Ultrazvočni in klasični dejavniki tveganja karotidne ateroskleroze pri bolnikih s sladkorno boleznijo tipa 2

Ultrasonographic and classical risk factors of carotid atherosclerosis in patients with type–2 diabetes mellitus

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Izvleček

Namen: *V raziskavi smo želeli ugotoviti prevalenco biokemičnih in kliničnih dejavnikov tveganja ter razširjenost ateroskleroze karotidnih arterij pri bolnikih s sladkorno boleznijo tipa 2 (SBT2).*

Metode: *V prospektivno presečno študijo smo vključili 289 bolnikov s SBT2 in 157 zdravih preiskovancev. Anamnestične in klinične podatke smo zajeli z enotnim vprašalnikom. Vrednosti celokupnega holesterola, LDL in HDL holesterola, trigliceridov, glukoze, fibrinogena ter visokoobčutljivega C–reaktivnega proteina (CRP) smo določili s standardnimi biokemijskimi postopki. Aterosklerozo karotidnih arterij smo ocenili z ultrazvokom in opredelili debelino intime in medije, tip plakov ter seštevek plakov.*

Abstract

Purpose: *We determined the prevalence of the clinical and biochemical risk factors as well as the extent of atherosclerosis in carotid arteries in patients with diabetes mellitus type 2 (DMT2).*

Methods: *A total of 289 subjects with DMT2 and 157 healthy subjects were enrolled in this prospective cross–sectional study. Levels of total cholesterol, high–density lipoprotein–cholesterol (HDL–C), low–density lipoprotein–cholesterol (LDL–C), triglycerides, fasting blood glucose, fibrinogen, and high–sensitivity C–reactive protein (hsCRP) were measured using standard biochemical methods. Carotid atherosclerosis was assessed by ultrasonography. Intima media thickness (IMT), plaque type and plaque score were also determined.*

Rezultati: *Bolniki s SBT2 so bili starejši in so imeli večji obseg pasu, večji indeks telesne mase, pogosteje povišan krvni tlak, višje vrednosti fibrinogena, D–dimera, glukoze, visoko občutljivega CRP, troponina in trigliceridov kot kontrolna skupina. Bolniki s SBT2 so imeli nižji LDL holesterol, vendar so bili v večjem deležu zdravljeni s statini glede na kontrolno skupino (70 % vs. 5 %). Bolniki s SBT2 so imeli večjo debelino intime–medije (1.09 ± 0.12 vs. 0.98 ± 0.14; P = 0.001), višji seštevek plakov in bolj napredovalo obliko plakov glede na kontrolno skupino.*

Zaključek: *Bolniki s SBT2 imajo večjo debelino intime–medije in bolj izraženo aterosklerozo karotidnih arterij glede na kontrolno skupino.*

Results: *In comparison with healthy controls, DMT2 patients: were older and had a larger waist circumference; higher body mass index; higher prevalence of hypertension; higher values of fibrinogen, D–dimer, glucose, hsCRP, troponin and triglycerides. Patients with DMT2 had lower levels of LDL–C and they were treated more often with statins (70% vs. 5%). In comparison with healthy subjects, patients with DMT2 had an increased intima media thickness (1.09±0.12 vs. 0.98±0.14; P=0.001), higher plaque score, and more advanced types of plaques.*

Conclusion: *In comparison with healthy subjects, patients with DMT2 had an increased carotid IMT and higher plaque burden.*

INTRODUCTION

Atherosclerotic vascular disease is the main cause of increased morbidity and mortality in patients with diabetes mellitus (DM) (1). Coronary heart disease, cerebrovascular disease and peripheral vascular disease are the reasons for a mortality of 80% and prevalence of hospitalization of 75% in patients with DM. Patients with DM have a twofold–to–fourfold increased risk for coronary heart disease and prognosis of myocardial infarction, whereas unstable angina pectoris is much worse in diabetic patients. Patients with DM also have a fourfold increased risk of cerebrovascular disease, and the clinical consequences after stroke are much more ominous. Periferal vascular disease is tenfold more common in patients with DM (2).

