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Clinical determinants of carotid intima-media thickness in patients with diabetes mellitus type 2

Kliniczne determinanty grubości kompleksu intima-media w tętnicach szyjnych u chorych na cukrzycę typu 2

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Abstract

Background and purpose: Early atherosclerotic changes in carotid arteries can be detected using ultrasound examination. The aim of this study was to assess correlations between intima-media thickness (IMT) and gender, age and clinical features of diabetes mellitus (DM).
Material and methods: The study group consisted of 73 patients with type 2 DM (mean age: 63.6 ± 7.5 years), and 74 controls without DM (mean age 62.2 ± 7.5 years). Analysed clinical features of diabetes included disease duration, anti-diabetic treatment, glycaemic control (HbA_{1c} level), presence of metabolic syndrome, and complications of macro- and microangiopathy. IMT was measured using ultrasonography in the carotid arteries (common – CCA, bifurcation, internal – ICA) bilaterally.
Results: Mean and maximum IMT in the CCA was greater in diabetic patients than in controls. Age and male sex, but not vascular risk factors, were independent predictors of increased IMT in all segments. Macroangiopathy correlated with IMT within both CCA in univariate analysis. After adjusting for age and gender, this relationship remained significant in the right CCA in middle-aged patients (59-67 years; $p = 0.01$ for mean IMT, $p = 0.02$ for maximum IMT). In patients without metabolic syndrome, IMT in the right CCA bifurcation correlated with HbA_{1c} level ($p = 0.05$). Patients treated simultaneously with insulin and oral antidiabetic drugs had smaller

Streszczenie

Wstęp i cel pracy: Ultrasonografia tętnic szyjnych umożliwia wykrycie wczesnych zmian miażdżycowych towarzyszących powikłaniom cukrzycy. Celem pracy było określenie zależności grubości kompleksu *intima-media* (KIM) od płci, wieku oraz cech klinicznych cukrzycy.
Materiał i metody: Zbadano 73 chorych na cukrzycę typu 2 (średnia wieku 63,6 ± 7,5 roku) oraz 74 osoby bez cukrzycy (średnia wieku: 62,2 ± 7,5 roku). Do cech klinicznych cukrzycy zaliczono: czas trwania choroby, leczenie przeciwcukrzycowe, kontrolę glikemii (stężenie HbA_{1c}), obecność zespołu metabolicznego oraz powikłań makro- i mikroangiopatycznych. Grubość KIM oceniono ultrasonograficznie obustronnie w trzech segmentach ściany dalszej tętnic szyjnych [wspólnej (CCA), bifurkacji oraz wewnętrznej (ICA)].
Wyniki: U chorych na cukrzycę średnia i maksymalna grubość KIM w CCA była większa niż w grupie kontrolnej. Wiek i płeć męska stanowiły niezależne czynniki rokownicze pogrubienia KIM przy jednoczesnym braku wpływu naczyniowych czynników ryzyka. W analizie jednoczynnikowej wykazano korelację powikłań makroangiopatii z grubością KIM w obrębie obu CCA. Po uwzględnieniu wieku i płci zależność ta pozostała istotna w prawej CCA u chorych w wieku 59–67 lat ($p = 0,01$ dla średniej grubości KIM i $p = 0,02$ dla maksymalnej grubości KIM). U chorych nieobciążonych zespołem metabolicznym stwierdzono korelację grubości KIM w ob-

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IMT in the right ICA than those treated with insulin only (0.471 ± 0.105 vs. 0.678 ± 0.209 mm; $p = 0.04$).
Conclusions: In diabetic patients, ultrasound IMT measurement can be used to assess the cardiovascular risk and to determine indications for intensified anti-diabetic treatment. IMT is a sensitive marker of early carotid atherosclerosis, particularly on the right side.

