Silent Coronary Atheromatosis in Type 1 Diabetic Patients and Its Relation to Long-Term Glycemic Control

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Type 1 diabetic patients have a pronounced risk of premature coronary artery disease and death. We sought to evaluate the prevalence of silent coronary atheromatosis and to evaluate the relation between coronary atheromatosis and glycemic control. Coronary atheromatosis was evaluated in type 1 diabetic patients with no symptoms of coronary artery disease by exercise electrocardiogram (ECG) in 39 patients and quantitative coronary angiography and by intravascular ultrasound (IVUS) examinations in 29 patients. The findings from the IVUS examinations were related to mean HbA_{1c} collected prospectively over 18 years. Abnormal exercise ECGs were found in 15% of patients, and angiographic diameter stenosis of >50% in one or more of the main coronary arteries was found in 34% of patients. All patients examined with intracoronary ultrasound had developed atherosclerotic plaques with an increased intimal thickness (>0.5 mm) in one or more of the coronary arteries. Coronary artery plaque formation, as judged by ultrasound, was significantly related to mean HbA_{1c} during 18 years ($P < 0.05$) after adjustment for total cholesterol and age. This study demonstrates a high prevalence of silent coronary atheromatosis in type 1 diabetic patients with no symptoms of coronary heart disease. Long-term glycemic control was shown to be associated with coronary atheromatosis.
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Near-normal blood glucose control in type 1 diabetic patients delays development of microvascular disease (1–6). The importance of good glycemic control in delaying macrovascular disease is still a matter of debate in type 1 diabetes, although some studies suggest a relation between glycemic control and development of coronary artery disease (7–9). Patients with diabetes have a two- to four-times greater risk of death from coronary heart disease than age-matched nondiabetic individuals (10). This risk is even greater for women (11). The prevalence of coronary atheromatosis is not known for type 1 diabetic patients without symptoms of heart disease. Coronary angiography has been considered to be the gold standard for evaluating coronary artery disease but is not sensitive enough to evaluate the early stages of the disease (12). Intravascular ultrasound (IVUS) examination of the coronary arteries can reveal pathological findings in angiographically normal arteries (13). The present study aimed to evaluate the prevalence of silent coronary atheromatosis and its relation to long-term HbA_{1c} in patients with type 1 diabetes of long duration and no symptoms of coronary heart disease. We performed exercise electrocardiogram (ECG), quantitative coronary angiography, and IVUS examinations to explore these questions.

RESEARCH DESIGN AND METHODS

Patients. A total of 45 type 1 diabetic patients were included in the Oslo study in 1982 (1,2). Criteria for inclusion were age 18–45 years, diagnosis of type 1 diabetes at <30 years of age, disease duration of >7 but <30 years, C-peptide <0.1 nmol/l 6 min after intravenous administration of 1 mg glucagon. Exclusion criteria were serum creatinine >150 μmol/l, diastolic blood pressure >100 mmHg, overt nephropathy, proliferative retinopathy, pregnancy, a history of neuropathy, and treatment with antihypertensive drugs or any other medication except insulin and oral contraceptives. The participants were randomized to three different treatment strategies: conventional insulin therapy with two injections of NPH insulin and regular insulin twice daily (n = 15), continuous subcutaneous insulin infusion by portable pumps (n = 15), or injections of insulin four to six times daily (n = 15). The Oslo study showed the importance of near normoglycemia in delaying the development of late complications and showed that intensive insulin treatment with multiple injections or pump treatment was superior in obtaining this effect. After 4 years, having identified the beneficial effects of intensive insulin treatment on microvascular complications, all patients were encouraged to use intensive insulin treatment. Most of the patients have been followed regularly since the study started in 1982. Two patients have died of causes not related to diabetes (chronic lung disease and breast cancer), and four patients have been lost to follow-up, leaving 39 patients for the present study. HbA_{1c} values are known for the whole group during the last 18 years and have been mostly determined three to four times yearly. Information on current medication and smoking habits was obtained. A total of 29 patients accepted coronary angiography and intracoronary ultrasound examinations. The Regional Ethics Committee approved the study. All patients gave written informed consent before they were examined.

