Carotid intima-media thickness and arterial stiffness in type 1 diabetic patients with and without microangiopathy

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Abstract

Introduction: The aim of the study was to assess carotid intima-media thickness (CIMT) as a subclinical marker of atherosclerosis and arterial stiffness in type 1 diabetic patients in relation to microangiopathy.

Material and methods: We included 87 type 1 diabetic patients (44 women, 43 men), median age 34 years (interquartile range [IQR] 29-43), median disease duration 10 years (IQR: 9-14), mean ± standard deviation (SD) glycated haemoglobin (HbA_{1c}) 8.4 ±1.4%. Fifty patients had at least one microangiopathic complication. Intima-media thickness (IMT) of the common carotid artery was measured using high resolution ultrasonography. Arterial stiffness was assessed using digital volume pulse analysis and tonometric measurement of wave reflection and central haemodynamics.

Results: Subjects with microangiopathy compared with those without had higher values of CIMT (median [IQR]: 0.53 mm [0.45-0.60 mm] vs 0.47 mm [0.34-0.52 mm], $p = 0.002$), higher central augmentation index (CAI_X) (mean ± SD: 120.2 ±19.4% vs. 110.5 ±17.1%, $p = 0.016$) and higher peripheral augmentation index (PAI_X) (65.7 ±18.1% vs. 57.2 ±14.9%, $p = 0.023$). In the logistic regression analysis, the duration of diabetes, systolic and diastolic blood pressure, postprandial glycaemia, HbA_{1c} and triglycerides predicted the presence of diabetic microangiopathy independently of age and sex. The CIMT, CAI_x and PAI_x were associated with the presence of diabetic microangiopathy only in the univariate model.

Conclusions: In type 1 diabetic patients with microangiopathic complications, increased carotid IMT and arterial stiffness were observed. The study confirms the role of traditional risk factors for late diabetic complications, such as the duration of the disease and metabolic control in the development of microangiopathy.

Key words: type 1 diabetes, carotid intima-media thickness, arterial stiffness, microangiopathy.

Introduction

Type 1 diabetes (DM1) is accompanied by increased risk of cardiovascular complications [1, 2]. The Pittsburgh Epidemiology of Diabetes Complications (EDS) study and the EURODIAB Prospective Complications Study

discovered the occurrence of coronary heart disease in 16% of DM1 patients after 10 years of follow-up [3, 4]. Moreover, the EDS study suggested that cardiovascular complications are responsible for the majority of deaths in DM1 subjects below 35 years [3]. Traditional risk factors for cardiovascular disease (CVD) such as hyperglycaemia, dyslipidaemia and hypertension do not fully explain the increased mortality in these subjects [5, 6]. Therefore, to prevent the development of diabetic angiopathy a search has been made for novel risk factors as well as for early markers of late diabetic complications. Microvascular complications are specific for diabetes and are also regarded as risk factors for CVD. It has been suggested that albuminuria predicts early mortality in both DM1 and DM2 [4, 7, 8]. Recently, measurements of carotid intima-media thickness (CIMT) and arterial stiffness have been proposed as useful non-invasive clinical tools in the diagnosis of macroangiopathy. The results of recent studies point to a relationship between increased arterial stiffness and CVD [9-11]. However, knowledge concerning any association between arterial stiffness and thickening of the intima-media complex with microangiopathy in diabetic patients is limited.

The aim of the study was to assess carotid IMT as an early marker of atherosclerosis and arterial stiffness in type 1 diabetic patients with, and without, microangiopathy.

