ORIGINAL ARTICLE

# Association between carotid plaque score and microvascular complications of type 2 diabetes

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**KEY WORDS**

microangiopathy, plaque score, type 2 diabetes

**ABSTRACT**

**INTRODUCTION** According to the "common soil" hypothesis, diabetic microangiopathy and macroangiopathy have a similar pathophysiological background. It has been well documented that carotid artery atherosclerosis in patients with type 2 diabetes is associated with cardiovascular complications; however, it remains unclear whether there is a similar association for microvascular complications.

**OBJECTIVES** We investigated whether the carotid plaque score and the carotid intima–media thickness (IMT) are associated with macroangiopathic and microangiopathic complications of type 2 diabetes.

**PATIENTS AND METHODS** We enrolled patients with type 2 diabetes and microvascular complications or overt macroangiopathy. A B-mode carotid ultrasound was performed in all participants, and anthropometric parameters, hemoglobin $A_{1c}$ ($HbA_{1c}$) levels, lipid profile, and smoking status were assessed.

**RESULTS** The study included 73 patients (mean [SD] age, 63.6 [7.5] years; 36 men [49%]). The mean (SD) diabetes duration was 11.7 (8.1) years. Microvascular complications were observed in 32 patients (43.8%), and overt macroangiopathy, in 42 (57.5%). Hypertension was reported for 60 patients (82%); dyslipidemia, for 56 (77%); obesity, for 37 (51%); and smoking, for 10 (14%). A multivariate regression analysis showed that the carotid plaque score, but not carotid IMT, was significantly associated with dyslipidemia ($P = 0.03$) and microangiopathy ($P = 0.01$).

**CONCLUSIONS** Our results indicate that, unlike carotid IMT, the carotid plaque score is independently associated with microangiopathic complications in type 2 diabetes. Patients with a high plaque score should receive special care and the most intensive treatment to stop progression of these complications.

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**INTRODUCTION** The estimated number of people with diabetes worldwide is 387 million, and it will reach 592 million by the year 2035.[1] Diabetes is a considerable public health problem. It can cause devastating long-term microvascular and macrovascular complications, which mainly affect the kidney, eyes, heart, and arteries.[2] Traditionally, the microvascular and macrovascular complications of type 2 diabetes have been viewed separately; however, there is a strong indication from clinical studies that they may share a common pathophysiological mechanism. This concept is known as the "common soil" hypothesis, which suggests a close link between diabetic microangiopathy and macroangiopathy. As supporting evidence, Brownlee[3] pointed out that hyperglycemia-induced overproduction of superoxide, which activates tissue-damaging pathways (ie, polyol, hexosamine, and protein kinase C), might be a single mechanism leading to these complications.[3] Moreover, he also indicated that insulin resistance induced by high free fatty acid levels led

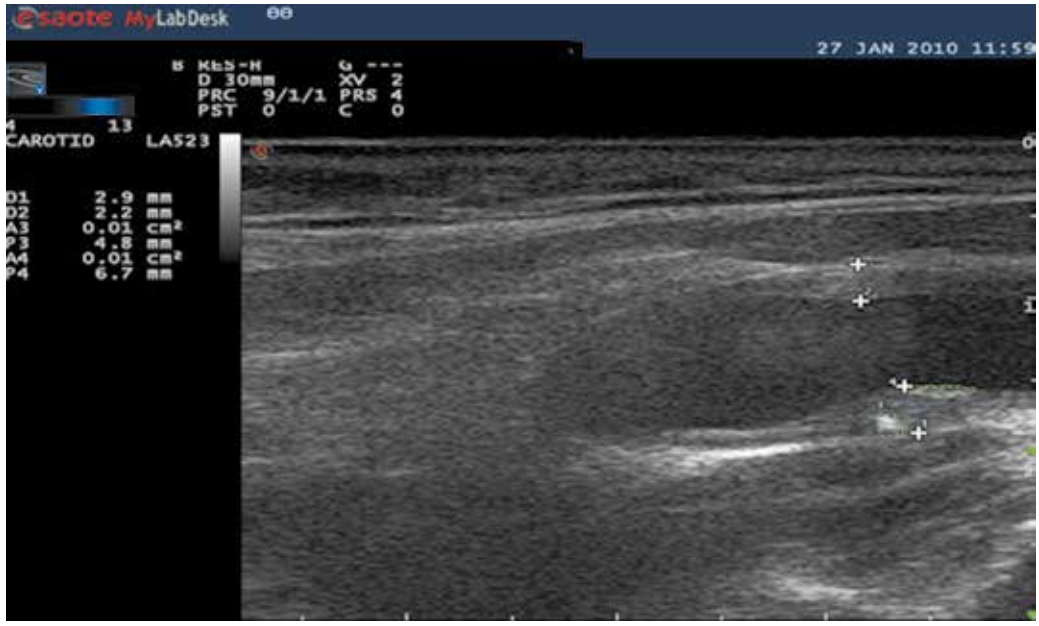


**FIGURE 1**
Measurement of the maximum thickness of atherosclerotic plaques in the plane of the maximum cross-sectional of longitudinal lesions

to increased production of superoxide in arterial endothelial cells.[4]