Laboratory methods. Lipid profiles were measured by conventional methods in the fasting state, and blood pressure was measured in the sitting position after at least 15 min rest. HbA_{1c} was measured prospectively by ion-exchange chromatography until 1987 (14) and by high-performance liquid chromatography (Variant; Bio-Rad, Richmond, CA) thereafter, except for a short period with DCA 2000 (Bayer Diagnostics, Tarrytown, NY). The methods correlated closely (r = 0.97 and 0.96, respectively), and no corrections of HbA_{1c} values were considered necessary (ref. values 4.1–6.4%). The intra-assay coefficient of variation was 5% for the first method and <3% for the later methods.

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ECG, electrocardiogram; IVUS, intravascular ultrasound.

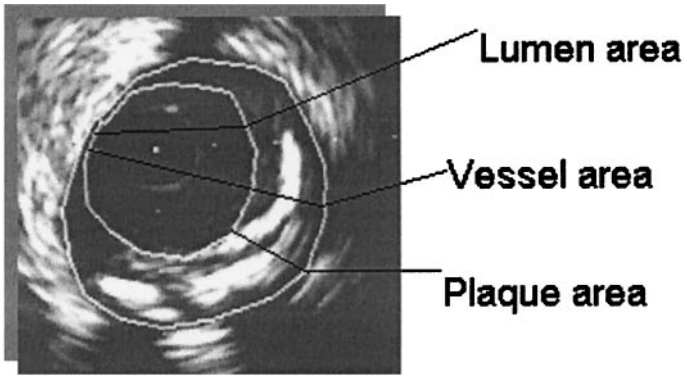

FIG. 1. An example of coronary atherosclerosis seen with IVUS. Percent vessel area stenosis is plaque area divided by vessel area × 100.

Urine samples (24 h) were collected and analyzed to determine urinary albumin excretion. Microalbuminuria was defined as urinary albumin excretion >30 mg/24 h in two of three samples and overt nephropathy as urinary albumin excretion >300 mg/24 h in two of three samples.

Exercise ECG and invasive coronary artery examinations. Exercise ECG on a bicycle was performed in all 39 patients using a standardized protocol (15) with continous increase in workload. Development of ST-segment depression >1 mm in any ECG lead was considered significant for myocardial ischemia.

All patients were catheterized from the right groin. The coronary arteries were catheterized with 8F Cyber femoral left and right guide catheters (Boston Scientific, Sunnyvale, CA) using standard Judkins technique. In all patients, low osmolar nonionic iopromide Ultravist (370 mg I/ml; Schering AG, Berlin, Germany) was used as X-ray contrast. The quantitative analysis of the coronary angiograms was done with an automated stenosis analysis program (General Electric Medical Systems, Buc Cedex, France). Vessel stenoses >50% of the lumen diameter, compared with the nearest normal segment, were classified as significant. The findings were classified as one-, two-, or three-vessel disease according to the presence of stenosis in one or more of the main coronary arteries.

The IVUS system used in this study consists of the Clear View Ultra with Automatic Pullback Device and Ultra Cross 3.2 F 30-MHz catheter (Boston Scientific). The ultrasound images were recorded on s-VHS videotape for offline analysis.

Intravenous access was assured, and premedication consisting of 0.5 mg atropine sulfate and 5 mg diazepam i.v. was given to all patients before arterial puncture. After placement of the introducer in the common femoral artery, all patients received 5,000 units heparin. After coronary angiography, a 0.014-inch, 182-cm guide wire (ChoICE PT; Boston Scientific) was placed in the coronary artery to be examined. The IVUS catheter was connected to the pullback device and advanced over the guide wire in the coronary artery, and the position of the ultrasound catheter was documented by angiography before starting the pullback device of the ultrasound recording system. The automatic pullback device speed was 1 mm/s. By IVUS, an intimal thickness of >0.3 mm in any segment of the coronary arteries was considered significant for atherosclerotic plaque formation, a limit proposed by Nissen et al. (12). In the present study, 8–10 segments, as defined in the American Heart Association's grading criteria for coronary arteries, were examined in each patient. In each segment, the maximal stenosis was identified and the corresponding cross-sectional vessel area, including the intima-media and lumen areas, was measured. The plaque area was calculated as the difference between the vessel area and the luminal area (Fig. 1).

