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Increased Echolucency of Carotid Plaques in Patients With Type 2 Diabetes

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Background and Purpose—Diabetes is associated with the presence of moderate to large atherosclerotic carotid plaques. Previous carotid ultrasound studies have associated plaques with low echogenicity with a higher risk of cerebrovascular events. The aim of this study was to evaluate whether patients with type 2 diabetes have different plaque echogenicity than do nondiabetic subjects.

Methods—Forty-seven type 2 diabetic and 51 nondiabetic subjects with a carotid plaque in the right artery were included in this study. All patients were born in 1935 to 1936 and were participants in a population-based study. Carotid ultrasonography was performed and the risk factors for cardiovascular disease were determined. Plaque echogenicity was assessed quantitatively on B-mode ultrasound images by standardized gray-scale median values.

Results—Gray-scale median values were significantly lower, indicating more echolucent plaques, in patients with type 2 diabetes compared with nondiabetics (37.0 ± 14.8 vs 45.5 ± 15.4 , $P=0.007$). Of the other risk factors studied, only triglycerides were significantly associated with the echogenicity of the plaque.

Conclusions—Patients with type 2 diabetes have more echolucent plaques compared with nondiabetic subjects. This might be associated with the higher risk of cardiovascular events among diabetics. (*Stroke*. 2007;38:2074-2078.)

Key Words: carotid plaque vulnerability ■ type 2 diabetes mellitus ■ ultrasound

Diabetes is a well-known risk factor for cardiovascular (CV) disease.¹ In the Multiple Risk Factor Intervention Trial, the risk for CV death in a diabetic population was 3 times higher than in nondiabetics.² The main underlying cause of CV events is atherosclerosis. However, there is a marked variation in CV risk between individuals with a similar degree of atherosclerotic plaque burden. Not all of the plaques lead to a CV event; ie, some plaques seem to be more prone to rupture.³ In the Asymptomatic Carotid Surgery Trial, the incidence of stroke in the group allocated to medical treatment was <10%.⁴ This indicates that although a high degree of stenosis in the carotid artery is a risk factor for developing cerebrovascular events, the vast majority of subjects with severe stenosis remain free from cerebrovascular events, at least during a 3.4-year follow-up period. Therefore, other factors have to be taken into account when evaluating the risk of cerebrovascular events in patients with carotid artery stenosis. Many studies have pointed to plaque composition as one of these factors.^{3,5-7}

In the last decade, it has become possible to perform a quantitative assessment of the echogenicity of plaques in a standardized and reproducible way.⁸ Plaques rich in calcium⁹ and fibrous tissue¹⁰ are more echogenic, whereas plaques with more elastin,⁹ lipids, and hemorrhage¹⁰ are more echolu-

cent. Echolucent carotid plaques are associated with a higher risk of ischemic cerebrovascular events than are echogenic ones.¹¹⁻¹³ Taking into account that diabetic patients have more CV events, one could hypothesize that besides a thicker carotid intima-media complex^{14,15} and a higher prevalence of plaques,¹⁴ diabetics may also have more echolucent, eventually more vulnerable plaques. The aim of this study was to explore whether type 2 diabetic and nondiabetic patients differ in carotid plaque echogenicity, as assessed by gray-scale median values (GSM values), measured on standardized images obtained with B-mode, high-resolution ultrasound.

Subjects and Methods

Subjects

Six-hundred thirty-one subjects born between 1935 and 1936 underwent a reexamination that was included in the Malmö Preventive Project.¹⁶ Two hundred forty-eight of these 631 had diabetes. The reexamination started in 2002 and included measurement of anthropometric values and blood samples. All participants completed a self-administrated structured questionnaire concerning clinical information, particularly smoking habits, diagnosis of diabetes, and treatment with antidiabetic and CV drugs. Two-hundred twenty-six of the 631 subjects were randomly selected and invited to participate in the current study. Seventy-two patients with diabetes and 111 nondiabetic subjects accepted the invitation. Forty-nine diabetic (68%) and 51 nondiabetic (46%) subjects fulfilled the inclusion