Material and methods

We examined 87 consecutive patients with DM1 (44 women and 43 men), hospitalized in the Department of Internal Medicine and Diabetology in Poznan. The median patients' age was 34 years (interquartile range [IQR]: 29-43), median disease duration 10 years (IQR: 9-14) and mean ± SD glycated haemoglobin (HbA_{1c}) value 8.4 ±1.4%. The DM1 was diagnosed due to presence of classical symptoms at the onset, blood glucose concentration > 11.1 mmol/l and C-peptide concentration < 0.5 µg/l [12]. The exclusion criteria were: age above 60 years, liver dysfunction (aminotransferases level 1.5 times over the normal range), stage 3 or higher chronic kidney disease, anaemia (haemoglobin level below 6.8 mmol/l), acute inflammatory process (high-sensitivity C-reactive protein [hsCRP] level above 10 mg/l) and diagnosed cardiovascular disease (coronary heart disease, cerebrovascular disease, peripheral vascular disease). The information about overt CVD was based on medical history of the patients and documentation including the following conditions: no history or absence of angina, no permanent ischaemic electrocardiogram abnormalities at rest or in the treadmill exercise test, no claudication, no abolished peripheral pulses and no foot lesions due to vascular disease demonstrated by Doppler echography, no history of stroke, and no significant carotid stenosis (> 50%) as assessed by Doppler echography.

In the study group 32 patients (37%) were treated with angiotensin-converting enzyme inhibitors (ACE-I). ACE-I were taken only in the group with microangiopathy. In this group 13 subjects had a positive history of hypertension and 3 patients had dyslipidaemia (2 were treated with statins and one with fibrate). Twenty-three subjects had a positive family history of CVD (16 patients in the group with microangiopathy and 7 subjects in the group without microangiopathy).

In this case-control study, the patients were divided according to the presence or absence of diabetic microangiopathy. All the subjects were informed about the aim of the study and gave their written consent. The study was approved by the Ethical Committee of Poznan University of Medical Sciences.

Diabetic retinopathy was diagnosed using direct ophthalmoscopy through dilated pupils followed in all the patients by fundus photography. Both eyes of each participant were photographed with a 45° digital camera VISUSCAM (Zeiss, Germany) and 9 pictures (optic disc and two pictures of each quadrant) of each eye were taken. Retinopathy was classified according to the American Academy of Ophthalmology as: mild non-proliferative, moderate non-proliferative, severe non-proliferative and proliferative.

Diabetic nephropathy was detected at the stage of albuminuria. Assessment of albuminuria was performed by measurement of urinary albumin excretion over 12 h. Albuminuria was defined as a urinary albumin excretion rate between 30 mg/day and 300 mg/day in two of three samples collected over 3 months after exclusion of secondary causes of microproteinuria (urinary tract infection, heart failure, acute febrile illness, haematuria, excessive physical activity). Diabetic nephropathy was defined as the presence of albuminuria in connection with diabetes of over 10 years duration or with diagnosed diabetic retinopathy [13].

Neuropathy assessment was performed using pressure sensation (10 g monofilament perception), vibration perception (128-Hz tuning fork) and ankle reflex tests. Diabetic neuropathy was diagnosed in patients with two or more of the following four components: the presence of symptoms of neuropathy, the absence of ankle tendon reflexes, abnormal scores for pressure and/or of vibration perception.

Intima-media thickness (IMT) of the common carotid artery was determined using high resolution ultrasonography (Accuson Cv 70, Siemens). CIMT was calculated automatically with the Carotid Analyzer for Research (CAD 5) program.

The assessment of arterial stiffness was performed with the patient in the horizontal position, after a 10-minute rest. Smoking and coffee consumption were not allowed for 12 h before evaluation.