Key words: intima-media thickness, ultrasonography, diabetes mellitus, microangiopathy, macroangiopathy, HbA_{1c}.

rębie bifurkacji prawej CCA ze stężeniem HbA_{1c} ($p = 0,05$). U chorych leczonych jednocześnie insuliną i lekami doustnymi stwierdzono mniejszą średnią grubość KIM w prawej ICA w porównaniu z osobami przyjmującymi wyłącznie insulinę (0,471 ± 0,105 *vs* 0,678 ± 0,209 mm; $p = 0,04$).
Wnioski: Grubość KIM u chorych na cukrzycę może służyć do oceny ryzyka chorób układu krążenia oraz ustalenia wskazań do intensyfikacji leczenia przeciwcukrzycowego. Jest czułym wskaźnikiem wczesnych zmian miażdżycowych, a większą wartość kliniczną mają pomiary przeprowadzane w obszarze bifurkacji i tętnicy szyjnej wewnętrznej po stronie prawej.

Słowa kluczowe: kompleks *intima-media*, ultrasonografia, cukrzyca, makroangiopatia, mikroangiopatia, HbA_{1c}.

Introduction

Atherosclerosis develops progressively in several stages and depends on exogenous and endogenous factors. The contribution of genetic abnormalities is unequivocal and includes mutations leading to the polymorphisms of genes involved in the basic atherothrombotic processes [1,2]. Among numerous exogenous factors, the influence of pathological glycation products and the oxidative stress induced by the chronic hyperglycaemia, insulin resistance and hyperinsulinaemia is highlighted [3-5]. Decreased production of nitric oxide (NO), as well as increased concentrations of adhesive molecules and free radicals, increases the endothelial damage, while the insulin resistance antagonizes the positive effects of insulin and accelerates progression of atheromatous lesions [6,7]. Increased intima-media thickness (IMT), as visualized with ultrasonography, has important prognostic value for the development of cardiovascular diseases and the development of atherosclerotic lesions in carotid and peripheral arteries [8-15].

A strong correlation was found between IMT thickness and the following variables: age, male sex, arterial hypertension, hyperlipidaemia, smoking, obesity, leukocytosis, concentrations of C-reactive protein, fibrinogen and homocysteine, *Chlamydia pneumoniae* infection, diabetes mellitus (DM) and insulin resistance [16].

Diabetes mellitus plays a crucial role as an independent risk factor for stroke in 37-42% of cases, especially among patients younger than 65 [17]. Microangiopathic complications, even in their preclinical stage (microalbuminuria due to nephropathy), are associated with acceleration of the atherosclerotic process and with an increased risk of cardiovascular disorders [18,19].

Atherosclerotic lesions, when assessed ultrasonographically, show faster increase of their area and volume than the more gradual and slow increase of IMT [20], but the high incidence of complications as well as important contribution of vascular and metabolic factors suggest the need for assessment of early lesions of vessel walls in patients with type 2 DM and for the determination of their clinical significance.

The aim of this study was to determine the relationship between IMT thickness assessed in duplex ultrasound examinations and sex, age, or predefined clinical features of DM.

Material and methods

The study included patients diagnosed with type 2 DM, aged between 50 and 70, who had no more than three risk factors for cardiovascular disorders that have a major impact on IMT in carotid arteries. Those risk factors included arterial hypertension, smoking and dyslipidaemia. The study group involved 73 patients with type 2 DM (mean age: 63.6 years; standard deviation [SD]: 7.5). The control group consisted of 74 subjects without DM (mean age: 62.2 years; SD: 7.5).

The protocol of the study was approved by the Bioethical Committee at the Silesian Medical University of Katowice. Each subject provided informed consent to participate in this study.