Carotid intima–media thickness (CIMT) and carotid plaques are markers of systemic subclinical atherosclerosis and predictors of incident myocardial infarction and ischemic stroke (3). Increased CIMT is also the consequence of arterial hypertension due to hypertrophy of media and fibromuscular hyperplasia. CIMT reflects the age of the vessels (4). In comparison with CIMT, carotid plaques are strongly influenced by environmental factors and less by genetic factors. Normal values of CIMT in the common carotid artery (CCT) in healthy populations of ages between 17 years and 65 years are 0.39–0.70 mm in men and 0.30–0.64 mm in women (5). Atherosclerotic plaques are a focal thickening of the intima and media >1.2 mm (1). Giannoukas et al. confirmed a higher incidence of ischemic stroke or transitory ischemic attack (TIA) in patients with hypoechogenic plaques in carotid arteries (6). Plaque types I–III are unstable and carry a higher risk of TIA or stroke in comparison with stable plaques (IV, V). Reports have confirmed a threefold increased risk of stroke in patients with unstable plaques. Krupinski et al. and Death et al. reported a higher proportion of unstable plaques in patients with DM compared with healthy controls (7, 8).

The aim of the present study was to determine the clinical and biochemical risk factors of atherosclerosis and the presence and extent of atherosclerosis in carotid arteries in patients with diabetes mellitus type 2 (DMT2).

MATERIALS AND METHODS

The research protocol was approved by the National Medical Ethics Committee of Slovenia. Written informed consent was obtained from all patients.

Patients. In this cross–sectional study, 289 subjects with DMT2 from the diabetic ambulance of the General Hospital Murska Sobota in Slovenia were enrolled. We also enrolled 157 healthy subjects. All the subjects enrolled in the study were Slovenian and were not related. Patients were classified as having DMT2 according to the current report of the WHO Classification of Diabetes Mellitus (http://www.who.int). An interview was conducted regarding smoking habits, the duration of DM, arterial hypertension, and hyperlipidemia. The body mass index (BMI) was calculated as weight in kilograms divided by the height in square meters. We measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the right upper arm of patients while they were sitting. Subjects with SBP ≥130 mmHg or DBP ≥85 mmHg and/or subjects who were using antihypertensive drugs were considered to be hypertensive.

Analyses of ultrasound images. Atherosclerotic changes in the carotid arteries were assessed by ultrasonography. High–resolution B mode, colour Doppler, and pulse Doppler ultrasonography of both carotid arteries were undertaken with a commercially available ultrasound system (Aplio; Toshiba, Tokyo, Japan) with a multifrequency linear array transducer. All examinations were conducted by a single expert radiologist (MŠL) blinded to the DM status of the participant. Patients were examined in the supine position with the head tilted backwards. The protocol involved imaging of the CCA, carotid bifurcations and origins of internal carotid arteries (ICA). In agreement with the consensus on CIMT (9), the CIMT was measured at three sites along a 10 mm–long segment of the far wall of the CCA free of plaques. CIMT on the left and right was calculated as the mean of three readings, whereas the mean of the left and right CCA–CIMT measurement was used in the analysis. A plaque was defined as focal intima–media thickening ≥1.2 mm. The plaque score was calculated by summing the total number of sites with plaques (each of the CCAs, bifurcations, and ICAs, bilaterally) (10). Moreover, we determined the type of plaques from type I to type V (11, 12). A type–I plaque was defined as being dominantly echolucent with a thin echogenic cap. A type–II plaque was predominantly echolucent with small areas of echogenicity. A type–III plaque was dominantly echogenic with small areas of echolucency (<25 %). A type–IV plaque was uniformly echogenic (equivalent to being homogenous). A type–V plaque was a predominantly calcified plaque. Plaque types I, II and III were considered to be unstable, whereas types IV and V were considered stable (13).

Biochemical analyses. Levels of total cholesterol, triglyceride, high–density lipoprotein–cholesterol ((HDL–C), low–density lipoprotein–cholesterol (LDL–C), high–sensitivity C–reactive protein (hsCRP), and fasting blood glucose were measured after an overnight fast. All blood biochemical analyses were determined by standard biochemical methods.

