Carotid intima-media thickness and its relations with the complications in patients with type 1 diabetes mellitus

Tip 1 diyabetes mellituslu hastalarda karotis intima-media kalınlığı ve komplikasyonlarla ilişkisi

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Abstract

Objective: Atherosclerosis is the major cause of the morbidity and mortality in type 1 diabetes mellitus (DM). Carotid intima-media thickness (CIMT) is the early sign of atherosclerosis and thereby, also the sign of macrovascular diseases. In this study, we aimed to evaluate the CIMT in patients with type 1 DM, and its association with diabetic microvascular complications (nephropathy-retinopathy).

Methods: One hundred and thirteen consecutive patients with type 1 DM without macrovascular disease were enrolled into this cross-sectional study. Age, gender, and body mass index matched 59 healthy subjects, were taken as the control group. Microvascular complications in diabetic patients were scanned. Ultrasonographic analysis of the carotid artery was performed with a high-resolution ultrasound scanner. Student's t, Mann Whitney U, Chi-square and Kruskal-Wallis tests, as well as multiple linear regression analysis were used for the statistical analysis.

Results: Patients with type 1 DM had significantly higher CIMT compared to control group (p<0001). The CIMT of the patients with microvascular complications (nephropathy and/or retinopathy) was significantly increased (0.70±0.11 mm) compared with the patients without complications (0.63 ± 0.09 mm) (p=0.001). The increase in CIMT in type 1 DM in multiple regression analysis was dependent on the presence of proliferative retinopathy (beta=0.037, 95%CI 0.010-0.065, p=0.008), macroalbuminuria (beta=0.043, 95%CI 0.019-0.068, p=0.001), increased urinary albumin excretion (beta=0.00003, 95%CI 0.00001-0.00005, p=0.005) and duration of diabetes (beta=0.002, 95%CI 0.001-0.003, p=0.009).

Conclusions: Increment of CIMT in type 1 diabetic patients was associated with microvascular complications, suggesting that diabetic microangiopathy is related with macroangiopathy. Therefore, there is a need for prospective studies to show the effect of increased CIMT on prognosis of type 1 DM. *(Anadolu Kardiyol Derg 2010; 10: 52-8)*

Key words: Type 1 diabetes mellitus, carotid intima-media thickness, retinopathy, nephropathy

Özet

Amaç: Ateroskleroz tip 1 diyabetes mellituslu (DM) hastalarda mortalite ve morbiditenin en önemli nedenidir. Karotis intima-media kalınlığı (KIMK) aterosklerozisin dolayısıyla da makrovasküler hastalıkların erken bir bulgusu olarak bildirilmektedir. Bu çalışmadaki amacımız, tip 1 DM'li hastaların KIMK'ını ve mikrovasküler komplikasyonlarla ilişkisini (nefropati ve retinopati) değerlendirmektir.

Yöntemler: Enine-kesitli olan bu çalışmaya, makrovasküler hastalığı olmayan 113 tip 1 DM'li hasta ardışık olarak ve yaş, cinsiyet, vücut kitle indeksi uyumlu 59 sağlıklı birey kontrol grubu olarak alındı. Diyabetik hastaların mikrovasküler komplikasyon taramaları yapıldı. Karotid arterlerin ultrasonografik değerlendirmesi yüksek rezolüsyonlu ultrasonografi ile yapıldı. İstatistiksel analizlerde Student's t, Mann Whitney U, Ki-Kare, Kruskal Wallis testleri ve çok değişkenli doğrusal regresyon analizi kullanıldı.