According to the history and medical records, the following clinical features of DM were defined: (1) disease duration (measured in years since the diagnosis was made); (2) method of anti-diabetic treatment (insulin, oral hypoglycaemics, or combination of insulin and oral medications); (3) control of glycaemia (HbA_{1c} level [%]);

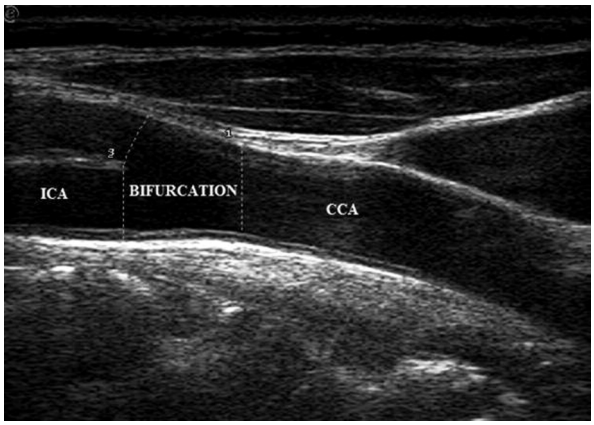
(4) prevalence of metabolic syndrome, diagnosed according to the International Diabetes Federation criteria; (5) prevalence of macroangiopathic complications (ischaemic heart disease, including myocardial infarction, peripheral artery disease, stroke or transient ischaemic attack [TIA]), analysed further in total; (6) prevalence of microangiopathic complications (retinopathy, nephropathy, neuropathy, diabetic foot), analysed further in total.

The prevalence of arterial hypertension, smoking, obesity, and dyslipidaemia was also noted.

Clinical examination involved the frequency and regularity of the heart rhythm, measurement of the systolic and diastolic blood pressure, body weight, and body mass index (BMI), as well as the signs of damage to the central and/or peripheral nervous system, including features of diabetic neuropathy.

Intima-media thickness was measured using high resolution duplex sonography (Esaote MyLab60 apparatus). Measurements were performed in patients lying down and with the head turned opposite to the side of the examined artery. A linear ultrasound probe emitting ultrasound with the frequency changing between 5.6 and 8.0 MHz was used and the lateral approach was utilized. IMT was measured manually in 2D images and B-mode presentation according to the Mannheim Intima-Media Thickness Consensus [9] within the three segments of the far wall of the carotid without atherosclerotic lesions (Fig. 1): (1) at the level of the common carotid artery (CCA), within a 10-mm distance (or 20 mm if an atherosclerotic lesion was present) from the bifurcation, at five points separated from each other by 2-4 mm; (2) at the level of the bifurcation, at three points chosen in regard of the length of the bifurcation segment and the presence of atherosclerotic lesions; (3) at the level of the internal carotid artery (ICA), at three points within a 10-mm distance from the bifurcation carina, or beyond that distance, if the atherosclerotic lesions were found in that location. The differentiation between thickened intima-media complex and atherosclerotic plaque was made using the definition provided by the Mannheim Carotid Intima-Media Consensus, which describes the latter as a focal structure thicker than 1.5 mm, or a small structure encroaching into the arterial lumen of at least 0.5 mm, or thicker by $> 50\%$ than the surrounding IMT value.

Data from IMT measurements within the CCA bifurcation and the initial ICA segment were provided separately. In each case, maximal and mean values of measurements within the CCA were reported, and the mean values of measurements within the bifurcation and ICA.



CCA – common carotid artery; ICA – internal carotid artery

Fig. 1. Carotid artery segments according to Mannheim Intima-Media Thickness Consensus

Statistical analysis

Statistical analysis was performed using the STATISTICA v. 5.5 statistical package as well as Excel 2007. A p-value of 0.05 or less was considered statistically significant. Distribution of most quantitative variables deviated significantly from normal (as assessed by Shapiro-Wilk test); thus, the univariate analyses were performed with non-parametric tests. Comparisons between two groups were made with Mann-Whitney U-test, and comparisons among three groups were made with Kruskal-Wallis test. The univariate analysis of dichotomous variables in 2×2 contingency tables was performed with Fisher exact test, and in the case of 3×2 contingency tables, a χ^2 test with Yates correction was used.