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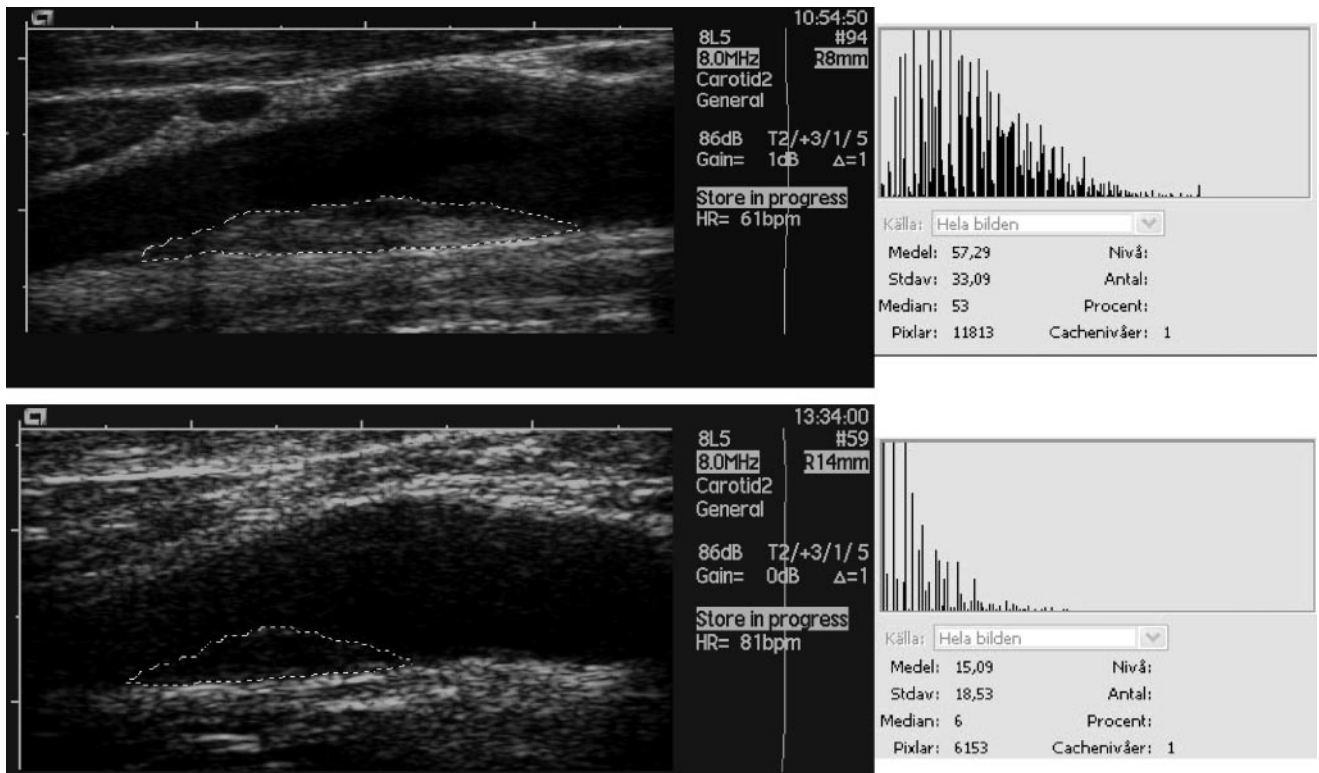


Figure 1. Two carotid plaque images obtained with high-definition B-mode ultrasonography (on the left) with a histogram showing the gray-scale distribution of pixels (on the right).

criteria of having an atherosclerotic plaque in the right carotid artery. These subjects returned for a second examination, when ultrasound images were obtained for further analysis.

Nondiabetic subjects were defined as those having no history of diabetes, no use of antidiabetic drugs, and blood glucose levels at the time of reexamination <5.0 mmol/L. Those who had self-reported diabetes diagnosed by a physician or used at least one diabetic drug were defined as having a history of diabetes. Forty-seven of the diabetic patients had type 2 diabetes, defined by the age of onset at >35 years and lack of dependence on insulin therapy during the first 6 months from diagnosis. One patient had type 1 diabetes, defined as dependence on insulin therapy from the onset of the disease and the age of onset at <35 years. One patient was pancreatectomized when she was 49 years old and became immediately dependent on insulin. These 2 patients were excluded in the statistical analysis. Data on diabetes diagnosis and drug treatment were collected from the questionnaire.