To assess arterial stiffness the following methods were used:

1. Photoplethysmography, with digital volume pulse (DVP) analysis based on changes in blood volume in the digital pulp (Pulse Trace 2000, Micro Medical Ltd., Rochester, United Kingdom). Ten consecutive cardiac cycles were analyzed and then automatically averaged. The stiffness index (SI) of the DVP was obtained from the subject's body height, divided by the time between the systolic and diastolic peaks of the DVP.
2. Peripheral and central pulse wave analysis with the SphygmocorMx system (AtCor Medical; software version 7.0). In order to trace the radial artery pulse shape, an arterial tonometer (CBM 7000; Colin Medical Instruments, Komaki, Japan) connected to the SphygmocorMx device was attached to the subject's wrist. The average peripheral and derived aortic waveforms were generated after acquisition of 10 sequential pulse wave forms. The central augmentation index (CAI_x) was derived from the reconstructed central pressure waveform. The augmentation index (AI_x) was calculated as the difference between the second and the first systolic peaks observed on the central arterial waveform and expressed as a percentage of the central pulse pressure. The peripheral augmentation index (PAI_x) was derived from the radial artery waveform.

Blood samples were collected in a fasting state defined as no caloric intake for at least 8 h. Plasma concentration of glucose (fasting and 2 h postprandial), serum concentration of cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides and C-peptide were measured using standard methods. The HbA_{1c}) was measured using high-performance liquid chromatography (HPLC).

Table I. Clinical characteristics of study group (median and IQR or mean ± SD)

Number (*n*)	87
Women/men	44/43
Age [years]	34 (IQR: 29-43)
Diabetes duration [years]	10 (IQR: 9-14)
Smoking, *n* (%)	21 (24)
BMI [kg/m²]	23 (IQR: 22-27)
SBP [mm Hg]	120 (IQR: 110-130)
DBP [mm Hg]	80 (IQR: 70-80)
FPG [mmol/l]	9.4 ±3
PPG [mmol/l]	9.4 (IQR: 8.3-10.3)
HbA_{1c} [%]	8.4 ±1.4
Total cholesterol [mmol/l]	4.8 (IQR: 4.2-5.3)
HDL cholesterol [mmol/l]	1.7 ±0.4
LDL cholesterol [mmol/l]	2.9 (IQR: 2.4-3.3)
Triglycerides [mmol/l]	2.1 (IQR: 1.6-3.2)
eGFR [ml/min]	111.4 (IQR: 85.6-135.5)
CIMT [mm]	0.52 (IQR: 0.44-0.58)
SI [m/s]	7.73 (IQR: 6.54-8.52)
CAI_x [%]	116.1 ±19
PAI_x [%]	62.1 ±17.2

BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, FPG – fasting glycaemia, PPG – 2-hour postprandial glycaemia, HDL – high density lipoproteins, LDL – low density lipoproteins, eGFR – glomerular filtration rate estimated using Modification of Diet in Renal Disease (MDRD) study equation, CIMT – intima-media thickness, SI – stiffness index, CAI_x – central augmentation index, PAI_x – peripheral augmentation index

Statistical analysis

Statistical analysis was performed using Statistical PL version 8.0 (StatSoft Inc., Tulsa, USA). The results of continuous variables are shown as means ± SD for normally distributed data, median values (IQR) when the data were skewed or as number and percentage of patients for categorical data. The Kolmogorov-Smirnov test with Lilliefors correction was used to test for normality. Using the Levene test the null hypothesis of homoscedasticity could not be rejected in any normally distributed variables. Comparisons between subgroups with and without evidence of microangiopathic complications were performed using Student's *t*-test for normally distributed variables, the Mann-Whitney *U* test for continuous variables with skewed distributions, and Fisher's exact test for categorical data. Logistic regression was used to determine predictors of diabetic microangiopathy, with multivariate analysis performed where the univariate *p* value was less than 0.1.

Results

In the study group 50 patients (cases) had at least one microangiopathic complication (retinopathy [*n* = 39] and/or nephropathy [*n* = 26] and/or neuropathy [*n* = 22]) and in the other 37 subjects (controls) there was no evidence of any late diabetic complications. The clinical characteristics of the study group are presented in Table I.