The analysis also included multiple regression. ANCOVA was used to test the effect of independent variables, if they were not presented in an ordinal scale. A logistic regression analysis was used if the dependent variable could be reported as a dichotomous variable. Age and disease duration were considered as the continuous covariables in ANCOVA. Tables include the p-value at the moment of removal from the model for the removed variables and the p-value for those variables that were left in the model. In the case of independent variables measured on an ordinal scale, a p-value is accompanied by a '+' or '–' sign to show the direction of relationship between dependent and independent variables (a '+' sign means that an increased value of the independent variable increases the value of the dependent variable and vice versa). A '+M' sign was added in cases where male sex had an important effect on the dependent variable.

Results

Patients with type 2 DM were similar to controls regarding sex and age. Table 1 provides demographic characteristics, as well as clinical and biochemical features of patients and controls. The distribution of the analysed cardiovascular risk factors among patients with type 2 DM and controls is also provided in Table 1. Obesity, metabolic syndrome, arterial hypertension and cardiovascular risk factors (macroangiopathic complications) were all more prevalent in patients with type 2 DM (Table 1).

Vast atherosclerotic lesions in examined segments of vessels, and, to a minor extent, also pathological obesity, precluded IMT assessment in 6.5% of patients with type 2 DM (29/444 segments), and in 2.7% of controls (12/438 segments). The completeness of measurements was highest in CCA (100% in both groups) and the lowest in ICA (90% in patients and 96% in controls).

Mean and maximal IMT was significantly greater in DM patients than in controls (Table 2).

Age and male sex, but not vascular risk factors, were independent predictors of increased IMT in all segments among patients with DM.

Univariate analysis showed a significant correlation between the presence of macroangiopathic complications and the IMT within the left and right CCA. Multiple regression analysis showed a strong effect of (1) age on the IMT in both CCAs and in the right-sided bifurcation, (2) male sex on the IMT in all left-sided segments, and (3) duration of the disease on the IMT within the left ICA. All those factors attenuated the correlation shown in univariate analysis with the exception of patients aged 59-67, in whom the correlation of IMT with the macroangiopathic complications remained significant for the right CCA (Tables 3 and 4). Among patients aged between 59 and 67, a significant influence

Table 1. Age, gender, clinical and biochemical characteristics in diabetic patients and controls

	Patients with diabetes (n = 73)	Controls (n = 74)	P-value
Age [years], mean ± SD	63.6 ± 7.5	62.2 ± 7.5	0.30
Women	37 (50.68%)	45 (60.81%)	0.22
Arterial hypertension	60 (82%)	49 (66%)	0.03
Dyslipidaemia	56 (77%)	49 (65%)	0.21
Smoking	10 (14%)	13 (17%)	0.67
Subjects treated with:			
oral hypoglycaemics	36 (49.3%)	–	–
insulin	24 (32.9%)	–	–
insulin and oral hypoglycaemics	13 (17.8%)	–	–
statins	44 (60.3%)	28 (37.8%)	0.01
any hypotensive drug	52 (71.2%)	34 (43.2%)	0.003
Microangiopathy	32 (43.8%)	–	–
Macroangiopathy	42 (57.5%)	30 (40.54%)	0.04
Blood fasting glucose [mmol/L]; mean ± SD	8.05 ± 2.44	5.64 ± 1.11	< 0.000001
HbA_{1c} level [%]	7.43 ± 1.29	–	–
Obesity	37 (51%)	17 (23%)	0.004
Body mass index; mean ± SD	30.29 ± 4.95	27.22 ± 3.99	0.08
Metabolic syndrome	55 (75%)	29 (39.2%)	0.00002
Diabetes duration [years]; mean ± SD	11.7 ± 8.1	–	–

SD – standard deviation
Data are presented as n (%), if not otherwise stated.

