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Original Article

Paediatrics Section

Association between Vascular Endothelial Markers and Carotid Intima-Media Thickness in Children and Adolescents with Type 1 Diabetes Mellitus

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ABSTRACT

Introduction: Type 1 Diabetes Mellitus (T1DM) is one of the important risk factor for cardiovascular disease. Endothelial dysfunction and increased Carotid Intima-Media Thickness (CIMT) result in cardiovascular complications. Vascular Cell Adhesion Molecule-1 (VCAM-1) and Intercellular Adhesion Molecule-1 (ICAM-1) are two adhesion molecules that are markers of early atherosclerosis and play a significant role in developing atherosclerosis.

Aim: To evaluate CIMT and its association with the levels of ICAM-1 and VCAM-1 in children and adolescents with T1DM.

Materials and Methods: In this descriptive, cross-sectional study conducted between April 2013 and September 2014, 29 children aged 7-20 years with T1DM for at least two years and 29 age and sex-matched, healthy individuals were evaluated. Plasma level of ICAM-1 and VCAM-1 was measured by ELISA, and CIMT via Doppler ultrasound was also assessed. The data were analysed by t-test and Pearson's correlation coefficient in SPSS 16.0 ($p \leq 0.05$).

Results: Independent t-test indicated that there is a significant difference in ICAM-1 level between the patients and controls ($p<0.001$). Further, CIMT was significantly higher in diabetic subject ($p<0.001$). CIMT was not significantly associated with the level of VCAM-1 and ICAM-1 in the patients ($p>0.5$).

Conclusion: ICAM-1 and VCAM-1 were not associated with CIMT but, CIMT and level of ICAM-1 were significantly, higher in diabetic patients, and therefore could be used as useful tools for identification of early atherosclerosis in children and adolescents with T1DM.

Keywords: Adhesion molecules, Atherosclerosis, Endothelial dysfunction

INTRODUCTION

T1DM is a chronic and heterogeneous disease caused by autoimmune destruction of pancreatic beta cells and hence, 'leading to' insulin deficiency. T1DM is diagnosed more commonly in children and adolescents [1]. Ninety percent of children with diabetes have T1DM. Less than half of the diagnoses, with diabetes are made in people under 15 years [2-4].

A variety of mutual interactions between environmental, genetic, and biological factors contribute to the pathogenesis of diabetic vascular complications [5]. Vascular complications in T1DM may be macrovascular and microvascular. Macrovascular diseases consist of coronary heart disease, carotid artery disease, peripheral vascular disease, and cerebral vessel disease that involve large arteries [6,7]. Macrovascular complications are the main reason for death in people with diabetes [7].

Atherosclerosis due to T1DM is a significant reason for mortality and morbidity [8]. Vascular variation begin much eariler than manifestation of vascular complications in young people with diabetes [9].

In several studies, subclinical atherosclerosis has been reported in children with diabetes as an introduction to macrovascular complications [10,11].

Cardiovascular complications increase in prevalence at puberty. Puberty causes reduction in insulin sensitivity. Cardiovascular complications increase at puberty because of declined insulin sensitivity [12].

Atherosclerosis is initiated by vascular infiltration with lymphocytes and monocytes, which is affected by adhesion molecules [13]. Adhesion molecules are released by damaged endothelial cells and cause inflammatory cells to enter into arterial wall [14]. Adhesion molecules consist of VCAM-1 and ICAM-1 that are known as the markers of early atherosclerosis [15].

VCAM-1 and ICAM-1 solutions are isolated from active endothelium and could be measured in peripheral blood [16]. Different studies have obtained widely inconsistent findings on the variations in serum levels of VCAM-1 and ICAM-1, and the severity of coronary artery disease, such that some studies have reported that these molecules are independent risk factors for coronary artery disease, and some others have reported no relationship [15-18]. The expression of VCAM-1 and ICAM-1 tends to be higher in children than adults [13].

Increased CIMT is a symptom of atherosclerosis and is considered the most obvious subclinical variation [19].