Bulgular: Tip 1 DM'li hastaların KIMK (0.67±0.11mm) kontrol grubundan (0.5±0.07 mm) anlamlı olarak yüksekti (p<0001). Mikrovasküler komplikasyonu (nefropati ve/veya retinopati) olan hastaların KIMK (0.70±0.11 mm)'ı olmayanlara (0.63±0.09 mm) göre anlamlı olarak artmıştı (p=0.001). Tip 1 DM'li hastalarda yapılan çok değişkenli regresyon analizinde artmış KIMK, proliferatif retinopatinin varlığı (beta=0.037, %95GA 0.010-0.065, p=0.008],

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The results of the study partly were presented as a poster presentation at the 29th Turkish Congress of Endocrinology and Metabolism Diseases, 6-10 September, 2006, Antalya, Turkey

Accepted/Kabul Tarihi: 12.09.2008

DOI:10.5152/akd.2010.012

makroalbuminuri (beta=0.043, %95GA 0.019-0.068, p=0.001), 24 saatlik idrarda albumin atılımı (beta=0.00003, %95GA 0.00001-0.00005, p=0.005) ve diyabet süresine (beta=0.002, %95GA (0.001-0.003), p=0.009) bağlı idi.
Sonuç: Tip 1 diyabetik hastalarda artmış KIMK mikrovasküler komplikasyonlar ile ilişkilidir. Bu bulgu da diyabetik mikroanjiyopati ve makroanjiyopatinin birbirleri ile bağlantılı olduğunu göstermektedir. Bununla birlikte artmış KIMK'ın prognoz üzerine etkilerinin değerlendirilmesi için prospektif çalışmalara ihtiyaç vardır. *(Anadolu Kardiyol Derg 2010; 10: 52-8)*
Anahtar kelimeler: Tip 1 diyabetes mellitus, karotid intima-media kalınlığı, retinopati, nefropati

Introduction

Diabetes mellitus (DM) type 1 is an important risk factor for the development of cardiovascular diseases (1). Carotid artery stiffness and intima-media thickness measured by ultrasonography are correlated with atherosclerosis and cardiovascular diseases in patients with type 1 diabetes (2). Patients with diabetes show a 2- to 10-fold risk for developing atherosclerotic lesions compared with the normal population. In type 1 DM, the presence of traditional cardiovascular risk factors may not entirely explain this excess cardiovascular risk (3, 4). Observations from postmortem studies have indicated that atherosclerosis in young adults is associated with prediabetic state (5). Therefore, children with type 1 DM have the risk of cardiovascular diseases that may appear later. Thus, defining factors responsible for atherosclerosis is of great importance.

The most significant changes in early subclinical period of atherosclerotic disease are endothelial dysfunction and increase in intima-media thickness observed in all arterial beds (6). A non-invasive ultrasound measurement of carotid wall intima-media thickness (CIMT) is a marker of generalized atherosclerosis that correlates with the extent of coronary artery disease in adults and predicts future cardiovascular events (7). Several groups have demonstrated that patients with type 1 DM have higher mean CIMT compared with matched control subjects. However, there are few studies regarding the relationship between diabetic microvascular complications and CIMT.

In this study, we aimed to evaluate the CIMT in patients with type 1 DM without manifest macrovascular disease and to investigate its relation with diabetic microvascular complications (diabetic nephropathy and retinopathy).

Methods

Patients

One hundred and thirteen consecutive patients with type 1 DM, 62 male and 51 female (ages between 16-46 years), who were hospitalized and treated in Ankara Numune Education and Research Hospital, Department of Endocrinology and Metabolism clinic and who visited our outpatient clinic were recruited to the study. Age, gender, and body mass index (BMI) matched 59 healthy cases, -32 male and 27 female- (ages between 15- 46 years), were taken as the control group in this cross-sectional study. Ethical committee approval was obtained. The patients and healthy control group were included into the study after consent forms were obtained from them.

The diagnosis of type 1 DM was based on the published criteria (8) with a typical clinical history of diabetic ketoacidosis and a requirement for insulin (9). Patients with coronary artery disease, cerebrovascular disease, peripheral artery disease, hypertension, and findings suggesting ischemia on electrocardiograph were excluded. Besides, the patients who were taking additional drug treatments other than insulin (such as angiotensin converting enzyme blockers, angiotensin receptor blockers, lipid lowering agents, beta-blockers and salicilates) were excluded as well. Patients were evaluated for the complications of nephropathy and retinopathy. Duration of diabetes was calculated as years by the time of the diagnosis. All patients were receiving intensive insulin therapy four times a day (short-acting in the morning, at noon and in the evening; moderate-acting at night). Total insulin doses were calculated as regular insulin. Patients who smoke were active smokers for at least three years. Heights and weights of the participants were measured and their body mass indexes (weight (kg)/ square of height (m^2) were calculated.