It is mainly diabetic retinopathy that has been confirmed to be related to macrovascular disease in clinical studies. It has also been shown to be an independent predictor of cardiovascular events and death.[5-7] Diabetic retinopathy and atherothrombosis may be pathophysiologically alike, as both include impaired endothelial function, inflammation, neovascularization, apoptosis, and the hypercoagulable state.[8] While de Kreutzenberg et al[9] proved that retinopathy and nephropathy were independently associated with the presence of carotid plaques, studies regarding other microvascular complications in relation to carotid atherosclerotic markers are lacking. An interesting question is whether all microvascular complications of type 2 diabetes are independently associated with the presence of carotid atherosclerosis. The issue is still under debate owing to the limited number of studies and equivocal results.

The B-mode ultrasound is a noninvasive method for examining the walls of the peripheral arteries. It enables the measurement of the intima–media thickness (IMT) and detection of atherosclerotic plaque in the common carotid artery. Increased carotid IMT and plaque score are known ultrasound markers of early atherosclerosis.[10,11] Therefore, the present study was designed to evaluate the atherosclerotic burden, as expressed by the carotid IMT and plaque score, among patients with type 2 diabetes with microangiopathic complications, as compared with patients with overt macroangiopathy.

## PATIENTS AND METHODS

### Patients

We enrolled consecutive patients (age, 50–70 years) with microvascular complications of type 2 diabetes or overt macroangiopathy (or both) who presented at the Outpatient Diabetology and Neurology Clinic, Medical University of Silesia in Zabrze, Poland. Patients with terminal disease (eg, malignant neoplasm) were excluded.

On the basis of a medical interview and documentation, the following data were recorded: date of diabetes onset, concomitant medication use and diseases, family history, alcohol drinking and smoking habits, as well as the prevalence of macrovascular and microvascular complications of type 2 diabetes. Macrovascular complications (macroangiopathy) included ischemic heart disease, peripheral artery disease, stroke, and transient ischemic attack. Microvascular complications included retinopathy, nephropathy, neuropathy, and diabetic foot. Neuropathy was diagnosed on the basis of medical records as well as the signs and symptoms such as neurogenic pain, lack of or weakened deep tendon reflexes, muscular atrophy, and sensory disturbances detected by a Semmes–Weinstein aesthesiometer.

Participants underwent a basic physical examination that included the measurement of blood pressure (mean of 3 measurements in the sitting position, 5 minutes apart) and anthropometric parameters such as height and weight. Arterial hypertension was defined as systolic blood pressure of 140 mm Hg or higher and/or diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive drugs. Hemoglobin $A_{1c}$ ($HbA_{1c}$) levels and lipid profile were also assessed. A smoker was defined as a patient who smoked at least 10 cigarettes a day for at least 6 months. The criteria for dyslipidemia were as follows: total cholesterol levels of 5.2 mmol/l or higher, low-density lipoprotein cholesterol levels of 3.4 mmol/l or higher, high-density lipoprotein cholesterol levels of 1.0 mmol/l or lower, and triglyceride levels of 1.7 mmol/l or higher, or the use of cholesterol-lowering medication. The study was performed according to the Declaration of Helsinki and was approved by the Ethical Committee of the Medical University of Silesia. All patients provided informed written consent to participate in the study.

**TABLE 1** Clinical and demographic characteristics and incidence of macroangiopathic and microangiopathic complications in patients with type 2 diabetes (n = 73)

| Variable | Value |
|---|---|
| Age, y, mean (SD) | 63.6 (7.5) |
| Women, n (%) | 37 (51) |
| Men, n (%) | 36 (49) |
| OAD, n (%) | 36 (49.3) |
| Insulin treatment, n (%) | 24 (32.9) |
| OAD + insulin, n (%) | 13 (17.8) |
| Diabetes duration, y, mean (SD) | 11.7 (8.1) |
| $HbA_{1c}$, %, mean (SD) | 7.43 (1.29) |
| Obesity, n (%) | 37 (51) |
| Positive family history of type 2 diabetes, n (%) | 38 (52) |
| Macroangiopathy, n (%) | 42 (57.5) |
| Ischemic heart disease, n (%) | 28 (38) |
| Myocardial infarction, n (%) | 13 (18) |
| Peripheral artery disease, n (%) | 5 (7) |
| Stroke, n (%) | 23 (30) |
| Microangiopathy, n (%) | 32 (43.8) |
| Retinopathy, n (%) | 14 (19.2) |
| Neuropathy, n (%) | 21 (28.8) |
| Nephropathy, n (%) | 1 (1.4) |
| Diabetic foot, n (%) | 4 (5.5) |
| BMI, kg/m$^2$, mean (SD) | 30.29 (4.95) |
| Hypertension, n (%) | 60 (82) |
| Dyslipidemia, n (%) | 56 (77) |
| Smoking, n (%) | 10 (14) |