A study on a large population of children with diabetes indicated that subclinical atherosclerosis could be assessed by CIMT [11]. A study on 314 children with T1DM reported a two to three-fold increase in CIMT in patients compared with controls despite short duration of diabetes and appropriate control of blood sugar, with no microvascular complications [20].

Atherosclerosis 'progression' and the resultant cardiovascular complications are developed more rapidly in children and adolescents than adults. Given that increase in CIMT and endothelial dysfunction are associated with higher cardiovascular morbidity in T1DM patients, it is necessary to study strategies of early diagnosis of vascular complications at younger ages and to detect effective factors on their incidence. Endothelial markers have been investigated mainly in adults, rather than children and adolescents, with diabetes and inconsistent findings have been reported.

Few studies have been conducted on children, with inconsistent findings. Therefore, the present study was conducted to compare

the CIMT and the level of ICAM-1 and VCAM-1 markers between the children with T1DM and controls, and to investigate the association between these vascular endothelial markers and CIMT. Because of high mortality rate of cardiovascular disease and hospital stay [21], it is possible to investigate the effective factors on development of diabetes complications and the strategies to treat it at early stages. Further, this study investigated the association of serum lipids, duration of diabetes, and HbA1C level with ICAM-1 and VCAM-1 levels and CIMT.

MATERIALS AND METHODS

This descriptive-analytical study was conducted between April 2013 and September 2014, 30 children and adolescents aged 7 to 20 years with diabetes for at least two years referring a university-affiliated endocrinology clinic in Shahrekord, Southwest Iran were enrolled to the case group. The sample size was determined by relevant formula with confidence interval 95% and test power 90%. The individuals having Fasting Blood Sugar (FBS) was ≥126 mg/dL or random blood sugar ≥ 200 mg/dL with accompanying clinical symptoms and/or Blood Sugar (BS) ≥ 200 mg/dL two hours after glucose tolerance test, were diagnosed as diabetics [22].

In addition, 30 age and gender-matched people without any chronic diseases and history of taking medications causing cardiovascular complications were selected, but only 29 cases in each group completed the study. One patient in each group was not refered for laboratory tests. This study was approved by the Research Ethical Committee of Shahrekord University of Medical Sciences with number 20-7-92. Informed consent was obtained from the parents of the participants in both groups.

Inclusion criteriton was 7-20-year-old children and adolescents with T1DM lasted at least two years.

In the case group, the people with diabetic nephropathy, retinopathy, or neuropathy and family history of coronary artery disease, hypertension, and smoking, were excluded.

After drawing a detailed description of the participants, we gathered the necessary data regarding age, gender, duration of diabetes, daily insulin dose, and the dosage of medications and the method of their administration. Then, the blood pressure, height, weight, and BMI of all the patients were measured. Kliegman RM et al., a paediatric endocrinologist determined the puberty stage of the participants by Marshall and Tanner stages [23].

Then, serum samples were taken after an overnight, 12-hour fasting for measurement of FBS, triglyceride, cholesterol, HDL, LDL, HbA1C, ICAM-1, and VCAM-1. FBS was measured by enzymatic, colorimetric analysis as single point by photometric method at 546 nm wavelength using GOD kit (Pars Azmon,Iran,Tehran). TG was measured by GPO-RAP kit, cholesterol by CHOD kit (Pars Azmon,Iran,Tehran) and HDL and LDL were evaluated photo metrically with no need for calculation and centrifugation.

All the used kits (Pars Azmoon, Iran) measured the variables of interest quantitatively. HbA1C level was directly measured by enhanced immunoturbidimetry using latex without measurement of total haemoglobin. HbA1C is glycosylated haemoglobin which is formed by glucose bonding to haemoglobin in a non-enzymatic reaction. The rate of glycosylation is directly proportionate to glycaemia concentration.

HbA1C test is done to represent glycaemia as percentage in the past three months. The levels of vascular endothelial markers, ICAM-1 and VCAM-1, were measured by ELISA (BT Laboratory kit, China).