Laboratory parameters

Blood samples were obtained at 8 am after 12 hours of fasting. Lipid profile (total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C)) were measured with colorimetric enzymatic method (Aerost device, Abbott Diagnostics, USA). Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's formula as follows: LDL-C=TC-(HDL-C)-(TG/5). Glycosylated hemoglobin (HbA1c) was measured by immunoturbidimetric method (C8000 device, Abbott Company, USA).

Diabetic microvascular complications

Eye involvement: Fundus was examined with an ophthalmoscope by a relevant specialist. Accordingly, patients were divided into three groups as the first group without retinopathy, the second group with background retinopathy, and the third group with proliferative retinopathy.

Renal involvement: For the diagnosis of nephropathy, the patients were asked to collect urine for 24 hours after urinating first urine in the morning and not to do exercise 24 hours before and during the collecting procedure. Urinary albumin excretion (UAE) was measured with Multigent microalbumin (μAlb) turbidimetric immunoassay method (Aerost device, Abbott Diagnostics, USA). We considered <30 mg/day as normoalbuminuria, 30-300 mg/day as microalbuminuria, and >300 mg/day as macroalbuminuria (10). Microalbuminuria is defined as a total of three positive 24-hour urine collections measured at different days to confirm the diagnosis.

Measurement of carotid intima-media thickness

Ultrasonographic analysis of the carotid artery was performed with a high-resolution ultrasound scanner, General Electric LOGIC 400 (General Electric, USA) equipped with a linear array 12 MHz transducer. Patients were examined in the supine position. Each scan of the common carotid artery began just above the clavicle, and the transducer was moved cephalad through the bifurcation and along the internal carotid artery. The near and distant walls of the common carotid artery, the carotid bulb, and the internal carotid artery were scanned for the presence of atherosclerotic plaques. Three segments were identified on each side: 1.0 centimeters (cm) distal to the common carotid artery proximal to the bifurcation, the bifurcation itself and 1.0 cm proximal to the internal carotid artery. At each of the three segments, for distant walls in the left and right carotid arteries, intima-media thickness was defined as the distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface. Maximum thickness of the wall was calculated at each side (11). The reported CIMT for each subject is the average of these 10 measurements of distant walls (5 measurements from the right and 5 from the left common carotid artery). The investigator (YA) performed all the ultrasonographic examinations blinded to the knowledge of the group the subjects belonged. Intraobserver variation was found as 5%.

Statistical analysis

Data were analyzed with SPSS software version 11.5 (Chicago, IL, USA). Continuous variables were demonstrated as mean±standard deviation, and median (minimum-maximum) values. Measurement features between cases and control group were evaluated with Student's t test or Mann Whitney U test, where applicable. Chi-square test was used for the categorical comparisons. The significance of difference in CIMT between the groups of nephropathy, retinopathy, and number of complications was assessed with Kruskal-Wallis test. When the p-value from the Kruskal-Wallis test statistics was statistically significant, multiple comparison test was applied for pairwise comparisons between 2 groups (12). The linear relation between CIMT and other continuous variables was analyzed by Spearman-Correlation tests. Continuation of multiple association of CIMT with variables having significant relation in univariance correlation test was evaluated with multiple linear regression analysis. The most important variables were included in the regression model with adjustment for age and sex. Coefficient of regression and 95% confidence intervals for independent variables were calculated. Logarithmic transformations were applied for CIMT in linear regression analysis because of the data were not normally distributed. For $p<0.05$, results were considered as statistically significant.

Results

There was no statistically significant difference between patient and control groups in terms of age, gender, BMI, TC, HDL-C, and LDL-C. The smoking ratio in the patient and the control groups were 34.5% and 33.9% respectively (p=0.94). Triglyceride levels and CIMT in patients with type 1 DM were significantly higher than in the control group (p=0.02, p<0.001, respectively). Table 1 shows demographic, laboratory, and ultrasonographic data of the patients and the controls.