Abbreviations: BMI, body mass index; $HbA_{1c}$, hemoglobin $A_{1c}$; OAD, oral antidiabetic drugs

**TABLE 2** Multivariate regression analysis of the association between the plaque score and age, sex, cardiovascular risk factors, and type 2 diabetes complications

| Independent variable | *P* value |
|---|---|
| Age | 0.002 |
| Male sex | 0.05 |
| Hypertension | NS |
| Dyslipidemia | 0.03 |
| Smoking | NS |
| Diabetes duration | NS |
| Macroangiopathy | NS |
| Microangiopathy | 0.01 |

Abbreviations: NS, nonsignificant

**Carotid ultrasound examination** All patients underwent a carotid B-mode ultrasound examination. An ultrasound of both carotid arteries was performed with a high-resolution Duplex scanner Esaote MyLab60 X-vision with a linear-array transducer operating at a frequency of 5.6 to 10.0 MHz. Patients were examined in the supine position with their head rotated in the opposite direction to the probe and with a lateral probe orientation. The carotid IMT was measured manually in accordance with the ultrasound scanning protocol recommended by the Mannheim Intima–Media Thickness Consensus.[10] Carotid IMT measurements were performed bilaterally in the 3 segments of the further wall of the carotid arteries that were free from atherosclerosis (FIGURE 1).[12] The results were reported as the maximum and mean carotid IMT, and the mean value of bifurcation and internal carotid artery. An IMT of 1 mm was selected as the cut-off value for carotid IMT.[13-15] Atherosclerotic plaques, defined as a "focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding carotid IMT value or demonstrates a thickness of 1.5 mm, as measured from the media adventitia interference to the intima-lumen surface," were diagnosed according to the recommendations of the Mannheim Intima-Media Thickness Consensus.[12] The plaque score indicates the severity of atherosclerosis; it is a sum of the cumulative thickness of plaques obtained in the longitudinal sections of the common carotid artery, bifurcation, and internal carotid artery. All measurements were performed by the same sonographer, who was blinded to the clinical data of the patients.

**Laboratory examination** Serum samples were collected to assess $HbA_{1c}$ levels and the lipid profile. $HbA_{1c}$ levels were determined using high-performance liquid chromatography and expressed in units recommended by the National Glycohemoglobin Standardization Program/Diabetes Control and Complications trial.[16] Total cholesterol and triglyceride levels were measured using enzymatic methods. High-density lipoprotein cholesterol levels were measured after precipitation of very low-density lipoprotein. Low-density lipoprotein cholesterol levels were estimated using the Friedewald equation.[17]

**Statistical analysis** Descriptive statistics for continuous parameters were expressed as arithmetic means (SD) or median (interquartile range). Qualitative variables were presented as absolute numbers (percentages). As most qualitative variables were not normally distributed (based on the Shapiro–Wilk test), nonparametric statistical tests were used in a univariate analysis. The Mann–Whitney test was used to compare 2 groups, and the Kruskal–Wallis test was used to compare 3 groups. For qualitative variables, the Fisher exact test or the $\chi^2$ test was applied. A multivariate regression analysis was used. A *P* value of less than 0.05 was considered significant. All analyses were performed using Statistica v 12.5.

**RESULTS** Of the 98 patients recruited to the study, 25 were excluded due to exclusion criteria. The final study sample included 73 patients with type 2 diabetes (mean [SD] age, 63.56 [7.51] years; men, 49%). The mean (SD) diabetes duration was 11.7 (8.1) years. Microangiopathic complications were reported for 32 patients (44%),

**TABLE 3** Multivariate regression analysis of the association between the carotid intima–media thickness and age, sex, type 2 diabetes duration, and diabetic complications

| Carotid IMT measurement | *P* value[a] | | | | |
|---|---|---|---|---|---|
| | Age | Sex | Diabetes duration | Macroangiopathy | Microangiopathy |
| Mean left CCA | 0.002[b] | 0.008[c] | 0.39 | 0.41 | 0.13 |
| Maximum left CCA | 0.02[b] | 0.004[c] | 0.21 | 0.29 | 0.11 |
| Mean left bifurcation | 0.34 | 0.04[c] | 0.47 | 0.26 | 0.86 |
| Mean left ICA | 0.17 | 0.03[c] | 0.72 | 0.71 | 0.23 |
| Mean right CCA | 0.003[b] | 0.72 | 0.07 | 0.36 | 0.13 |
| Maximum right CCA | 0.004[b] | 0.63 | 0.06 | 0.59 | 0.18 |
| Mean right bifurcation | 0.03[b] | 0.28 | 0.46 | 0.99 | 0.63 |
| Mean right ICA | 0.08 | 0.60 | 0.005[b] | 0.57 | 0.33 |