CIMT was measured by a radiologist at supine position using Doppler ultrasound (G-50, Siemens, Germany) and linear probing (5-10 MHz) from the middle one-third of the common carotid. The radiologist was blind to the grouping of the subjects.

Ultrasound is a reliable and non-invasive method to detect structural changes and function of atherosclerosis and can predict cardiovascular disease [19]. Carotid ultrasound was performed to examine common carotid artery from the lowest point of the neck till above submandibular or distal internal carotid artery at the uppermost point of the neck. In addition to examining CIMT, carotid ultrasound was able to detect stenosis degree in external carotid system and atherosclerotic plaque as well [24].

Demographic characteristics such as age, gender, BMI, and systolic and diastolic blood pressure and puberty stage were examined in both groups. Pearson's correlation coefficient was used to investigate the association between CIMT and the levels of ICAM-1 and VCAM-1. The levels of cholesterol, TG, HDL, LDL, and HbA1c were measured and their potential association with CIMT, VCAM-1, and ICAM-1 was investigated. Also, we evaluated the association between duration of diabetes and CIMT, VCAM-1, and ICAM-1.

STATISTICAL ANALYSIS

The data were analysed by t-test and Pearson's correlation coefficient in SPSS version 16.0.

RESULTS

Two female cases (1 diabetic and 1 control) did not complete study and finally 29 children with diabetes (14 males and 15 females) and 29 healthy children (16 males and 13 females) were studied. The two groups were age and sex-matched. Regarding age, BMI, and systolic blood pressure, no difference was drawn between the two groups, but the difference in diastolic blood pressure between the two groups was significant (p=0.002) [Table/Fig-1]. Furthermore, puberty stage was not significantly different between the two groups (p=0.64) [Table/Fig-2].

Independent t-test indicated a significant difference in CIMT between the two groups (p<0.001). At Confidence Interval (CI) 95%, VCAM-1 was not significantly different between the two groups, but at CI 90%, this difference was significant. Furthermore, the difference in ICAM-1 was significant (p<0.001) [Table/Fig-3].

To investigate the association of CIMT with the levels of ICAM-1 and VCAM-1 in the patients, Pearson's correlation coefficient was used. This test indicated no significant association between CIMT and the levels of ICAM-1 and VCAM-1 [Table/Fig-4].

Pearson's correlation coefficient was used to study the association of cholesterol, TG, HDL, LDL, HbA1C, and duration of diabetes with CIMT, ICAM-1, and VCAM-1 in the patients [Table/Fig-5]. Pearson's correlation coefficient indicated that in the patients, CIMT and ICAM-1 was not significantly associated with cholesterol, TG, HDL, and LDL and duration of diabetes, and only VCAM-1 and HbA1c

Variables	Mean±SD		p-value*
Age (year)	11.74±1.96	Case group	0.06
	10.72±2.05	Control group	
BMI (kg/m^2)	17.33±0.47	Case group	0.33
	18.07±0.58	Control group	
SBP (mmHg) Systolic blood pressure	92.41±4.69	Case group	0.64
	94.65±1.31	Control group	
DBP (mmHg) Diastolic blood pressure	58.96±1.39	Case group	0.002*
	53.62±0.92	Control group	

[Table/Fig-1]: Mean and standard deviation of age, BMI and blood pressure in study groups.
* Significant at 0.05.

Puberty stage	I	II	III	IV	V
Case	14	5	4	5	1
Control	19	5	3	1	1

[Table/Fig-2]: Frequency of pubertal stage in T1DM and control groups evaluated by Marshall Tanner staging (stage I to V) (p=0.64).

Variables	Groups (mean±SD)		p-value (Independent t tests)
	Control n=29	Case n=29	
CIMT (cm)	0.42±0.01	0.51±0.01	< 0.001
VCAM-1 (ng/ml)	8.35±0.78	10.48±0.72	0.052
ICAM-1 (ng/ml)	509.85±27.95	902.69±67.62	<0.001

[Table/Fig-3]: Comparison of mean levels of CIMT *, VCAM-1 **, and ICAM-1 *** between the two groups.
* Carotid intima-media thickness, ** vascular cell adhesion molecule-1, *** Intercellular cell adhesion molecule-1.