We found higher values of CIMT in patients with microangiopathy compared to subjects without complications (median [IQR]: 0.53 mm [0.45-0.60 mm] vs. 0.47 mm [0.34-0.52 mm], $p = 0.002$]. There were also significant differences between cases and controls in the parameters of arterial stiffness: higher CAI_x (mean ± SD: 120.2 ±19.4% vs. 110.5 ±17.1%,

p = 0.016) and PAI_x (65.7 ±18.1% vs. 57.2 ±14.9%, p = 0.023) (Table II).

The predictors of diabetic microangiopathy were determined using logistic regression. In the univariate analysis patient's age, duration of diabetes, systolic and diastolic blood pressure, postprandial glycaemia, HbA_{1c} value, IMT of common carotid artery (CIMT), CAI_x and PAI_x were associated with the presence of diabetic microangiopathy. In the multivariate logistic regression analysis the duration of diabetes, systolic and diastolic blood pressure, postprandial glycaemia, HbA_{1c} and triglycerides remained predictors of diabetic microangiopathy after adjustment for age and sex (Table III).

Discussion

Type 1 diabetes is an important risk factor for the development of cardiovascular diseases. In DM1, the presence of traditional cardiovascular risk factors may not entirely explain this excess cardiovascular risk [14]. In type 2 diabetic patients the presence of microalbuminuria is considered a marker of endothelial dysfunction and arterial damage especially in connection with arterial hypertension [15, 16]. The EURODIAB Prospective Complications Study supported the evidence for a strong predictive role of albuminuria in the pathogenesis of CVD in type 1 diabetes [4]. A few studies indicated that albumin excretion was associated with subclinical atherosclerosis [17, 18]. This study shows that type 1 diabetic patients with microangiopathy have greater CIMT and arterial stiffness than subjects without complications. The above results might suggest that micro- and macrovascular complications in diabetic subjects could have common pathomechanisms, since both complications share several traditional risk factors, i.e. hyperglycaemia, arterial hypertension and dyslipidaemia [13, 14]. Our results are consistent with the findings of other authors, but conducted in type 2 diabetic patients. In the Chennai Urban Rural Epidemiology Study (CURES-2) both CIMT and the augmentation index were higher in subjects with retinopathy. Additionally, this study showed that carotid IMT had a strong association with diabetic retinopathy even after adjusting for age, duration of diabetes, HbA_{1c} value, serum cholesterol and triglycerides. The AI was strongly associated with retinopathy even after adjusting for all above parameters except age and duration

Table II. Comparison of intima-media thickness (IMT) and indices of arterial stiffness in subjects with diabetic microangiopathy (cases) and subjects without late diabetic complications (controls). Student's *t*-test (mean ± SD), Mann-Whitney U test (median and IQR) and Fisher's exact test [*n* (%)]

Variable	With microangiopathy (n = 50)	Without microangiopathy (n = 37)	Value of p
Women/men	23/27	21/16	0.39
Age [years]	36 (IQR: 31-48)	30 (IQR: 28-38)	**0.006**
Diabetes duration [years]	11 (IQR: 10-22)	9 (IQR: 8-11)	**0.001**
Smoking, *n* (%)	12 (24)	9 (24)	1.0
BMI [kg/m^2]	23.6 (IQR: 22-27.2)	23 (IQR: 21.5-25.5)	0.17
SBP [mm Hg]	125 (IQR: 120-130)	120 (IQR: 105-120)	**0.0006**
DBP [mm Hg]	80 (IQR: 70-80)	70 (IQR: 60-80)	**0.006**
FPG [mmol/l]	9.8 ±3.1	8.9 ±2.8	0.20
PPG [mmol/l]	9.6 (IQR: 8.5-11.2)	8.8 (IQR: 8.0-9.7)	**0.01**
HbA_{1c} [%]	8.7 ±1.3	7.8 ±1.3	**0.003**
Total cholesterol [mmol/l]	4.9 (IQR: 4.4-5.6)	4.6 (IQR: 4.0-5.6)	0.11
HDL cholesterol [mmol/l]	1.6 ±0.4	1.7 ±0.4	0.18
LDL cholesterol [mmol/l]	3 (IQR: 2.7-3.2)	2.6 (IQR: 2.3-3.3)	**0.036**
Triglycerides [mmol/l]	1 (IQR: 0.8-1.8)	0.8 (IQR: 0.6-1.3)	**0.045**
eGFR [ml/min]	107.4 (IQR: 79.8-129.5)	112 (IQR: 96.3-140.5)	0.22
CIMT [mm]	0.53 (IQR: 0.45-0.60)	0.47 (IQR: 0.34-0.52)	**0.002**
SI [m/s]	7.43 (IQR: 6.83-8.71)	7.01 (IQR: 6.31-7.86)	0.068
CAI_x [%]	120.2 ±19.4	110.5 ±17.1	**0.016**
PAI_x [%]	65.7 ±18.1	57.2 ±14.9	**0.023**