**a** A *P* value of less than 0.05 was considered significant.
**b** A positive association (ie, higher values of the dependent variable were associated with higher values of the independent variable)
**c** A positive association only in men

Abbreviations: CCA, common carotid artery; IMT, intima–media thickness; ICA, internal carotid artery

and overt macroangiopathy, for 42 patients (58%). Demographic characteristics of the patients, selected data from the medical history, and macroangiopathy and microangiopathy complications are presented in TABLE 1.

An ultrasound examination showed that 67.1% of the patients had atherosclerotic plaques in the carotid arteries: 13.7% of the patients revealed carotid artery stenosis of 40% to 69%, and 4.1% of the patients showed the stenosis of 70% or higher.

In the multivariate regression analysis, the plaque score was associated with dyslipidemia ($P = 0.03$) and microangioapthy ($P = 0.01$), whereas there was no significant association between the plaque score and macroangiopathy, diabetes duration, hypertension, or smoking. The plaque score was also significantly associated with male sex and age (TABLE 2).

Carotid IMT was not associated with microangiopathic or macroangiopathic complications of diabetes or with $HbA_{1c}$ levels in the multivariate regression analysis. However, in one segment of the right carotid artery, carotid IMT was associated with diabetes duration. In addition, in several segments of the right and left carotid arteries, carotid IMT was associated with age, and in several segments of the left carotid artery, it was associated with male sex (TABLE 3).

**DISCUSSION** Carotid IMT is considered a marker of subclinical atherosclerosis and can be used to predict macroangiopathy both in diabetic and nondiabetic patients.[11,18] In addition, diabetic microvascular complications, such as diabetic retinopathy, have previously been shown to be independently associated with carotid IMT and endothelial dysfunction.[19] Furthermore, diabetic retinopathy was shown to be an independent predictor of cardiovascular events and death.[6,7] However, data regarding the association between carotid atherosclerosis and microvascular complications other than diabetic retinopathy have been inconsistent.

In our study, we found that microvascular complications of type 2 diabetes (ie, nephropathy, neuropathy, and retinopathy analyzed together) were independently associated with the carotid plaque score but not carotid IMT. To our knowledge, this is the first report of the association between the carotid plaque score and different types of microvascular complications among patients with type 2 diabetes.

Cardoso et al[20] found that retinopathy was the only diabetic microvascular complication that was independently associated with the carotid plaque score. Similarly, de Kreutzenberg et al[9] proved that carotid plaques are associated with retinopathy and retinopathy plus nephropathy in patients with type 2 diabetes.[9] In agreement with our findings, Yuan et al[21] showed that the plaque score was associated with the development of dyslipidemia. However, unlike Yuan et al,[21] we found no association between the plaque score and hypertension.

Our results also indicated that carotid IMT is unrelated to diabetes duration, except for one segment of the right carotid artery. However, carotid IMT was associated with age in several segments of both carotid arteries and with male sex in several segments of the left carotid artery. These findings are in accordance with those obtained by Cardoso et al,[20] who showed that IMT and plaques are significantly associated with age and male sex. The possible reason for the association with male sex might be the protective role of estrogen in women, which suppresses the progression of arteriosclerosis. Indeed, Hayashi et al[22] previously showed sex difference in cardiovascular risk factors, which may reflect the sex-related difference in carotid IMT observed in our study.

Our study must be interpreted within the context of its limitations, of which the small sample size seems to be the most important. Further studies on a larger patient cohort are needed to confirm our findings.

In conclusion, the carotid plaque score could be considered a risk factor for microangiopathic complications in diabetic patients. Therefore, diabetic patients with a high plaque score may require special care and more intensive treatment to stop the progression of these complications. While further studies with more participants are required, our pilot study has revealed some potential new diagnostic tools for minimizing the risk of diabetic complications that compromise the quality of life and survival of patients with type 2 diabetes.

**Contribution statement** WB performed the ultrasound examination and designed the research. KN analyzed the data, helped in the research design, and wrote the manuscript. HK wrote the manuscript. TS performed statistical analysis. AT performed statistical analysis and reviewed the manuscript. KP conceived the idea for the study. MA-S, AM-M, and BŁ-R were involved in data collection and verification. WG and JG reviewed and corrected the manuscript. All authors edited and approved the final version of the manuscript.

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