significantly related to IMT.

Toikka et al. proposed that the modified LDL particles either by oxidation or glycation are the ones to be accused as possible causal agents in arterial dysfunction, increased CIMT, decreased arterial elasticity, different degree of acute coronary syndromes severity [22].

Ehara et al. assured the previous findings of Toikka et al. and considered that the modification of the native LDL particles is important for the development of atherosclerosis [23].

Therefore, these data support the idea that oxidative modification of LDL may have a role in the development of early structural atherosclerotic vascular changes in children with diabetes and the most recent studies found that glycemic control and lipid levels are independently associated with type-1 and type-2 diabetes [24]. In the present study HbA1c (Table 3) and daily insulin dose (Table 5) was found to be independent predictors of left and right carotid-IMT. These results were consistent with the results of the Diabetes Control and Complication Trial (DCCT) [1] which revealed that after six years of follow up of diabetic children, IMT was greater in diabetics and the progression of the IMT was less with intense therapy and correlates with age, SBP, LDL and HbA1c. The accelerated development of atherosclerosis in diabetics may be due to the gradual accumulation of advanced glycosylation end products.

A study done by Larsen et al. [25] supported the important role of long term hyperglycemia in the development of atherosclerosis, especially in women with type-1 diabetes and found HbA1c as a good predictor of CIMT.

The strongest evidence of the relation of type-1 diabetes and cardiovascular complications comes from the Diabetes Control and Complication Trial (DCCT) [26] which concluded that the intensive glycemic therapy reduce the risk of cardiovascular events by 42%.

This was also supported by Dirk et al. [27] who demonstrated a positive relation between increasing levels of HbA1c and CIMT and explained the progression of thickness by the combination of hyperglycemia and inflammation.

Regarding the site of beginning of the atherosclerotic changes, in contrary to our results, Mikko et al. [28] concluded that aortic IMT provides a better marker for atherosclerosis than CIMT as he found that the atherosclerosis begins first in the intima of the aorta but agrees with us in that the CIMT is still a good marker for atherosclerosis in high risk children.

In the present study, we failed to find a significant correlation between CIMT and microalbuminuria in patients with diabetic microangiopathic complications presented by microalbuminuria. However, this subgroup was very small. We explained the presence of

microalbuminuria in some patients due to the inclusion criteria in our study for patients with diabetes duration more than 5 yrs.

In contrary, Ana et al. [29] supported the association of endothelial dysfunction and type-1 diabetes and found the microalbuminuria excretion as a very early marker of vascular disease in type-1 diabetes even before 5 yrs duration of diabetes.

In our study, we found that increased carotid IMT was on the right and left common carotid arteries (Table 1) meaning that the preclinical atherosclerosis may be similar on both sides. This result was consistent with Gareth et al. [30] who stated that atherosclerosis of human carotid arteries is bilateral and symmetrical and that plaque calcification was found in both left and right human carotid arteries. This suggests that the diagnostic information about results.

The characteristics of some study populations were not comparable to that of our patients, so the results are not easily comparable.

Limitations

Atherosclerosis in one carotid can be used for inflammation of the contralateral artery.

Arbel et al. [31] found no differences in intimal medial thickness between left and right carotid arteries in the young and concluded that the possibility of increased thickness on the left than the right IMT in older patients may be due to mechanical stress forces which take a relatively long time to enhance the LCCA-IMT and become evident.

In contrast, Sergio et al. [32] reported higher thickness on the left side and explained this difference of increased IMT on the left side due to greater intimal hyperplasia or more extensive medial hypertrophy as a sequel of increased hemodynamic stress on the left side, which could be related to the specific anatomy of the carotid vessels. Whereas the right common carotid artery arises from the brachiocephalic trunk (generally at a right angle to the flow of the innominate artery), the left one stems directly from the aortic arch and runs more in an even line with the ascending aorta. Energy transfer from systolic emptying forces may be greater in the left carotid than in the right one, where part of the flow vector energy will be reduced by the innominate artery. But there is no sufficient evidence that this explanation works on diabetic normotensive patients.

As long as, studies have been finding increased CIMT in diabetic children, still others can't catch this finding.

Different study techniques were used for CIMT detection ranging from manual tracing, high resolution ultrasound systems with ultrasound probes up to 12 MHz, whereas others used a computed automatic contour analyzing software. Within all of these investigations, healthy controls varied significantly.

Study of fate of atherosclerotic vascular changes in diabetic children needs high technical tools and properly expert staffs to obtain trustworthy facts.

However, we tried to select our patients' group to be representative of all diabetic children treated in our hospital as regards to age, duration of T1DM, glycemic control, and levels of serum lipids.

Conclusions

We concluded that CIMT is increased in children with T1DM compared to normal non-diabetic children. CIMT positively correlates

with age, duration of T1DM, BMI, DBP, LDL, TG, Hs-CRP, HbA1c, as well as daily insulin dose and correlates negatively with HDL.

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Authors' Contributions

AM, MA, gives us the idea and suggest the plan of the work. AM, planned the study, AM, MA, LH conducted the study, AM and LH did analysis data and wrote the paper. AM and LH is the one responsible for final content. All authors have read and approved the final manuscript.

Consent for Publication

Informed consent from the patients' caregivers is available.

Ethics Approval and Consent to Participate

The study was carried out according to the principles of declarations of Helsinki, and its appendices [33] and was approved the hospital ethical review board in El Minia university hospital (code 75a, March, 2015). Written informed consents from patients' caregivers were obtained for the use of their study-related information and for participation in the ongoing research.

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