Statistical analyses. Data are the mean ± standard deviation. Continuous clinical data were compared by the unpaired Student's t–test. The chi–square test was used to compare discrete variables. $p<0.05$ was considered significant. Statistical analyses were carried out using SPSS ver19 (SPSS, Chicago, IL, USA).

RESULTS

The clinical and biochemical characteristics of patients with DMT2 and controls are shown in Table 1. Patients with DMT2 were older and had: a greater waist circumference; higher BMI; higher prevalence of hypertension; higher values of activated partial thromboplastin time (aPTT), fibrinogen, D–dimer, glucose, hsCRP, troponin and triglycerides. The control group had higher levels of total cholesterol, HDL–C and LDL–C than patients with DMT2. Patients with DM had been treated more extensively with statins (70% vs. 5%).

Table 1: *Clinical and biochemical characteristics of patients with diabetes mellitus type 2 (DMT2) and controls (C).*

		Number	Value ± SD	p
Waist circumference (cm)	DMT2 C	289 157	108.53 ± 12.95 93.31 ± 13.17	<0.001
Body mass index	DMT2 C	289 157	31.6 ± 0.7 27.1 ± 0.4	<0.001
Prevalence of hypertension	DMT2 C	289 157	203 (70%) 50 (32%)	<0.001
aPTT (s)	DMT2 C	289 157	32.35 ± 8.02 30.13 ± 4.28	<0.001
Fibrinogen (g/L)	DMT2 C	289 157	4.38 ± 1.21 3.68 ± 0.76	<0.001
D-dimer (mg/L)	DMT2 C	289 157	0.70 ± 1.01 0.46 ± 0.36	<0.001
Glucose (mm/L)	DMT2 C	289 157	8.02 ± 2.57 5.27 ± 0.87	<0.001
Total cholesterol (mmol/L)	DMT2 C	289 157	4.64 ± 1.11 5.36 ± 1.08	<0.001
Triglycerides (mmol/L)	DMT2 C	289 157	2.52 ± 1.92 1.54 ± 0.93	<0.001
HDL-C (mmol/L)	DMT2 C	289 157	1.18 ± 0.33 1.43 ± 0.36	<0.001
LDL-C mmol/L)	DMT2 C	289 157	2.63 ± 0.88 3.23 ± 0.97	<0.001
hsCRP	DMT2 C	289 157	4.49 ± 7.94 2.22 ± 2.37	<0.001
Troponin (µg/L)	DMT2 C	289 157	0.037 ± 0.569 0.022 ± 0.006	<0.001
Age (years)	DMT2 C	289 157	62.75 ± 9.77 59.93 ± 9.35	<0.001

aPTT – activated partial thromboplastin time; hsCRP – high-sensitivity C-reactive protein

Patients with DMT2 had larger CIMT than controls (Table 2). Compared with controls, patients with DMT2 had a higher plaque score; fewer patients with DMT2 had no plaques or a plaque score of 0, and fewer patients had a plaque score of 1 and 2, and more patients with DMT2 had a plaque score 3, 4, 5 or 6 (Table 3). Patients with DMT2 also had more prevalent advanced forms of plaque types IV and V (Table 4).

The characteristics of patients with DMT2 according to CIMT are shown in Table 5. Older patients have larger CIMT and patients with lower triglycerides have larger CIMT. There were no differences in other parameters.

The characteristics of patients with DMT2 according to plaque type are shown in Table 6. Patients with a longer duration of DMT2 had more stable plaques. Also, patients with longer–lasting hypertension had more stable plaques. Patients with higher levels of fibrinogen had more stable plaques. Patients with higher SBP had more unstable plaques.

Table 7 shows the characteristics of patients with DMT2 according to the plaque score. Patients with a higher plaque score were older, and had higher levels of fibrinogen. There were no significiant differences in the other parameters tested.

Table 8 shows increased CIMT with a higher plaque score and with unstable plaques in patients with DMT2.