Table 2. Mean values of intima-media thickness in diabetic patients and controls

	Intima-media thickness [mm]		*P*-value
	Diabetic patients *n* = 73	Control group *n* = 74	
Max. right CCA	0.852 ± 0.2	0.763 ± 0.185	0.004
Mean right CCA	0.731 ± 0.167	0.667 ± 0.155	0.01
Mean right bifurcation	0.816 ± 0.263	0.788 ± 0.227	0.3
Mean right ICA	0.593 ± 0.206	0.557 ± 0.189	0.17
Max. left CCA	0.916 ± 0.236	0.786 ± 0.162	0.0004
Mean left CCA	0.775 ± 0.19	0.681 ± 0.133	0.0009
Mean left bifurcation	0.866 ± 0.23	0.8 ± 0.247	0.09
Mean left ICA	0.616 ± 0.218	0.552 ± 0.167	0.1

CCA – common carotid artery; ICA – internal carotid artery

Table 3. Comparison of age, gender, and intima-media thickness in relation to the macro- and microangiopathic complications in diabetic patients (univariate analysis)

	Patients with macroangiopathy (*n* = 43)	Patients without macroangiopathy (*n* = 30)	*P*-value	Patients with microangiopathy (*n* = 32)	Patients without microangiopathy (*n* = 41)	*P*-value
Age [years]*	66 ± 6.8	60 ± 7.5	0.004	65 ± 7.6	62 ± 7.3	0.12
Men [*n* (%)]	22 (51)	14 (47)	0.18	12 (37.5)	24 (58)	0.10
Intima-media thickness [mm]*						
Mean left CCA	0.807 ± 0.203	0.724 ± 0.164	0.03	0.806 ± 0.208	0.751 ± 0.173	0.20
Max. left CCA	0.962 ± 0.249	0.85 ± 0.2	0.03	0.95 ± 0.24	0.89 ± 0.23	0.22
Mean left bifurcation	0.907 ± 0.240	0.81 ± 0.199	0.09	0.851 ± 0.208	0.88 ± 0.247	0.82
Mean left ICA	0.625 ± 0.222	0.6 ± 0.215	0.52	0.653 ± 0.211	0.59 ± 0.22	0.18
Mean right CCA	0.757 ± 0.138	0.687 ± 0.197	0.05	0.726 ± 0.153	0.734 ± 0.18	0.86
Max. right CCA	0.878 ± 0.161	0.81 ± 0.242	0.12	0.85 ± 0.197	0.85 ± 0.20	0.95
Mean right bifurcation	0.865 ± 0.266	0.815 ± 0.256	0.34	0.845 ± 0.29	0.847 ± 0.243	0.57
Mean right ICA	0.593 ± 0.213	0.585 ± 0.2	0.90	0.65 ± 0.24	0.55 ± 0.17	0.15

**mean ± standard deviation*
CCA – common carotid artery; ICA – internal carotid artery

of macroangiopathic complications was noted for mean IMT in the right CCA [$F(1,21) = 7.51, p = 0.01$] and for maximum IMT in the right CCA [$F(1,21) = 7.01$, $p = 0.02$]. Presence of complications was associated with higher values of those measurements. No correlation was found between IMT and the presence of microangiopathic complications among DM patients.

Intima-media thickness did not correlate with HbA_{1c} concentration in the whole study group. When patients with metabolic syndrome were excluded, such a correlation was found for the mean IMT within the bifurcation of the right CCA (Spearman rank correlation coefficient, $r = 0.61, p = 0.05$).

A significant association was found between the method of anti-diabetic treatment and the mean and maximal IMT within the right CCA and the mean IMT within the right ICA – the lowest IMT in those segments was noted among patients treated with oral hypoglycaemics when compared to those treated with insulin alone or to the patients treated with both insulin and oral

Table 4. Intima-media thickness (IMT) in relation to clinical characteristics of diabetes characteristics – multiple regression analysis (*p*-values are reported; for significant relationships, beta coefficient values were also provided)