The atherosclerotic plaque was defined as a focal thickening of the intima-media complex >1.2 mm. A plaque >10 mm² (a cutoff value used in other studies to separate small from moderate-size plaques)^{7,17} was considered large enough for assessment of plaque echogenicity. The study was approved by the local ethics committee. All participants gave informed consent.

Risk Factors

Fasting blood samples were analyzed at the local Department of Clinical Chemistry and included total cholesterol, triglycerides, HDL cholesterol, and glucose. Analyses were done according to standard procedures at the laboratory. LDL cholesterol was calculated with the Friedewald formula. Waist circumference was measured in the standing position. Blood pressure was measured twice with the subject in a supine position after a 5-minute rest with an automatic device (Omron M5-I, Omron Matsusaka Co Ltd). The mean value of the 2 measurements was used. The mean time between the initial visit and the ultrasound examination was 20 months, with a range of 12 to 29 months. The glycosylated hemoglobin (HbA1c) level was

obtained from clinical records of the patients. The mean time between HbA1c determination and ultrasound examination was 2.7 ± 2.5 months.

Ultrasound Method

The ultrasound examinations were performed with an Acuson Sequoia with a linear 5- to 8-MHz transducer (Acuson, Mountain View, Calif) with the patient in a supine position and the head turned $\approx 45^\circ$ to the left. The settings for the ultrasound machine, as shown in Figure 1, were the same for all examinations. The tissue-equalization technology function on the ultrasound machine was not used. The ultrasound images were saved in digital form on magneto-optical discs. All images were taken at the R-wave peak of the ECG, simultaneously shown on the screen. The largest recordable plaque present in a predefined window of the carotid vessel¹⁸ was chosen for assessment of plaque echogenicity. Images recorded were of the optimal projection that represented the total echogenicity of the plaque. The gain was set equal all over the screen when images for analysis of plaque morphology were saved. At least one image with color Doppler was saved to ensure the best possible outlining of the plaque. Images were also taken for measurement of mean intima-media thickness (IMT) in the far wall of the common carotid artery 1 cm proximal to the carotid bulb. For analysis of IMT, an automated computerized analyzing system was used¹⁹ for measuring mean thickness. The degree of stenosis was determined by the maximal blood flow velocity according to criteria used in local clinical practice.²⁰ The size of the plaque was measured by using the trace function of the ultrasound machine. Ultrasound examinations and measurements were performed by a single investigator (G.Ö.) blinded to clinical data, including the diagnosis of diabetes.

Plaque Echogenicity

Assessment of plaque echogenicity was made in Adobe Photoshop 8.0 according to a method previously described,⁸ based on the standardization of the gray scale of each image, wherein the echoes representing blood in the lumen and the media-adventitia transition

TABLE 1. Characteristics of Subjects With (n=47) and Without (n=51) Type 2 Diabetes

	Type 2 Diabetes (n=47)	No Diabetes (n=51)
GSM	37.0±14.8	45.5±15.4†
Age, y	69.5±0.5	69.4±0.7
Male sex, %	72.3‡	31.4
Total cholesterol, mmol/L	4.98±0.99	5.93±0.92‡
LDL cholesterol, mmol/L	3.16±0.78	4.04±0.88‡
HDL cholesterol, mmol/L	1.11±0.29	1.42±0.35‡
Triglycerides, mmol/L*	1.52±0.95‡	1.04±0.43
Glucose, mmol/L	9.14±3.08‡	4.69±0.20
HbA1c, %	6.26±1.15	...
Systolic blood pressure, mm Hg	146.5±18.7‡	134.6±14.3
Waist circumference, cm	100.1±11.5‡	85.5±8.6
Smoker, %	15.9	19.1
Statin treatment, %	42.6‡	5.9
CV medication, %	85.1‡	27.5
Diabetes duration, y	10.0±5.8	...

Student's *t* test for continuous variables and the χ^2 for categorized variables were used to test for statistical significance between groups. Data are presented as mean±SD or proportions.

*Skewed variables (triglycerides, plaque area) were logarithmically transformed before statistical testing.