Table 2: *Carotid intima media thickness (CIMT) of patients with diabetes mellitus type 2 (DMT2) and controls.*

	CIMT left (mm)	CIMT right (mm)	CIMT average (mm)	p
DMT2 patients	1.09 ± 0.14	1.10 ± 0.13	1.09 ± 0.12	0.001
Controls	0.98 ± 0.15	0.97 ± 0.15	0.98 ± 0.14	

Table 3: *Plaque score in patients with diabetes mellitus type 2 (DMT2) and controls*

	Plaque score 0	Plaque score 1 and 2	Plaque score 3, 4, 5, or 6	p
DMT2 patients (287)	33 (11.5%)	85 (29.6%)	169 (58.9%)	<0.005
Controls (157)	40 (25.5%)	61 (38.8%)	56 (35.7%)	

Table 4: *Type of plaque in patients with diabetes mellitus type 2 (DMT2) and controls*

	No plaque	Type I, II, or III	Type IV or V	p
DMT2 patients (287)	33 (11.5%)	157 (54.7%)	97 (33.8%)	<0.005
Controls (157)	40 (25.5%)	98 (62.4%)	29 (18.5%)	

DISCUSSION

Clinical and biochemical characteristics of patients with DMT2

Our group of patients with DMT2 had a higher BMI and greater waist circumference than those of controls. Adiposity per se is not an independent predictor for atherosclerosis, but is a part of the metabolic syndrome, which includes central adiposity, arterial hypertension, dyslipidemia, and insulin resistance (14).

Seventy percent of enrolled patients with DMT2 had arterial hypertension. The prevalence of arterial hypertension in this group of patients with DMT2 was similar to that observed in other European countries (70–80%) (15). In comparison with some other studies, our patients had higher values of SBP. The United Kingdom Prospective Diabetes Study (UKPDS) reported that 10–mmHg higher blood pressure increased the cardiovascular risk by 15% in patients with DM (16).

Dyslipidemia in our patients with DMT2 and in those described in the literature is characterized by increased levels of triglycerides and decreased levels of HDL–C (14). In the present study, the value of triglycerides was 2.5 mmol/L, so it was not well–controlled according to current guidelines. In addition, HDL–C levels were low, but the results were similar to those of other authors (1,14). LDL–C levels in our patients showed only a mild elevation (2.6 mmol/L) but were lower than in controls, and were probably a consequence of statin treatment. Seventy percent of patients with DM were treated with statins compared with 5% of healthy controls. The literature suggests that LDL–C levels are similar in patients with DM and the healthy population, but LDL–C molecules in diabetic patients are smaller, more susceptible to oxidation, and tend to accumulate in the vessel wall (14). Total cholesterol was well controlled in diabetic patients, but higher values in healthy controls reflect treatment with statins in patients with DMT2.

DM is a chronic inflammatory disease characterized by elevated levels of hsCRP (17). This group of patients had elevated levels of hsCRP (4.4±7.9 mg/L). High levels of hsCRP in patients with DM predict a higher risk of cardiovascular morbidity and mortality (18). CRP is a pathogenetic factor in atherosclerosis. CRP increases the expression of adhesion molecules on endothelial cells (19), assists in the macrophage absorption of LDL–C molecules (20) and amplifies

Table 5: *Characteristics of patients with diabetes mellitus type 2 (DMT2) according to carotid intima media thickness (CIMT).*

	CIMT ≤1 mm	CIMT >1 mm	P
Age (years)	58.9 ± 10.1	63.9 ± 9.5	<0.001
Presence of DMT2 (years)	8.5 ± 7.6	9.9 ± 8.4	0.15
Systolic blood pressure (mm Hg)	141.1 ± 16.9	143.7 ± 20.3	0.42
Diastolic blood pressure (mm Hg)	85.7 ± 10.4	84.8 ± 14.9	0.71
Presence of hypertension (age)	31.8 ± 5.3	31.7 ± 9.2	0.93
Waist circumference (cm)	107.1 ± 11.5	109.2 ± 13.4	0.20
Troponin I (mg/L)	0.003 ± 0.007	0.05 ± 0.7	0.52
hsCRP (mg/L)	3.7 ± 4.6	4.9 ± 8.8	0.27
Glucose (mmol/L)	7.8 ± 2.8	8.1 ± 2.5	0.40
Fibrinogen (g/L)	4.2 ± 1.1	4.5 ± 1.2	0.07
D-dimer (mg/L)	0.7 ± 1.4	0.6 ± 0.8	0.61
Total cholesterol (mmol/L)	4.8 ± 1.0	4.8 ± 1.2	0.93
HDL-C (mmol/L)	1.2 ± 0.4	1.2 ± 0.3	0.43
LDL-C (mmol/L)	2.6 ± 0.8	2.7 ± 0.9	0.43
Triglycerides (mmol/L)	2.9 ± 2.5	2.4 ± 1.6	0.03