IMT	Age	Gender	Diabetes duration	Macroangiopathy	Microangiopathy
Mean left CCA	0.002 (+) β = 0.34 ± 0.11	0.008 (+M) β = 0.29 ± 0.11	0.39	0.41	0.13
Max. left CCA	0.02 (+) β = 0.26 ± 0.11	0.004 (+M) β = 0.33 ± 0.11	0.21	0.29	0.11
Mean left bifurcation	0.34	0.04 (+M) β = 0.25 ± 0.12	0.47	0.26	0.86
Mean left ICA	0.17	0.03 (+M) β = 0.27 ± 0.12	0.72	0.71	0.23
Mean right CCA	0.003 (+) β = 0.37 ± 0.11	0.72	0.07 (+) β = 0.20 ± 0.11	0.36	0.13
Max. right CCA	0.004 (+) β = 0.35 ± 0.11	0.63	0.06 (+) β = 0.22 ± 0.11	0.59	0.18
Mean right bifurcation	0.03 (+) β = 0.27 ± 0.12	0.28	0.46	0.99	0.63
Mean right ICA	0.08	0.60	0.005 (+) β = 0.35 ± 0.12	0.57	0.33

CCA – common carotid artery; ICA – internal carotid artery
'+' sign means that an increased value of the independent variable increases the value of the dependent variable.
A '+M' sign suggests that male sex has an important effect on the dependent variable.

Table 5. Characteristics of diabetic patients treated with insulin alone or taking insulin and oral hypoglycaemics together

	Diabetic patients treated with insulin only (*n* = 24)	Diabetic patients treated both with insulin and oral hypoglycaemics (*n* = 13)
Maximal daily dose of insulin [IU]	53.04 ± 21.8	49.8 ± 22.2
Obesity, *n* (%)	11 (45.8%)	12 (92.3%)
Metabolic syndrome, *n* (%)	20 (83.33%)	11 (84.6%)
Systolic blood pressure [mm Hg]	142.9 ± 19.67	144.6 ± 16.13
Diastolic blood pressure [mm Hg]	80.42 ± 11.97	78.07 ± 10.9
HbA_{1c} [%]	7.89 ± 1.1	7.41 ± 1.38
LDL [mmol/L]	3.23 ± 1.2	2.68 ± 0.8
HDL [mmol/L]	1.25 ± 0.29	1.23 ± 0.23
Triglycerides [mmol/L]	2.00 ± 1.07	1.97 ± 0.52
Statins, *n* (%)	13 (54.2%)	8 (61.5%)

SD – standard deviation
Data are presented as mean ± standard deviation, if not otherwise stated.

hypoglycaemics (mean IMT in right CCA = 0.692 ± 0.157 vs. 0.790 ± 0.164 vs. 0.727 ± 0.418 mm, respectively, $p = 0.03$; maximum IMT in right CCA = 0.804 ± 0.104 vs. 0.920 ± 0.210 vs. 0.862 ± 0.245 mm, respectively, $p = 0.03$; mean IMT in right ICA = 0.569 ± 0.206 vs. 0.678 ± 0.209 vs. 0.471 ± 0.105 mm, respectively, $p = 0.01$). Duration of the disease correlated positively with mean and maximal values of IMT in the right CCA, as well as with mean IMT values in the right ICA. It is worth noting that patients receiving oral

hypoglycaemics had shorter duration of the disease (8.5 ± 6.4 years) than those treated with insulin alone (14.4 ± 9.0 years) or patients receiving both insulin and oral hypoglycaemics (15.6 ± 7.5 years, $p = 0.002$). Therefore, a separate analysis was performed among patients treated either with insulin or both with insulin and oral hypoglycaemics, in whom the duration of the disease was similar. Again, in patients receiving combined treatment, lower mean IMT was noted in the right ICA. Patients receiving combined treatment were more often obese, had higher BMI, lower HbA_{1c} concentration and lower LDL cholesterol concentration, and received statins more commonly (Table 5).