In the patient group, CIMT (0.71±0.14 mm) in smokers was higher than in the nonsmokers (0.64±0.08 mm) and the CIMT of the men (0.68±0.09 mm) was higher than of women (0.64±0.11 mm) (p=0.01, p=0.02, respectively). In the control group, CIMT (0.56±0.08 mm) in smokers was higher than the nonsmokers (0.51±0.05 mm) but there was no significant difference between men (0.54±0.07 mm) and women (0.51±0.05 mm) (p=0.01, p=0.07, respectively). The CIMT of the patients with diabetic microvascular complications (nephropathy and/or retinopathy) was significantly increased (0.70±0.11 mm) compared with the patients who did not have these complications (0.63±0.09 mm) (p=0.001).

In the patient group, mean HbA1c was 10.70±2.93%, whereas the duration of diabetes was 8.45±7.69 years, daily total insulin dose was 57.98±21.83 units and UAE was 222.17±501.30 mg/24 hours. Positive correlation was found between CIMT and age, duration of diabetes, number of microvascular complications and UAE in 24 hours. No statistically significant correlation was

Table 1. Demographic, laboratory and ultrasonographic data of patients and controls

Variables	Patients (Mean±SD)	Median (Min-max)	Controls (Mean±SD)	Median (Min-max)	p*
Age, years	26.6±7.6	24 (16-50)	27.5±7.1	28 (15-46)	NS
BMI, kg/m^2	22.1±3.2	22 (15.8-33.3)	22.6±3.4	22.8 (16.4-31.1)	NS
TC, mg/dl	166.6±35.4	162 (82-261)	165.2±32.8	157.5 (99-264)	NS
TG, mg/dl	110.2±65.5	94 (35-369)	89.5±50.9	76 (26-243)	0.02
HDL-C, mg/dl	44.3±11.7	42 (22-79)	47.7±12.4	45 (24-83)	NS
LDL-C, mg/dl	100.7±27.2	98 (39-162)	100.8±25.6	97 (58-176)	NS
CIMT, mm	0.67±0.11	0.65 (0.43-1.28)	0.53±0.07	0.52 (0.40-0.85)	<0.001

* Mann Whitney U test.

BMI - body mass index, CIMT - carotid intima-media thickness, F - female, HDL - C-high-density lipoprotein cholesterol, LDL - C-low-density lipoprotein cholesterol, M - male, mm-millimeter, TC - total cholesterol, TG - triglycerides, SD - standard deviation, NS - non significant (p>0.05)

determined between CIMT and HbA1c levels, daily total insulin dose, TC and LDL-C levels in patients with type 1 DM. In the control group, positive correlation was determined between CIMT and age, TC and LDL-C levels (Table 2).

Comparison of CIMT values in patients with diabetic microvascular complications is shown in Table 3. Patients were grouped, as 1-normoalbuminuria (n=66) (without nephropathy); 2-microalbuminuria (n=26); 3-macroalbuminuria (n=21) according to renal involvement and there was a statistically significant difference between the groups with regard to CIMT (p=0.002). Subgroup analysis showed, a statistically significant higher CIMT value in patients with microalbuminuria than in patients without nephropathy (p=0.041). There was also a more evident difference between patients without nephropathy and with macroalbuminuria; in terms of CIMT (p<0.001). Although CIMT in patients with microalbuminuria was lower than in patients with macroalbuminuria, this difference did not reach statistical significance (p=0.13).

According to eye involvement, patients were grouped as 1-normal findings (n=82) (without retinopathy); 2-background retinopathy (n=14); and 3-proliferative retinopathy (n=17). There was a statistically significant difference between the groups with regard to CIMT (p=0.002). In subgroup analysis we found that, CIMT values of patients with background retinopathy were higher than in the patients without retinopathy (p=0.039). Patients with proliferative retinopathy had significantly higher CIMT than patients without retinopathy (p<0.001). Comparison of CIMT in patients with background retinopathy and proliferative retinopathy showed that proliferative retinopathy was associated with higher CIMT, yet there was no statistically significant difference (p=0.32).