hsCRP – high-sensitivity C-reactive protein

atherothrombosis with increased activity of plasminogen activator inhibitor–1 (PAI–1) in endothelial cells (21).

Our group of patients with DMT2 had significantly higher values of D–dimer compared with the control group (0.70 vs. 0.46 g/L). D–dimer is a characteristic degradation product of crosslinked fibrin and an index of coagulation activity. There have been reports of elevated levels of coagulation markers in DMT2, predominantly D–dimer. Elevated levels of D–dimer have been reported in subjects with coronary artery disease. Hence, D–dimer levels have been proposed as potential diagnostic and management tools for cardiovascular diseases (CVDs). There is no clear consensus as to whether D–dimer levels are associated with the progression of DM (including progression to CVDs) (22).

We did not achieve tight glycemic control in our study cohort. The mean fasting blood glucose concentration was 8 mmol/L. There are firm data demonstrating that improved glycemic control decreases the risk of microvascular complications, but evidence of the beneficial effect of intensive therapy on macrovascular outcomes in individuals with long–standing DMT2 is less convincing. The most effective approach for the prevention of macrovascular complications appears to be reduction of multifactorial risk factors (16, 23).

In patients with DMT2, higher values of fibrinogen than in the control group were observed (4.3 vs. 3.6 g/L). Fibrinogen has an affinity for binding to hydrophobic, atheromatous lipid surfaces and accumulation in plaques (24). As the atheromatous plaque forms, it incorporates fibrinogen and fibrin, which provide a scaffold for the migration and proliferation of smooth muscle cells but also for calcium deposition (9, 25).

Markers of carotid atherosclerosis

In patients with DMT2, we observed thicker intima–media compared with controls, a finding that is in accordance with other studies (9–11). Our older patients

Table 6: *Clinical and biochemical characteristics of patients with diabetes mellitus type 2 (DMT2) according to the type of plaque (TP).*

	TP 0	TP I, II, or III	TP IV or V	P
Presence of DMT2 (years)	9.2 ± 10.0	8.6 ± 7.1	11.4 ± 8.9	0.027
Systolic blood pressure (mmHg)	133.9 ± 13.7	145.8 ± 20.6	142.7 ± 18.2	0.039
Diastolic blood pressure (mmHg)	83.7 ± 9.4	86.7 ± 16.8	83.6 ± 9.5	0.38
BMI (kg/m2)	31.6 ± 5.4	31.6 ± 10.0	31.8 ± 5.5	0.98
Presence of hypertension (years)	11.7 ± 9.5	10.4 ± 8.4	14.3 ± 9.4	0.031
Waist circumference (cm)	109.6 ± 10.5	108.1 ± 13.7	108.7 ± 12.7	0.82
Troponin I (mg/L)	0.002 ± 0.004	0.004 ± 0.009	0.1 ± 0.9	0.37
hsCRP (mg/L)	3.9 ± 6.0	4.5 ± 5.3	4.8 ± 11.0	0.83
Glucose (mmol/L)	7.7 ± 2.7	8.1 ± 2.5	8.0 ± 2.5	0.69
Fibrinogen (g/L)	3.8 ± 0.93	4.3 ± 1.2	4.7 ± 1.2	0.001
D-dimer (mg/L)	0.4 ± 0.2	0.8 ± 1.2	0.6 ± 0.5	0.06
Total cholesterol (mmol/L)	4.7 ± 0.9	4.9 ± 1.2	4.9 ± 1.1	0.58
HDL-C (mmol/L)	1.2 ± 0.5	1.1 ± 0.3	1.2 ± 0.3	0.56
LDL-C (mmol/L)	2.5 ± 0.7	2.6 ± 0.9	2.7 ± 0.9	0.41
Triglycerides (mmol/L)	2.4 ± 1.7	2.6 ± 2.1	2.5 ± 1.6	0.84
CIMT - left (mm)	0.95 ± 0.19	1.12 ± 0.11	1.10 ± 0.13	<0.001
CIMT - right (mm)	0.94 ± 0.19	1.12 ± 0.11	1.11 ± 0.10	<0.001