Discussion

Diabetes mellitus is an independent risk factor for atherosclerosis and resulting cardiovascular complications. Patients with impaired glucose tolerance and, to a greater extent, DM patients have increased IMT [21]. Increased IMT in carotid arteries can be noted even in patients diagnosed de novo with DM, which suggests that this abnormality occurs before the clinical manifestation of the disease [22]. Major determinants of increased IMT among diabetic patients include obesity, dyslipidaemia and hyperinsulinaemia, which constitute the cardinal features of insulin resistance syndrome. Thickening of the intima-media complex is especially clear in patients who have experienced macroangiopathic complications [23].

Intima-media thickness within the CCA is greater in diabetic patients than in controls, especially on the left, which results from the anatomical and hemodynamic differences in the biomechanical forces affecting the vessel wall and generated by the blood flow on both sides [24].

Age and male sex were strong determinants of IMT in diabetic patients, similarly to the relationship noted in healthy subjects. No relationship was found between IMT and analysed cardiovascular risk factors (although the *p*-value was close to significant in the case of IMT within the bifurcation of the right CCA), probably because of the strong impact of age and due to the greater impact of the metabolic abnormalities typical for DM, as noted also by others [25,26].

We observed an association between IMT and the prevalence of macroangiopathic complications of DM; this association remained significant in patients aged 58-67 when the impact of age and male sex was controlled for.

A strong association between IMT and vascular risk factors, ischaemic heart disease and symptomatic atherosclerosis in other locations, including stroke, has been confirmed in numerous studies [27-29].

Among patients with stroke of atherothrombotic origin, the risk of stroke increases proportionally to the IMT, and greater IMT within the CCA is associated with increased risk of stroke recurrence [30]. Our findings confirm the significance of IMT assessed with ultrasonography as a predictor of cardiovascular disease risk in patients with type 2 DM. It is interesting that a correlation was found in some segments of the studied arteries between IMT and glycaemic control as defined by the HbA_{1c} concentration. It was shown in patients with DM who had no metabolic syndrome, and in whom the disturbances related to the disease itself prevail over the effect of cardiovascular risk factors.

Both the ARIC and INVADE studies showed that the HbA_{1c} concentration is an independent factor related to the IMT in patients with DM and with cardiovascular disease risk [31]. No cut-off point for the development of complications was suggested, however. Nevertheless, it was stated that the reduction of HbA_{1c} concentration by 1% decreases the risk of incident myocardial infarction by 14% and stroke by 11%. There was no difference, however, in terms of the incidence of cardiovascular complications between those treated aggressively ($HbA_{1c} \leq 7.0\%$) and patients receiving dietary treatment only ($HbA_{1c} = 7.9\%$) during the 15-year follow-up [32,33].

Better glycaemic control translates into the dynamics of the development of early atherosclerotic lesions and into the decreased risk of cardiovascular diseases, as suggested by the meta-analysis of ACCORD, ADVANCE, UKPDS, and VADT studies [34]. Even in patients with good glycaemic control ($HbA_{1c} = 5.8\text{-}6.4\%$) further improvement in glycaemic control prevents thickening of the intima-media complex in carotid arteries, and ultrasonography is a valuable method enabling monitoring of the progression of those lesions [35]. IMT depends on the duration of the DM, while the increase of HbA_{1c} by 1% per year of the disease increases the risk of intima-media thickening by 30% [36].

The gradual increase of the atherosclerotic lesions in carotid arteries, noted in healthy subjects, patients with newly diagnosed DM and in those with previously diagnosed DM, points to the important effect of disease duration on atherosclerosis development within the carotid arteries and to the presence of the lesions even in a preclinical stage [37].