Patients were grouped in terms of microvascular complications, respectively, as 1-without microvascular complications (n=60); 2-one microvascular complication (n=28); 3-two microvascular complications (n=25) and CIMT was found to be significantly different between groups (p<0.001). When subgroup analysis was performed, patients with one

Table 2. Correlation of mean carotid intima-media thickness with other clinical and laboratory variables in patient and control groups

Variables	Patient (n=113)		Control (n=59)	
	r	p*	r	p*
Age, years	0.53	<0.001	0.56	<0.001
TC, mg/dl	0.06	NS	0.35	0.007
TG, mg/dl	0.11	NS	0.09	NS
HDL-C, mg/dl	0.09	NS	0.09	NS
LDL-C, mg/dl	0.01	NS	0.38	0.003
BMI, kg/m^2	0.06	NS	0.24	NS
HbA1c, %	0.16	NS	-	-
Duration of diabetes, years	0.46	<0.001	-	-
Total insulin dose, units/day	-0.08	NS	-	-
UAE, mg/day	0.36	<0.001	-	-
Number of complication	0.37	<0.001	-	-

*Spearman correlation test.
BMI - body mass index, HbA1c - glycosylated hemoglobin, HDL - C-high density lipoprotein cholesterol, LDL - C-low density lipoprotein cholesterol, n - number of patients, NS - non significant (p>0.05), r - correlation coefficient TC - total cholesterol, TG - triglycerides, UAE - urinary albumin excretion

Table 3. Comparison of mean carotid intima-media thickness in patient subgroups with diabetic nephropathy, diabetic retinopathy, and number of complications

Microvascular complication	CIMT, mm		Chi-square	p
	Mean±SD	Median (Min-max)		
Diabetic nephropathy			12.530	0.002*
Normal, n=66	0.64±0.09	0.63 (0.43-0.90)		
Microalbuminuria, n=26	0.68±0.09	0.65 (0.57-0.94)		
Macroalbuminuria, n=21	0.72±0.14	0.68 (0.58-1.28)		
Diabetic retinopathy			12.871	0.002**
Normal, n=82	0.65±0.10	0.64 (0.43-0.94)		
Background, n=14	0.69±0.08	0.67 (0.59-0.90)		
Proliferative, n=17	0.73±0.15	0.70 (0.58-1.28)		
Number of complications			15.393	<0.001***
No complication, n=60	0.64±0.09	0.63 (0.43-0.89)		
One complication, n=28	0.69±0.10	0.66 (0.57-0.94)		
Two complications, n=25	0.72±0.13	0.68 (0.58-1.28)		

Kruskal-Wallis test
Postest comparisons: * Normal vs Microalbuminuria - p=0.041 and normal vs macroalbuminuria - p<0.001
** Normal vs background - p=0.039 and normal vs proliferative - p<0.001
*** No complication vs one complication - p=0.009 and no complication vs two complications - p<0.001.
CIMT - carotid intima - media thickness, min - max - minimum - maximum, mm - millimeter, n - patient of number, SD - standard deviation

microvascular complication had significantly higher CIMT compared with those without microvascular complications (p=0.009). This difference was more evident when patients with two microvascular complications were compared with those without microvascular complications (p<0.001). CIMT in patients with one microvascular complication and patients with two microvascular complications, were similar, nevertheless the latter patients had higher CIMT (p=0.19) (Table 3).

The most important variables were analyzed again, with linear regression model after adjustments for age and sex. In diabetic group, multiple regression analysis demonstrated a significant relation between CIMT and the presence of microvascular complications. The increase in CIMT in young diabetics was dependent on the presence of proliferative retinopathy (beta=0.037, 95%CI 0.010-0.065, p=0.008) and macroalbuminuria (beta=0.043, 95%CI 0.019-0.068, p=0.001), increased UAE (beta=0.00003, 95%CI 0.00001-0.00005, p=0.005) and duration of diabetes (beta=0.002, 95%CI 0.001-0.003, p=0.009) (Table 4). In controls the increase of CIMT was associated only with smoking (beta=0.031, 95%CI 0.004-0.058, p=0.025), no association was found for TC and LDL-C.