Percent vessel area stenosis was defined as plaque area divided by vessel area multiplied by 100, as previously described by Erbel et al. (13). For the purpose of statistical analysis, the mean percent vessel area stenosis of all segments analyzed was calculated in each patient.

Statistical analyses. SPSS version 10.0 (SPSS, Chicago) was used for all calculations. Data are presented as means ± 1 SD, unless otherwise indicated. To study the association between mean HbA_{1c} over 18 years and mean percent vessel area stenosis after adjustment for age and total cholesterol, we used linear regression analysis with 5% significance level.

RESULTS

Table 1 describes some demographic characteristics and putative risk factors for atheromatosis in the patients at the time of the study as well as at randomization for treatment intervention in 1982. Sixty percent of the patients were men, the mean age was 43 years, and the mean diabetes duration was 30 years. Mean HbA_{1c} over 18 years was 8.2%. Fourteen percent of the patients who underwent intracoronary examinations were on lipid-lowering drugs and 14% on antihypertensive drugs. Twenty-four percent were current smokers.

Abnormal exercise ECG with >1 mm ST-segment depression was noted in 6 of 39 (15%) patients. None of the patients experienced chest pain during their exercise test. The mean duration of the exercise test was 14 min, mean workload was 178 W, and the mean value of maximum heart rate was 167/min.

Coronary angiography showed 34% (10 of 29) prevalence of significant coronary heart disease, i.e., >50% stenosis in one or more of the main coronary arteries. Four patients had one-vessel disease, three patients had two-vessel disease, and three patients had three-vessel disease (two of the latter had positive exercise ECG). One of the patients with three-vessel disease underwent bypass surgery, the two others had diffuse disease and were not offered revascularization. In all 29 patients, the IVUS examination showed atherosclerotic plaques with >0.5 mm thickening of the intima in at least one of the main coronary arteries. Average percent vessel area stenosis was >40% in 10 of 29 patients, between 20 and 40% in 9 patients, and <20% in 10 patients (Table 2). In all, 258 coronary artery segments were examined from 29 left main coronary arteries, 27 left anterior descending coronary arteries, 25 left circumflex coronary arteries, and 26 right coronary arteries, amounting to a total coronary artery length of 6,219 mm for the entire group. We could not demonstrate significant correlations between mean vessel area stenosis, as seen on IVUS, and the following factors were examined individually: sex, systolic and diastolic blood pressure, BMI, smoking, microalbuminuria, triglycerides, and HDL cholesterol. HbA_{1c} was significantly related to the mean percent vessel area stenosis on IVUS after adjustment for age and fasting total cholesterol. Table 3 indicates that a 1% increase in mean HbA_{1c} over 18 years implied a 6.4% rise in vessel area stenosis on IVUS. Total cholesterol was also significantly related to percent vessel area stenosis on IVUS when adjusted for age and HbA_{1c}. A 1-mmol increase in total cholesterol implied a 10% rise in mean vessel area stenosis. For comparison, a 10-year increase in age implied a 16.2% rise in vessel area stenosis.

DISCUSSION

In the present study, we have demonstrated a high prevalence of silent coronary atheromatosis in type 1 diabetic patients. We have also shown that long-term glycemic control was a significant predictor of coronary atherosclerosis. Also, coronary atherosclerosis was significantly related to age and total cholesterol level, as expected.

