

Angiographic Severity and Extent of Coronary Artery Disease in Patients With Type 1 Diabetes Mellitus

[Coronary Artery Disease]

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Abstract

Studies of the characteristics of coronary artery disease (CAD) in diabetic patients have shown conflicting results. Only 2 studies exploring the severity of CAD, specifically in type 1 diabetes, have been published, and neither of them has used computer-aided quantitative coronary angiography. This retrospective study comprised 64 (24 women and 40 men) type 1 diabetic patients and nondiabetic control subjects. To estimate the severity, extent, and overall "atheroma burden" of CAD, we used quantitative coronary angiographic-based segmental analysis of coronary angiograms. Type 1 diabetic patients had greater global severity ($p < 0.001$), global extent ($p < 0.001$), and global atheroma burden ($p < 0.001$) indexes than nondiabetic control subjects. Quantitative coronary angiographic-derived indexes of CAD were, on average, 1.4- to 4.3-fold higher in diabetic than in nondiabetic patients. These differences were particularly marked in women. We found that type 1 diabetic patients with a clinical indication for coronary angiography, especially women, have more severe, extensive, and distal type of CAD than individually matched nondiabetic control patients. Our findings, including a loss of sex difference for CAD among type 1 diabetic patients and a marked impact of type 1 diabetes in women, are not explained by established risk factors.

Only 2 studies exploring the severity of coronary artery disease (CAD), specifically in type 1 diabetic patients, have been published.^{1,2} Thus far, no study has used computer-aided quantitative coronary angiographic (QCA) techniques to study this question. To estimate the severity, extent, and overall "atheroma burden" of CAD exclusively in type 1 diabetic patients, we used the same QCA-based segmental analysis of coronary angiograms as in our recent study with type 2 diabetic and matched nondiabetic CAD patients.³

METHODS⁴

Subjects: All patients with type 1 diabetes who underwent cardiac catheterization for symptoms of CAD at Helsinki University Central Hospital between 1982 and 1997 were identified. All patients had previously diagnosed diabetes fulfilling the World Health Organization criteria for insulin-dependent diabetes mellitus.⁴ Nondiabetic control subjects, randomly selected from the same population, were matched individually with diabetic patients for sex, age (within 5 years), date of angiography (within 3 years), and serum creatinine value (<100, 100 to 300, >300 $\mu\text{mol/L}$, or dialysis). Clinical data, including lipid and other laboratory parameters, were retrieved from catheterization and medical records.

Records of 89 type 1 diabetic patients were identified. The angiograms of 8 patients were unsuitable for quantitative analysis, and 9 female and 8 male diabetic patients were excluded because no age-matched control subjects were available. Compared with the diabetic patients included, the excluded patients were younger (43 years [37, 47] vs 47 years [42, 53], median [25th, 75th percentile]; $p < 0.02$), but had similar angiographic characteristics (data not shown). After exclusions, this study comprised 64 matched pairs (24 women and 40 men). The study was approved by the ethics committee of the Department of Medicine, Helsinki University Central Hospital.

Acquisition and visual analysis of coronary angiograms: Coronary angiography was recorded on 35-mm cine film and performed by the percutaneous femoral approach using standard techniques, including sublingual nitroglycerin. As described earlier,³ 1 investigator (MS) selected frames for QCA analyses.

Quantitative analysis of coronary angiograms: We used third-generation QCA software, Cardiovascular Measurement System (QCA-CMS) version 3.0 (Medis, Nuenen, The Netherlands).⁵ QCA analyses were performed by the same investigator (PP). Segments with a diameter of <1.5 mm were excluded and a stenosis was defined as a narrowing diameter stenosis of >25% suggested by QCA, or by visual analysis. These criteria are based on work in our laboratory.⁶ All steps in analyses were performed with the clinician blinded to the identity and the diabetic status of the subjects.

Angiographic indexes: QCA-derived data were integrated into indexes, as reported elsewhere in detail.³ Briefly, the severity index is defined as the average of the most severe stenoses (ranging from zero if no stenosis was present to 100% in case of a total occlusion) in the left main, the left anterior descending, the left circumflex, and the right coronary arteries. Extent index is the percentage of coronary segments involved in stenoses, calculated as $100 \times [\text{n-ary summation}](\text{stenosis lengths})/[\text{n-ary summation}](\text{segment lengths})$. Atheroma burden index is based on "plaque area," reflecting severity and extent, calculated as $100 \times [\text{n-ary summation}](\text{plaque areas})/[\text{n-ary summation}](\text{segment lengths})$. One "global" severity, extent, and atheroma burden index was calculated for each patient. For totally occluded vessels that were unavailable for analysis, we imputed the extent and plaque area values according to the

most severe values found in each patient group (diabetic or nondiabetic) and in each type of segment.

Coronary territories and segments: The left main coronary artery was considered a segment and a territory of its own. The severity, extent, and atheroma-burden indexes were separately calculated for different coronary segments (i.e., left main, proximal, mid-, and distal segments), and severity indexes also for different vessel territories (left main, left anterior descending, left circumflex, and right coronary arteries).