† $P<0.01$, ‡ $P<0.001$.

are used as references for black (0–5) and white (185–195). After standardization of the image the plaque was outlined. When needed, the image with color Doppler was used to ensure correct outlining. A histogram of the gray-scale values of the plaque was obtained, and the GSM was used for assessment of echogenicity of the plaque (Figure 1). Intraobserver variability for repeated measurements of plaque echogenicity in this study (n=42) was 1.4%, and the coefficient of variation was 5.8%.

Statistical Methods

Variables with a skewed distribution were logarithmically transformed. Student's *t* test and the χ^2 test were used to test differences in CV risk factors between patients with and without diabetes. GSM values were categorized in quartiles. A general linear model and χ^2 were used to compare the distribution of CV risk factors and treatment in categories of GSM. A general linear model was used to assess the relation between GSM and diabetes, taking potential risk factors into account. A probability value of <0.05 was considered statistically significant.

Results

Characteristics of the type 2 diabetic and nondiabetic groups are shown in Table 1. Patients with type 2 diabetes had a significantly increased waist circumference, higher systolic blood pressure and triglycerides, and lower HDL cholesterol. Total and LDL cholesterol values were significantly lower in type 2 diabetic patients. Patients with type 2 diabetes were treated more often with statins and CV drugs. Type 2 diabetic patients had a larger plaque area compared with nondiabetics (27.8±21.8 versus 22.0±11.7 mm², $P=0.05$). There was no significant difference in carotid IMT and lumen reduction between the groups (0.95±0.19 mm and 28.2±16.4% versus 0.94±0.19 mm and 22.4±12.7%, respectively). Only 4 subjects, of whom 3 had type 2 diabetes, had a stenosis $>30\%$.

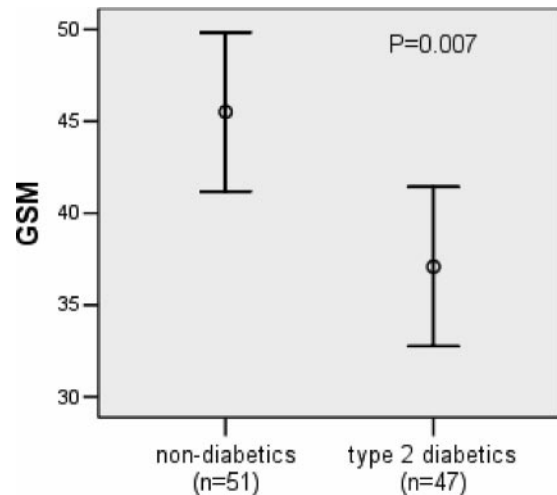


Figure 2. GSM in type 2 diabetic and nondiabetic subjects. Mean value and 95% CI. $P=0.007$ for difference between groups.

Women had significantly higher total and LDL cholesterol values and lower HDL cholesterol values, whereas men had more treatment for blood lipids and CV disease. Men had significantly higher blood glucose, increased waist circumference, and a higher degree of atherosclerosis measured as plaque area and lumen reduction at the site of the plaque (data not shown).

GSM, Type 2 Diabetes, and Other Risk Factors

The GSM was significantly lower in the type 2 diabetic group compared with the nondiabetics, 37.0±15.0 versus 45.5±15.4 ($P=0.007$; Figure 2). This significant difference in GSM between the 2 groups remained after adjustment for sex and triglyceride values ($P=0.034$). The linear association between risk factors and quartiles of GSM was assessed (Table 2). Type 2 diabetes and triglycerides showed an inverse linear association with GSM ($P=0.018$ and $P=0.026$, respectively). Treatment, other blood lipids, glucose, HbA1c, blood pressure, or sex was not associated with the GSM level.

Discussion

The main finding of this study was that type 2 diabetic patients with moderately sized carotid plaques (>10 mm²) had more echolucent plaques compared with nondiabetic subjects. To our knowledge, this has not been described previously, neither with a subjective classification²¹ nor with this standardized method.

It has been shown in previous studies that echolucent plaques are more prone to rupture and are associated with an increased risk of the patient's having a cerebrovascular event.^{11–13} Our finding that moderately sized carotid plaques in type 2 diabetics are more echolucent than those in nondiabetic subjects may partially explain the higher risk for cerebrovascular events among diabetics.