We evaluated silent coronary heart disease with three different methods of varying levels of sensitivity. The prevalence of silent ischemia in type 1 diabetes evaluated by exercise ECG has previously been documented (16) at comparable levels to that of the current results. The sensitivity of the exercise ECG might be too low for

TABLE 1
Demographic characteristics and putative risk factors for atheromatosis in the total group of patients who underwent exercise ECG (n = 39) and in the patients who underwent intracoronary examinations (n = 29). Data are from the present study or at randomization (1982)

	Total group	Intracoronary group
n	39	29
Sex distribution (M/F)	23/16	18/11
Age (years)	42.9 (35–58)	43.2 (35–58)
Duration of diabetes (years)	30.3 (4.4)	30.6 (4.9)
HbA_{1c} over 18 years (%)	8.2 (1.0)	8.3 (0.9)
HbA_{1c} (%)	8.7 (1.2)	8.8 (1.2)
HbA_{1c} 1982 (%)	8.3 (1.3)	8.1 (1.1)
Systolic blood pressure (mmHg)	129 (14.5)	129 (16.3)
Systolic blood pressure 1982 (mmHg)	126 (14)	124 (13.5)
Diastolic blood pressure (mmHg)	80 (9.7)	79 (9)
Diastolic blood pressure 1982 (mmHg)	78 (7.7)	78 (8.3)
BMI (kg/m^2)	25.0	24.8
BMI 1982 (kg/m^2)	22.7	22.8
Total cholesterol (mmol/l)	5.3 (0.7)	5.3 (0.7)
Total cholesterol 1982 (mmol/l)	5.0 (0.8)	5.0 (0.9)
LDL cholesterol (mmol/l)	3.1 (0.7)	3.0 (0.8)
HDL cholesterol (mmol/l)	1.8 (0.4)	1.8 (0.3)
HDL cholesterol 1982 (mmol/l)	1.3 (0.5)	1.4 (0.6)
Triglycerides (mmol/l)	1.1 (1.0)	1.1 (1.2)
Triglycerides 1982 (mmol/l)	0.8 (0.4)	0.8 (0.4)
Total cholesterol/HDL cholesterol ratio	3.2 (0.9)	3.1 (0.9)
Microalbuminuria (n)	4	3
Microalbuminuria 1982 (n)	2	1
Overt nephropathy (n)	1	1
Current smokers (n)	10	7
Smokers in 1982 (n)	12	10
Patients on antihypertensive treatment (n)	7	4
Patients on lipid-lowering medication (n)	5	4

Data are means ± 1 SD or median (range).

evaluation of silent ischemia in type 1 diabetes. Janand-Delenne et al. (17) screened type 1 diabetic patients with stress testing (exercise ECG or thallium myocardial scintigraphy with exercise testing and/or dipyridamole injection) and subjected the patients with signs of ischemia on the registrations to coronary angiography. They estimated the prevalence of coronary artery disease to be 4.2% among 73 patients with type 1 diabetes aged 41 ± 10.9 years and a mean duration of disease of 20.9 ± 7.7 years. Our results, which show that 34% had angiographic-defined coronary artery disease, indicate that this is a significant underestimation. Because Janand-Delenne et al. only performed angiographic examinations on patients with positive stress tests, they probably missed many patients with asymptomatic coronary heart disease.

Coronary angiography is usually indicated only in patients suspected to have coronary artery disease; therefore, the prevalence of coronary atheromatosis in the normal population is not known. The prevalence of angiographic coronary stenosis >50% was found to be 7.3% in 331 patients with tachycardia, which is considered nearly representative for the general population. The mean age of the patients was 53 ± 7 years, 27.8% had hypertension, 31.2% were current smokers, 5.4% had diabetes, and 51.8% had hyperlipemia (18,19). The corresponding prevalence found in our study (34%) was significantly higher than the 7.3% with angiograhic stensoses >50% found in the above-mentioned study ($P < 0.001$). This difference cannot be explained by age, smoking habits, or hyperlipemia because our patients are younger, smoke less, and have lower blood lipid levels.

Type 1 diabetic patients with symptoms of cardiac

TABLE 2
Number of patients with various percent vessel area stenosis as determined by intracoronary ultrasound

Degree of vessel area stenosis	n
Normal intima (<0.3 mm)	0
<20% vessel area stenoses	10
Between 20 and 40% vessel area stenoses	9
>40% vessel area stenoses	10
Total	29

TABLE 3
Increase in coronary artery area stenosis among 29 type 1 diabetic patients that is associated with specific changes of mean HbA_{1c} over 18 years, mean total serum cholesterol value, and age (linear regression analysis)

	Increase in vessel area stenosis (%)	95% CI	P
Increase of 1% mean HbA_{1c} over 18 years	6.4	0.4–12.4	0.043
Increase of 1 mmol/l total serum cholesterol	10.5	2.3–18.7	0.018
Increase of 10 years of age	16.2	6.2–26.2	0.003

disease have a higher prevalence and more extensive angiographic findings than symptomatic nondiabetic patients (20), indicating that type 1 diabetic patients have a more rapidly developing form of coronary artery disease than nondiabetic subjects.