CVD – cardiovascular disease, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, FPG – fasting glycaemia, PPG – 2-hour postprandial glycaemia, HDL – high density lipoproteins, LDL – low density lipoproteins, eGFR – glomerular filtration rate estimated using Modification of Diet in Renal Disease (MDRD) study equation, CIMT – intima-media thickness, SI – stiffness index, CAI_x – central augmentation index, PAI_x – peripheral augmentation index

Table III. The relationship between investigated parameters including measures of CIMT and arterial stiffness and presence of diabetic microangiopathy, with multivariate analysis adjusted for age and sex

Variable	Univariate regression analysis		Multivariate regression analysis	
	β	Value of *p*	β	Value of *p*
Age	**0.07**	**0.006**		
Duration of diabetes	**0.15**	**0.004**	**0.13**	**0.02**
Cigarette smoking	–0.02	0.972		
BMI	0.08	0.252		
SBP	**0.06**	**0.002**	**0.05**	**0.009**
DBP	**0.06**	**0.006**	**0.06**	**0.009**
HbA_{1c}	**0.51**	**0.005**	**0.53**	**0.005**
Cholesterol	0.01	0.08	–0.004	0.48
LDL cholesterol	0.01	0.07	0.01	0.19
HDL cholesterol	–0.02	0.18		
Triglycerides	0.009	0.06	**0.01**	**0.045**
eGFR [ml/min]	–0.003	0.60		
CIMT [mm]	**6.54**	**0.009**	4.57	0.09
SI [m/s]	0.17	0.20		
CAI_x [%]	**0.03**	**0.03**	0.02	0.13
PAI_x [%]	**0.03**	**0.02**	0.03	0.09

β – standardized regression coefficient, SBP – systolic blood pressure, DBP – diastolic blood pressure, FPG – fasting glycaemia, PPG – 2-hour postprandial glycaemia, CIMT – carotid intima-media thickness, CAI_x – central augmentation index, PAI_x – peripheral augmentation index

of diabetes [19]. A similar association between retinopathy and increased CIMT was reported in type 2 diabetes in the work of Malecki *et al.* [20]. Recently, Cardoso *et al.* demonstrated that increased central arterial stiffness measured by pulse wave velocity (PWV) is associated with the presence of microvascular complications (retinopathy and peripheral neuropathy) independently of other established determinants of aortic stiffness [21]. There was a significant positive association between the presence of diabetic retinopathy and PWV, but not with the AI of pulse waveform among Japanese type 2 diabetic patients without macroangiopathy [22].