Variable		ICAM-1	VCAM-1
CIMT	Pearson correlation coefficient	-0.10	0.007
	p-value	0.59	0.97

[Table/Fig-4]: Association between CIMT * and the levels of ICAM-1 ** and VCAM-1 *** in diabetic patients.
*Carotid intima-media thickness, **Intercellular cell adhesion molecule-1, ***Vascular cell adhesion molecule-1.

Variables	HbA1C (%)	Cholesterol (mg/dl)	Triglyceride (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	Duration of disease (year)
CIMT Pearson correlation coefficient	-0.31	0.09	0.04	0.02	-0.09	0.04
p-value	0.11	0.63	0.81	0.90	0.64	0.81
VCAM-1 Pearson correlation coefficient	-0.42	-0.30	-0.04	-0.27	-0.06	0.07
p-value	0.03	0.13	0.84	0.18	0.75	0.71
ICAM-1 Pearson correlation coefficient	-0.29	-0.01	-0.11	-0.05	-0.14	-0.05
p-value	0.13	0.92	0.58	0.77	0.48	0.79

[Table/Fig 5]: Pearson's correlation coefficient between CIMT, VCAM-1, and ICAM-1 and studied variables in the patients.

were significantly associated (p=0.03). Furthermore, ICAM-1 had no statistically significant association with these variables.

DISCUSSION

This study compared the mean CIMT, VCAM-1, and ICAM-1 between 29 children and adolescents with T1DM and 29 healthy children. The mean CIMT was derived as 0.42±0.01 cm in the controls and 0.51±0.01 cm in the patients with a significant difference (p<0.001). Most studies have reported increased CIMT in adults. However, few studies have been conducted on children.

Study by Alizadeh A et al., on adults with type 2 diabetes in Iran demonstrated that the mean CIMT was 0.9 mm in people with diabetes and 0.6 mm in healthy people, and that common carotid artery IMT and diabetes were significantly associated, concluding that measuring common carotid artery intima media thickness by ultrasound is useful for screening people with diabetes [25], which is in agreement with the present study.

In addition, study by Margeirsdottir HD et al., confirmed increase in CIMT in children aged 8-18 years with T1DM for 5.1±3.3 years [20]. This was also consistent with the present study, and indicates that T1DM is a risk factor for increase in CIMT and atherosclerosis of children.

In this study, the mean level of ICAM-1 was drawn 902.69±67.62 ng/mL in the patients and 509.85±27.95 ng/ml in the controls with a significant difference (p<0.001), but VCAM-1 was not significantly different between the two groups despite being higher than the controls (p=0.052). The main purpose of this study was to investigate the association between CIMT and the levels of ICAM-1 and VCAM-1. Pearson's correlation coefficient indicated that CIMT was not associated with ICAM-1 and VCAM-1 levels.

Similarly, study by Glowinska B et al., on endothelial dysfunction markers found, that the ICAM-1 level was higher in 28 children aged 10.5-18 years with T1DM than control group, but no difference in VCAM-1 level was observed between the patients and the controls [13].

Głowińska OB et al., study on 76 patients with T1DM, the mean age of 15.6±2.5 years, and the mean HbA1c of 8.4±1.5% and 33 healthy children matched to the patients, determined the levels of adhesion molecules and endothelial function using Flow Mediated Dilation (FMD) of brachial artery and ultrasound. This study reported increase in ICAM-1 and E-selectin and dysfunction of brachial artery FMD [14]. In another study on young people with T1DM aged 25.8±6 years, no increase in levels of VCAM-1 and P-selectin was observed [26].

Regarding adhesion molecules in people at risk of atherosclerosis, consisting of 17 with obesity, 25 with obesity and hypertension, and 51 with T1DM, indicated that ICAM-1 level increased in all the three groups, ICAM-1 was associated with BMI and systolic blood pressure, and adhesion molecules were related to early atherosclerosis [27].