hsCRP – high-sensitivity C-reactive protein

also had increased CIMT compared with younger subjects, a finding that was in accordance with a report on the correlation between age and CIMT (26). CIMT does not reflect only early atherosclerosis, but also compensatory thickening of media due to hypertrophy of smooth muscle cells and proliferation of connective tissue in the tunica media (13). We do not know how to differentiate between early plaque development and compensatory thickening of media. In our patients, we did not observe an association between increased CIMT and arterial hypertension (Table 5). A possible explanation could be the association of multiple risk factors clustered as the metabolic syndrome (central obesity, dyslipidemia) in our patients. Increased CIMT reflects multiple risk factors, regardless of the report stating that macroangiopathic complications in patients with DM were more common in patients with hypertension (16, 27). Koskinen et al. reported an association between increased CIMT with the metabolic syndrome in young adults, which suggested a pathophysiological role for obesity, dyslipidemia, and hyperinsulinemia in predicting the development of atherosclerosis (27). Patients with increased CIMT have been shown to have a 1.4–3.2–times increased relative risk for myocardial infarction and 2.3–3.5–times increased risk for cerebrovascular infarction. On average, the cardiovascular risk is increased by 2.3–times in patients with increased CIMT (26).

We observed an association between increased CIMT with higher plaque score (Table 8). A higher plaque score is a marker of advanced atherosclerosis. Sakaguchi et al. reported that advanced coronary artery disease (CAD) is associated with a higher plaque score (28). Morito et al. observed a more strict association of higher plaque score and larger plaque surface with

Table 7: *Clinical and biochemical characteristics of patients with diabetes mellitus type 2 (DMT2) according to the plaque score.*

	Score 0, 1, or 2	Score 3, 4, 5, or 6	P
Age (years)	59.1 ± 10.2	65.1 ± 8.9	0.000
Presence of DMT2 (years)	9.8 ± 7.6	9.3 ± 8.9	0.62
Systolic blood pressure (mmHg)	141.1 ± 16.9	143.7 ± 20.3	0.15
Diastolic blood pressure (mmHg)	85.7 ± 10.4	84.8 ± 14.9	0.65
Duration of hypertension (years)	11.4 ± 9.4	11.9 ± 8.8	0.91
Waist circumference (cm)	107.1 ± 11.5	109.2 ± 13.4	0.67
Troponin I (mg/L)	0.003 ± 0.005	0.06± 0.06	0.37
hsCRP (mg/L)	4.6 ± 9.4	4.4 ± 5.0	0.83
Glucose (mmol/L)	8.0 ± 2.5	7.9 ± 2.6	0.73
Fibrinogen (g/L)	4.2 ± 1.1	4.5 ± 1.2	0.02
D-dimer (mg/L)	0.8 ± 1.01	0.6 ± 0.9	0.23
Total cholesterol (mmol/L)	4.8 ± 0.9	4.9 ± 1.2	0.18
HDL-C (mmol/L)	1.2 ± 0.4	1.2 ± 0.3	0.84
LDL-C (mmol/L)	2.5 ± 0.7	2.7 ± 0.9	0.10
Triglycerides (mmol/L)	2.5 ± 1.7	2.5 ± 2.1	0.97

hsCRP – high-sensitivity C-reactive protein

advanced CAD than with increased CIMT (29). Lee et al. reported that patients with DMT2 who suffered from cerebrovascular infarction had a higher plaque score (30). Several other authors also reported the association between increased CIMT with a higher plaque score (31–34).