Discussion

This study showed that in patients with type 1 DM, CIMT is higher than in the control group and each increment in its value is related with diabetic microvascular complications (nephropathy and retinopathy), duration of diabetes, and 24-hour UAE.

The Pittsburgh study indicated more than 11-fold higher prevalence of cardiovascular complications in patients with juvenile-onset type 1 DM at an average age of 21 years compared with the general population (13). This finding emphasizes the importance of early detection and prevention of the macrovascular disease in juvenile-onset type 1 DM. Studies demonstrated that CIMT in adolescent type 1 DM is significantly increased when compared with the controls (14-17). The Atherosclerosis Risk in Communities Trial demonstrated that CIMT was greater in both diabetics (especially in type 2 DM) and non-diabetics with moderate hyperglycemia, compared to individuals with normal glucose levels (18). The present study shows that CIMT is increased significantly in adults with type 1 DM compared with the healthy control subjects. This finding indicates that the patients with type 1 DM without manifest macroangiopathy have already been susceptible to atherosclerosis when they are young. It is likely that CIMT reflects the earliest changes in diabetic macroangiopathy (19).

In our study, there was no difference between diabetic patients and control subjects in terms of TC, HDL-C, LDL-C whereas TG levels were increased significantly in the diabetic group. In a study of 50 type 1 diabetics and 35 healthy controls, TC and LDL-C concentrations were similar between the groups, while diabetic group had higher HDL-C and lower TG levels (15). Hypertriglyceridemia is a characteristic of poor glycemic control. Plasma very low-density lipoprotein and TG levels were increased in patients with type 1 DM who have microalbuminuria or more severe nephropathy (20). One of the reasons for hypertriglyceridemia could be the high levels of mean HbA1c in our patient group. We also found no significant correlation between CIMT and TC, LDL-C, HDL-C, and TG levels in the patient group, but an association of CIMT with LDL-C and TC levels was found in the control group. However, when adjusted for age and sex in the control group, this association was also of no significance. As concordant with our results, several studies in type 1 DM patients did not show any correlation between lipid levels and CIMT (17, 19, 21). Although lipoproteins are important biomarkers for vascular risk, they do not completely account for the excess risk of vascular complications in diabetes. Therefore, more recently, plasma biomarkers of inflammation and endothelial dysfunction have been investigated as possible risk factors for diabetic complications (22). Studies in adults have shown that LDL oxidation is increased in diabetes and may explain some of the enhanced cardiovascular risk in type 1 DM (23). Because we did not check out oxidized LDL-C levels, this would be a limitation of our study.

The role of hyperglycemia or glycemic control as a risk factor for atherosclerosis or cardiovascular diseases in type 1 diabetes is poorly understood. Recent data in type 1 diabetes

Table 4. The effects of the duration of diabetes, smoking, 24-hour urine albumin excretion, nephropathy and retinopathy on CIMT after adjustments for age and sex in the patient groups

Independent Variables	Unstandardized Coefficients		p*	95% Confidence Interval for β	
	β	Std. Error		Lower Bound	Upper Bound
Duration of diabetes	0.002	0.001	0.009	0.001	0.003
Smoking	0.007	0.011	0.566	-0.016	0.029
24-hour UAE	0.00003	0.000	0.005	0.00001	0.00005
Microalbuminuria	0.020	0.012	0.093	-0.003	0.042
Macroalbuminuria	0.043	0.012	0.001	0.019	0.068
Background retinopathy	0.013	0.015	0.374	-0.016	0.043
Proliferative retinopathy	0.037	0.014	0.008	0.010	0.065