We have analysed the possible impact of anti-diabetic treatment and found significantly smaller IMT in patients receiving oral hypoglycaemics. They had the shortest disease duration, which persuaded us to perform a separate analysis limited to patients treated with insulin only or with insulin plus oral hypoglycaemics who had similar duration of the disease. It showed the advantage of the combined treatment for the IMT in the right ICA. Few studies have been published so far regarding the IMT within the carotids in patients treated with insulin only and in those treated with oral agents; their results are divergent. Large prospective studies conclude that more intense anti-diabetic treatment may result in significantly lower incidence of serious cardiovascular complications [34]. This applies to patients treated with oral hypoglycaemics and to those receiving insulin. The EDIC study, conducted in young (13-40 years) patients without additional cardiovascular risk factors, did not show significant differences in IMT within CCA or ICA between those treated aggressively and in patients treated conventionally. Intensive therapy with insulin reduced the risk of any incident cardiovascular complication by 42%, reduced the risk of myocardial infarction or stroke by 57% and significantly reduced the risk of microangiopathic complications [38].

Comparison of type 2 DM patients treated with insulin of mixed content (Mix 30) and those receiving insulin injections more often (4 times daily) showed a beneficial effect of more aggressive treatment on the glycaemic control (HbA_{1c} concentration) but not for the IMT in carotid arteries [39]. Six-month observation suggested a benefit of intensive polytherapy (three oral medications with divergent mechanisms of action) in terms of the IMT in carotid arteries among patients with newly (< 1 year) diagnosed DM (0.88 ± 0.26 mm vs. 0.96 ± 0.22 mm) [40]. New and more persuasive evidence may be provided by the Copenhagen Insulin and Metformin Therapy Trial (CIMT), which began in 2008 and whose final findings are expected in 2014. The primary outcome is the progression of the IMT in carotid arteries in patients with type 2 DM treated simultaneously with insulin and metformin in comparison to those treated with insulin only [41].

In our study, patients receiving aggressive treatment were more frequently treated also with statins with consequent normalization of lipid profile; no association was found between the IMT and the presence of dyslipidaemia. It is worth, however, taking into account the vast and pleiotropic mechanism of action of statins, which is independent of their lipid-lowering effect [42]. Our findings suggest that the intensification of anti-diabetic treatment has a positive impact on the early changes occurring in the ICAs and, indirectly, on the risk of cardiovascular diseases.

It is noteworthy that most of the correlations among IMT and analysed clinical features of DM were related to the specific segments and predominated on the right side. IMT in young subjects does not differ between sides [43], while in the following years it is greater on the left. Among subjects aged over 65 and burdened with cardiovascular diseases this difference diminishes [44], suggesting the domination of the atherosclerotic processes over the biomechanical forces remodelling the vessel walls. It may be supposed that the decreased adaptation of the carotid artery walls to the haemodynamic conditions is responsible for the excessive response and the faster progression of abnormalities on the right side. Greater IMT on the right side was reported in patients with borderline hypertension or with isolated systolic hypertension; IMT of the right CCA is also a predictor of acute coronary events in patients with stable ischaemic heart disease [45]. The diverse distribution of lesions within the walls of carotid arteries has also been reported by others. The results of the CARDIA study suggested that DM, arterial hypertension and smoking had a greater impact on IMT within the bifurcation, while the LDL concentration affected mostly IMT within the ICA [46].

In the CAPS study, vascular risk factors, including diabetes, correlated to a greater extent with the IMT progression in the ICA than in the CCA [47]. This suggests the divergent response of the intima-media complex on each side for the effect of specific haemodynamic, metabolic and biochemical factors, and the divergent predictive value of the measurements performed within the carotid arteries on both sides.

Conclusions

1. The findings of this study confirm the high utility of ultrasonographic assessment of IMT in patients with type 2 DM as a sensitive marker of early atherosclerotic changes in carotid arteries, showing the greater clinical value of measurements performed within the bifurcation and ICA on the right side.
2. The association between IMT in carotid arteries and the occurrence of macroangiopathic complications and glycaemic control in diabetic patients in a specific age and with vascular risk factors, as well as the association between IMT and the method of anti-diabetic

treatment, might be used for the assessment of risk of cardiovascular diseases and for the determination of indications for more aggressive treatment in order to achieve optimal metabolic control.

Disclosure

Authors report no conflict of interest.

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