Another study found no significant association between ICAM-1 and common carotid artery IMT [28]. In a study, the levels of endothelial markers, including VCAM-1, were higher in adults with T1DM than controls, and VCAM-1 and CIMT were significantly associated, which is inconsistent with our study [29].

Therefore, different studies on the association between adhesion molecules and CIMT have reported inconsistent findings. This may be due to the fact that in most previous studies adults with type 2 diabetes and people with diabetes complications were investigated. However, difference in the methods of measuring the variables in the referenced studies could explain inconsistent results of these studies.

In this study, the two groups were approximately matched for puberty stage and no statistically significant difference was seen in this variable between the two groups.

Because of differences between adults and children, the findings on adults cannot be generalized to children. Although cardiovascular complications may be observed in adults, the process of vascular variations is very likely to start much earlier [30]. The levels of ICAM-1 and VCAM-1 are thought to contribute to initiating atherosclerosis in people with type 2 diabetes [31].

In the present study, HDL, LDL, TG, cholesterol, HbA1C, and diabetic duration of the patients were investigated. In addition, the association of these with CIMT and the levels of ICAM-1 and VCAM-1 were investigated by Pearson's correlation coefficient, and only VCAM-1 was found significantly associated with HbA1C (p=0.03). Increase in cholesterol, TG and LDL causes increased risk of cardiovascular diseases, and HDL level is inversely correlated with the risk of cardiovascular diseases. Altogether, these variables were not associated with the levels of ICAM-1 and VCAM-1, and CIMT.

Donahue RP and Orchard TJ, study on 50 children with T1DM and mean age of 12.1 years reported no association of CIMT with HDL, LDL, TG, cholesterol, and HbA1C levels as well as diabetes duration [32], which is consistent with our study. A study on 169 people with cardiovascular risk factors demonstrated no association between ICAM-1 and HDL-C (p=0.070) [33], which confirms the present study. According to Alizadeh A et al., study on 80 adult patients, hyperlipidemia was not associated with IMT [25], which confirms the present study.

However, Kota SK et al., study demonstrated that hyperlipidemia and duration of diabetes were associated with CIMT in adults with type 2 diabetes and stroke [34], which is inconsistent with

the present study probably due to stroke. Choi SW et al., study demonstrated that HbA1C was associated with carotid plaque and peripheral artery disease in adults with type 2 diabetes [35], which is in agreement with the present study.

In Rad MP et al., study on 40 patients (10.67±4.18 years) with T1DM, CIMT in diabetic patients was significantly higher that it was consistent with our study but CIMT increases in patients as the disease progresses [36].

A study on adolescents with T1DM by Fusaro MF et al., showed increased CIMT in diabetic patients and positive association with total cholesterol, LDL, duration of T1DM and systolic blood pressure. The observed association was inconsistent with our study that may be related to difference in age of patients [37].

The range of lipid profile of our patients was narrow and most of our patients had a normal lipid profile. This could be an explanation of no association with CMIT.

Hypertension, prevalently seen in T1DM patients, increases the risk of cardiovascular complications [38]. In this study, the difference in diastolic blood pressure between the patients and controls was derived significant. Control of blood pressure is the key to reducing the risk of cardiovascular complications in diabetic patients, which should not be disregarded.

LIMITATION

Limitation of the present study was relatively small sample size. HbA1c indicates the average blood glucose during 8-12 weeks and investigating the mean of HbA1c level could be more helpful.

CONCLUSION

T1DM leads to increased CIMT, damage to vascular endothelium, and expression of adhesion molecules that increase the risk of atherosclerosis and the mortality due to cardiovascular complications in these patients. The levels of VCAM-1 and ICAM-1 were increased in the patients but CIMT was not associated with the levels of the adhesion molecules, ICAM-1 and VCAM-1. Since a significant difference in VCAM-1 between the patients and the controls was not drawn at 95% CI but was drawn at 90% CI, studies with larger populations are recommended to investigate the level of VCAM-1 in the patients with diabetes.

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