* Logarithmic transformations were applied for CIMT in multiple linear regression analysis
CIMT - carotid intima-media thickness, UAE - urinary albumin excretion

suggest little, if any, effect of HbA1c on cardiovascular diseases (24-26). The Diabetes Control and Complications Trial (DCCT) which compared intensive and standard therapies in patients with type 1 DM show that although intensive therapy reduced the risk of development and progression of microvascular and neuropathic complications from 76 to 35 percent, the incidence of cardiovascular events was not significantly different (27). Epidemiology of Diabetes Interventions and Complications (EDIC) is a multicenter longitudinal observational study of the DCCT cohort. However, in EDIC study no association was demonstrated with HbA1c level and CIMT of diabetic children (28). In our study, we also found no correlation between HbA1c levels and CIMT of the patients. On the contrary, in several studies, a positive correlation has been shown between HbA1c and CIMT (29, 30). These findings indicate that blood glucose level on its own is not a major risk factor for the development of atherosclerosis in type 1 DM. As shown in previous studies, risk of developing atherosclerotic disease in people with type 1 DM is increased 2-4 times and this can not be sufficiently accounted for conventional risk factors such as dyslipidemia, hypertension and hyperglycemia. Therefore, other risk factors may be operational in diabetes (1).

Most of the studies in the literature found a correlation between CIMT and duration of diabetes (17, 25), and age (17, 19). We also determined a positive correlation between CIMT and duration of diabetes and age. After adjustments for age and sex were made, effect of duration of diabetes sustained. Hayaishi-Okano et al. (16) found a positive correlation between smoking habit and CIMT, and smoking was determined as an independent risk factor in multiple regression analysis. In our study, we determined a statistically significant difference between smoking and non-smoking subjects, in terms of CIMT, both in patient and control groups. In linear regression analysis, the difference continued in the control group but not in the patient group.

The relation between microvascular complications of type 1 DM and CIMT was investigated in few studies. Frost et al. (31) found increased CIMT only in type 1 DM patients with diabetic complications. In a study with 142 patients with type 1 DM, CIMT was reported to be higher in those with diabetic complications (hypertension, retinopathy, and microalbuminuria) (32). Abdelghaffar et al. (29) found that increased CIMT was associated with the presence of microvascular complications. According to the authors, both microvascular and macrovascular complications may have occurred with the same pathogenetic mechanism and presence of one complication may warn to screen the other (29). In our study, patients with microvascular complications had higher CIMT than those who did not have these complications and there was a positive correlation between the number of complications and CIMT.

Yokoyama et al. (19) found that CIMT in the patient group with proliferative retinopathy was higher than in the group without retinopathy. These findings indicate the association of diabetic microangiopathy and macroangiopathy (19). Głowińska-Olszewska et al. (33) showed that CIMT was higher in adolescents with diabetic retinopathy in comparison to patients without complications. Cardiovascular disease is a significant cause of mortality in type 1 DM, with proteinuria as the strongest predictor (34, 35). Mykkanen et al. (36) showed microalbuminuria to be associated with increased CIMT. Also, positive correlation between CIMT and urinary albumin, endothelin, and cortisol excretion in patients with type 1 DM was reported (37). Frost et al. (38) demonstrated that CIMT had greater and faster progression in patients with microvascular complications, particularly in patients with nephropathy. In our study, CIMT was positively correlated with urinary albumin excretion in 24 hours, a sensitive marker of diabetic nephropathy. This finding indicates that albumin excretion was associated with atherosclerosis. In addition, patients with nephropathy and retinopathy had higher CIMT compared to the patients without complications. As the severity of nephropathy and retinopathy are increased, CIMT increased as well. Although not statistically significant, there was a difference between patients with microalbuminuria and macroalbuminuria, and patients with background and proliferative retinopathy in terms of CIMT. The reason for this could be relatively small number of patients in the subgroups. Our results support findings on a strong relation between CIMT and early stages of microangiopathy and macroangiopathy. Thus, when microvascular complications -either nephropathy or retinopathy have developed, one should be alert to take precautions for atherosclerosis.

Limitations of the study

It is not always possible to explain increased atherosclerosis with traditional risk factors like hyperglycemia and hyperlipidemia in patients with type 1 DM. Plasma biomarkers of inflammation and endothelial dysfunction or oxidized LDL would be helpful to determine factors effecting atherosclerosis, but we were not able to do this due to technical reasons.

Conclusion

Our study demonstrated that each increment of CIMT in type 1 diabetic patients was associated with microvascular complications. Therefore, there is a need for prospective studies to show the effect of increased CIMT on prognosis, in patients with type 1 DM.

Conflict of interest: None declared

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