Noninvasively measuring the echogenicity of a plaque is a method that intends to reflect plaque composition. Echolucent plaques are richer in elastin, lipids, and inflammatory cells, whereas echogenic plaques contain more calcium and fibrous tissue.^{9,10} Burke et al²² have shown that the necrotic core and

TABLE 2. CV Risk Factors and Treatment, in Quartiles of GSMVs

	GSM Quartile 1 8–30	GSM Quartile 2 31–40	GSM Quartile 341–52	GSM Quartile 4 53–105	P for Trend
Type 2 diabetes, %	64.0	52.0	44.0	30.4	0.018
Male sex, %	64.0	40.0	52.0	47.8	0.418
Total cholesterol, mmol/L	5.38±1.18	5.45±1.02	5.63±1.13	5.43±0.96	0.727
LDL cholesterol, mmol/L	3.46±0.99	3.66±0.95	3.72±1.04	3.68±0.80	0.411
HDL cholesterol, mmol/L	1.16±0.32	1.25±0.36	1.41±0.36	1.26±0.37	0.150
Triglycerides, mmol/L*	1.66±1.17	1.20±0.56	1.11±0.47	1.10±0.47	0.026
Glucose, mmol/L	6.81±2.14	7.90±4.04	6.44±3.17	6.09±2.45	0.197
HbA1c, %	6.29±0.91	6.48±0.69	5.96±1.31	6.26±1.15	0.663
Systolic blood pressure, mm Hg	142.6±22.8	137.6±14.5	141.9±16.1	138.9±15.8	0.685
Waist circumference, cm	96.7±12.4	89.6±11.0	93.0±10.7	90.4±15.0	0.173
Current smoker, %	21.7	4.0	16.7	31.6	0.294
Statin treatment, %	28.0	24.0	16.0	26.1	0.701

Data presented as mean±SD or percentage of the total No. of subjects in each quartile.
*Skewed variables (triglycerides) were logarithmically transformed before statistical testing.

the area of macrophages in the plaque are larger in diabetic patients compared with nondiabetics. This is consistent with our findings, because echolucent plaques have been shown to have a higher content of macrophages,²³ increased activity of metalloproteinases,²⁴ and a larger necrotic core²⁵ than do echogenic plaques. High levels of triglycerides have previously been shown to be correlated with echolucency in plaques,²⁶ which is in agreement with our data.

Systemic inflammation is associated with atherosclerosis and CV events, particularly in diabetic patients.^{14,27} According to Sigurdardottir et al,²⁸ in a study of nonstandardized analysis of echogenicity in femoral arteries, echolucent plaques were more frequent in subjects with the metabolic syndrome, higher levels of oxidized LDL, and high-sensitive C-reactive protein. In the present study, the relation between inflammatory markers and GSM was not addressed. However, it has recently been shown that echolucent carotid plaques are associated with higher degrees of systemic inflammation.²⁹ This association could be even stronger in diabetic patients, considering the higher echolucency of their plaques.

According to previous studies, patients with diabetes have a thicker intima-media complex in the carotid arteries,^{14,15} a sign of an early stage of the atherosclerotic process, and an increased prevalence of moderate to large plaques³ compared with nondiabetics. In the present study, subjects with type 2 diabetes had significantly larger plaques. There was no significant difference in IMT between groups in the present study. This could perhaps be explained by the transverse nature of the inclusion procedure, wherein the presence of a carotid plaque >10 mm² was required, and therefore, the subjects included in this study had approximately the same degree of carotid atherosclerosis.

The relatively small sample size and the average time of 20 months between anthropometric measurement and blood sampling are some aspects to take into consideration when interpreting the results. Additionally, one might think that the skewed sex distribution could have influenced the findings. However, the relation between GSM and diabetes remained

significant even after taking sex into account in the multivariate analysis. Further studies on the possible relation between plaque morphology and diabetes would be of interest in assessing larger plaques and higher degrees of stenosis.

Summary

The enhanced risk for diabetic patients to have a CV event is not fully understood. This study supports the hypothesis that type 2 diabetes is related not only to a higher degree of atherosclerosis but also to a different, more vulnerable, type of plaque, which appears more echolucent. Finding methods to identify patients at high risk for developing ischemic events is of great importance. Standardized analysis of B-mode ultrasound images to determine plaque echogenicity could be one of these methods.

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Disclosures

None.

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