The results of studies on type 2 diabetic patients cannot be extrapolated directly to type 1 diabetes. Type 2 diabetic patients typically are older, obese and have hypertension, dyslipidaemia and diagnosed CVD. In our study type 1 diabetic patients were relatively young, without previously diagnosed coronary heart disease, with IMT of the common carotid artery in normal ranges in both groups (with and without microangiopathy). Frost *et al.* found in a prospective observation that patients with DM1 with advanced progression rate of CIMT had a higher incidence of nephropathy [13]. Prince *et al.* reported that augmentation pressure was univariately associated with albuminuria level, estimated glomerular filtration rate (eGFR) and cystatin C in DM1 [23]. A study that estimated the relationship between microangiopathy and CIMT in type 1 diabetes was performed by a Turkish research group. They supported the finding that patients with diabetic retinopathy and nephropathy have increased CIMT in comparison to subjects without chronic complications and there was a positive correlation between the number of complications and CIMT. Moreover, multiple regression analysis demonstrated a significant relationship between CIMT and the presence of microvascular complications [17].

In the present study, we found increased values of central and peripheral augmentation indices and CIMT in relation to microangiopathy in young DM1 patients. Additionally, we observed that patients with microangiopathy in comparison to those without microangiopathy exhibited significantly higher values of systolic and diastolic blood pressure, postprandial glycaemia, HbA_{1c}, LDL cholesterol and triglycerides. This indicates that even a persistent small elevation in blood pressure and worsening of metabolic control of diabetes are responsible for the development of pathology in small and large vessels. There is good evidence that dyslipidaemia and hypertension are risk factors of atherosclerosis in both the general and the diabetic population [24]. The results of the Epidemiology of Diabetes Interventions and Complications (EDIC) study did not show any correlation between present glycaemic control and CIMT, but Larsen *et al.* in their 18-year follow-up of DM1 patients revealed a sig-

nificant association between CIMT and mean HbA_{1c} [25, 26].

The process of arterial stiffening is related to decreased elastin content, increased collagen content, change in the type of collagen and collagen cross-links from advanced glycation end products [27]. The AI is an indirect measurement of arterial stiffness and shows a consequent increase in left ventricular afterload, a decrease in diastolic blood pressure and impaired coronary perfusion. It is known that age and blood pressure are the main factors influencing arterial stiffening [28, 29]. Reduced arterial compliance has also been described in diabetic subjects [30]. Arterial stiffness seems to be a validated independent predictor of cardiovascular mortality [31]. However, the knowledge concerning the mechanisms linking reduced compliance in large arteries and changes in small vessels is still limited. We have shown the relationship between AI and microangiopathy. It has been suggested that in diabetes the widespread microcirculatory disease might place an increased impedance burden on the heart through reflected waves. This increased load may contribute to left ventricular remodelling and diabetic cardiomyopathy [32].

Our results suggest that in patients with microangiopathy there is need for careful search for early signs of changes in large vessels. Thus, we might conclude that in young type 1 diabetic patients the development of late complications in small vessels indicates higher risk for cardiovascular disease. However, we should state the limitation of the study which is mainly quite a small study group. This fact might influence loss of significance between arterial stiffness as well as CIMT and microangiopathy after multi-variable adjustment. Moreover, it needs to be noted that the use of some variables that are non-cumulative over time in regression is associated with considerable bias and sometimes lead to erroneous results. Some variables, presenting one-point measurements, were used in this analysis only because we did not have more appropriate parameters (e.g. BP measurements, HbA_{1c}). We also included serum cholesterol, LDL and triglycerides because we considered them relatively stable parameters. We are aware of the limitations of this approach but the non-cumulative variables are clearly defined and it is generally acknowledged that using their values as predictors is limited. We decided to use logistic regression because it can be used to analyse cross-sectional data. Indeed, this tool is often used to determine predictors of an event that takes place later, but from the mathematical point of view it is only the association between variables that is being analysed. Therefore, the "cause-effect" relationship between variables is a matter of interpretation of the results. Future prospective observations are needed to demonstrate the actual interdependence of changes in small and large vessels in diabetes.

In conclusion, one advantage of our study is a description of subclinical changes in the vessels in connection with microangiopathy in a young DM1 population. The study confirms the role of traditional risk factors for late diabetic complications, such as the duration of the disease and metabolic control in the development of microangiopathy.

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