Coronary angiography has been considered the gold standard for evaluation of coronary artery disease. However, IVUS examinations of the coronary arteries reveal earlier signs of atherosclerosis and give more details about atherosclerotic plaques (12). Earlier histopathological studies have shown that the intimal thickness progresses with age; the expected intimal thickness for the group aged 36–40 years would be <0.25 mm (21). The value for intimal thickness in young subjects is typically 0.15 ± 0.07 mm (22). In the present study, all the patients were judged to have evidence of atherosclerosis in their coronary arteries, and 19 of 29 (65%) had >20% mean vessel area stenosis. It has also been shown that atheroma measurements, as performed in our study, correlate closely to histology (23,24). Interpretation of our findings is hampered by the lack of an age-matched control group and the scarcity of references in the literature. The study by St. Goar et al. (25) described a group of patients who received donor hearts with angiographically normal coronary arteries documented at the time of transplantation. One month after transplant, atherosclerotic plaque was detected in the donor heart by IVUS in 24% of patients. This is far less than in our study population, in which atherosclerotic plaques were detected in 100% of the examined patients. For comparison, none of our patients had <0.5 mm thickening of the intima, which was the criteria used by St. Goar et al. In patients with symptoms of coronary heart disease and normal angiograms, Mintz et al. (26) found that 94% had positive IVUS findings. This is close to our finding of 100% in type 1 diabetic patients with no symptoms of coronary heart disease and indicates that type 1 diabetic patients, even without symptoms of coronary artery disease, may be in the same risk category for developing cardiovascular events as nondiabetic patients with clinical coronary artery disease.

The present results, which show long-term glycemic control to be a significant predictor of atherosclerosis, strongly support the hypothesis that increased HbA_{1c} over time increases the risk of developing coronary artery disease in type 1 diabetes. Whereas earlier studies have focused on indirect ways of showing this, we have documented it in a more direct manner, visualizing and measuring the coronary vessel wall thickening. In the Diabetes and Complications Trial, the number of macrovascular events were fewer in the intensively treated group, but the difference between intensively and conventionally treated groups was not statistically significant (7). The development of atherosclerosis, as judged indirectly by endothelial function and carotid artery stiffness, has been related to HbA_{1c}, and a positive effect of tight blood glucose control over 10 years has been shown (9). In a prospective study of 177 type 1 diabetic patients diagnosed after 30 years of age, the incidence of coronary events in a 7-year follow-up was significantly related to HbA_{1c} at the time of inclusion in the study (8). Recently, it was shown in a prospective study that HbA_{1c} predicted mortality and manifest cardiovascular disease even in nondiabetic subjects (27). All these findings underline the relation between glycemia and atherosclerosis, and the current results underline the potential of tighter blood glucose control in slowing down the process of atherosclerosis.

Cholesterol is an established risk factor of coronary heart disease in nondiabetic patients. In our study, total cholesterol significantly predicted coronary atherosclerosis. Mintz et al. (26) also found a relation to atherosclerosis demonstrated by IVUS in patients with symptoms of coronary heart disease, a finding that correlates to the present results. In our study, a reduction of 1 mmol/l in total cholesterol could give a considerable effect (Table 3), and we believe that lipid-lowering medication should be considered at an early stage in type 1 diabetic patients.

In conclusion, we have shown that, in a direct manner, mean HbA_{1c} over 18 years predicted coronary atherosclerosis in type 1 diabetic patients with no symptoms of coronary heart disease. We would speculate that a tighter glycemic control could reduce the well-known premature coronary heart disease in these patients. Silent coronary atheromatosis is highly prevalent, and the present results should also lead to reconsideration of diagnosis and early treatment of this disease in type 1 diabetes.

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