We observed a significant association between fibrinogen concentration and the plaque score. Patients with stable plaques and a higher plaque score had a higher concentration of fibrinogen. These patients were older than the controls. Several authors reported an association between high concentrations of fibrinogen and carotid atherosclerosis (35–37). Green et al. reported the association between fibrinogen level and atherosclerosis to be age–dependent. In the fourth decade, age and smoking modify the synthesis of fibrinogen and the association with CVDs (35–37).

A total of 54.7% of our patients with DMT2 (157 from 289) had unstable plaques in their carotid arteries. The percentage of unstable plaques was even higher in control groups of subjects without DM (62.4%; 98 from 157). Our results are different from the results of Ostling et al., who reported a higher prevalence of unstable carotid plaques in patients with DM compared with controls without DM (1, 38). Our patients with DMT2 and hypertension had a higher prevalence of unstable plaques in carotid arteries compared with patients with lower SBP. Unstable atherosclerotic plaques have a high probability of rupture and progression to thrombotic complications if vessels are occluded, and thromboembolic phenomena may occur. In general and in the present study, plaque types I, II and III are considered unstable, whereas types IV and V are considered stable. We observed that patients with plaque types I and II were younger compared with patients with plaque type V. Similar results were observed by Giannoukas et al., who reported that patients with plaque type I were younger than patients with plaque type IV (6). Our patients with DMT2 were older than those in the con-

Table 8: *Relationship between intima-media thickness and plaque score and plaque type in patients with diabetes mellitus type 2 (DMT2).*

	Carotid intima-media thickness (CIMT)		
	≤ 1 mm	≥ 1 mm	p
Plaque score 0, 1, or 2	51 (42.1%)	28 (16.9%)	<0.001
Plaque score 3, 4, 5, or 6	70 (57.9%)	138 (83.1%)	
Unstable plaque (type I, II, or III)	30 (38.0%)	127 (61.1%)	<0.001
Stable plaque (type IV or V)	28 (35.4%)	69 (33.2%)	
No plaque	21 (26.6%)	12 (5.7%)	

trol group, which could explain the greater proportion of plaque types IV and V compared with plaque types I, II and III. One of the reasons for such findings is the changing of the structure and size of carotid plaques with time. Using ultrasound, we observed a more echogenic structure during the progression of atherosclerosis, which is a consequence of the increased amount of fibrous tissue. With ultrasound we observed with time the transfer of plaque types I and II to plaque types III and IV, or regression of echolucent areas and progression in homogenous echogenic areas and calcification. Whether calcification within plaques also provides mechanical instability at the site of contact of calcification with the soft plaque surface (34) as proposed by Prabhakaran et al. in a Nothern Manhattan study is controversial. They observed a higher incidence of plaque calcification in carotid artery plaques in older patients which was proposed to be due to embolisation (34). Arterial calcification is a balanced process that incorporates the area of chronic inflammation in plaque and limits inflammation. Plaques develop primarily on the bifurcation of the CCA or in the proximal part of the ICA due to turbulent flow. Localized plaques probably represent a late stage in atherogenesis (26, 39). Calcified plaques in carotid arteries may also cause cerebrovascular symptoms due limitation of blood flow. A consequence of occlusion or thromboembolic phenomena in carotid arteries is TIA or cerebrovascular infarction (40, 41).

The progression of atherosclerosis is a complex, multifactorial process in which systemic risk factors such as genetics, increased hypercholesterolemia, DM, smoking, reactive oxygen species and other potential atherogenic factors cause inflammatory reactions (36). Recent studies have described the importance of phenotype and structure of plaques as well as the plaque score. Different carotid phenotypes observed with ultrasound as CIMT, plaque surface, percent stenosis, plaque structure and plaque score have different biological and genetic backgrounds and probably different clinical consequences (42, 43).

CONCLUSIONS

Our patients with DMT2 had a higher BMI, and a high prevalence of central obesity, arterial hypertension and hypertriglyceridemia, thereby suggesting a high prevalence of the metabolic syndrome. Patients with DMT2 had increased CIMT, higher plaque score and more prevalent advanced atherosclerotic plaque types IV and V in comparison with a control group of subjects without DMT2.

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