Proximal segments comprised the proximal parts of the left anterior descending, the left circumflex, and the right coronary arteries. Midsegments consisted of the midparts of the 3 main coronary arteries, and of the proximal 1 to 2 cm of major diagonal and obtuse marginal branches. Segments distal to midsegments were considered distal. If technically possible, distal segments also included the smaller branches of the left circumflex and right coronary arteries.

Statistical analyses: Data are expressed as the median (25th, 75th percentile). Comparisons between the matched groups were performed using Wilcoxon's signed rank test for continuous variables and conditional logistic regression analysis for categorical variables. Comparisons between women and men were performed with unpaired t tests or Mann-Whitney rank-sum tests for continuous variables, and chisquare or Fisher's exact test for categorical variables. Univariate Spearman's correlation coefficients were calculated to assess associations between variables separately in the diabetic and nondiabetic groups.

RESULTS

Clinical characteristics: Type 1 diabetic and nondiabetic groups had similar age and kidney function due to matching ([Table 1](#)). Seven diabetic and 1 nondiabetic patient had received a kidney transplant. One diabetic and 1 control subject were on dialysis. In the control group, the reason for abnormal kidney function in 5 of the patients was glomerulonephritis; 1 subject had only 1 kidney, and 1 had amyloidosis. Five diabetic subjects were blind.

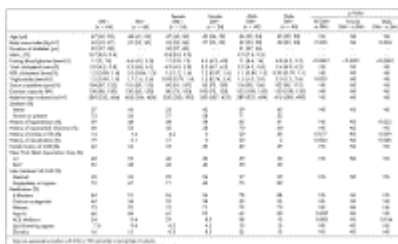


TABLE 1 Clinical and Biochemical Characteristics of the Study Groups

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The median age of diabetes onset was 14 years (range 2 to 33). All diabetic subjects had been treated with insulin since the time of diagnosis. At the time of coronary angiography, 53 were on a multiple injection insulin regimen.

The diabetic and nondiabetic groups were similar with respect to total and high-density lipoprotein cholesterol concentrations in both sexes. On average, diabetic patients were leaner

and had lower triglyceride levels than control subjects. None of the diabetic or nondiabetic patients had previously undergone angioplasty or bypass operation.

Severity and extent of coronary atherosclerosis: When both sexes were analyzed together, type 1 diabetic patients had significantly greater global severity indexes than nondiabetic control subjects (49 [37, 62] vs 34 [16, 52], $p < 0.001$; global extent, 35 [20, 44] vs 18 [5, 28]; $p < 0.001$; and global atheroma burden, 21 [12, 34] vs 13 [3, 22], respectively; $p < 0.001$). [Figure 1](#) shows that these differences were large and statistically significant among women. For men, there was no significant difference in global severity, but CAD was more extensive, and the global atheroma burden was borderline greater in diabetic than in nondiabetic men ([Figure 1](#)).

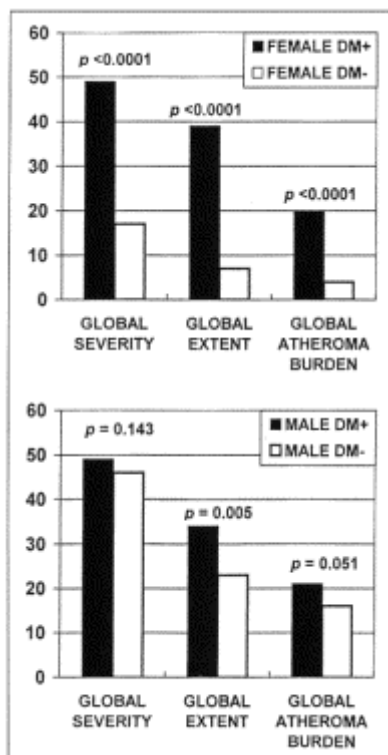


FIGURE 1. Severity, extent, and atheroma burden indexes of CAD in 24 female and 40 male type 1 diabetic and nondiabetic matched pairs.

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There were 9 diabetic and 10 nondiabetic patients who had some degree of left main disease; the remaining patients had no left main disease. In the diabetic group, 1 patient had 1-vessel, 7 had 2-vessel, and 54 had 3-vessel disease compared with 10, 17, and 37 patients, respectively, in the nondiabetic group ($p = 0.005$).

Diabetic women had more severe and extensive CAD in all territories and segments ([Table 2](#)) than nondiabetic women. The most marked differences were for the midsegment severity, extent, and atheroma burden indexes, and for the global extent index, in which the QCA-based scores were on average 3.6-, 6.5-, 6.4-, and 3.2-fold higher in diabetic than nondiabetic women. There was no influence of diabetes seen in the proximal segments in men.

	Diabetic	Nondiabetic	Diabetic	Nondiabetic	Diabetic	Nondiabetic	Diabetic	Nondiabetic	Diabetic	Nondiabetic	Diabetic	Nondiabetic	Diabetic	Nondiabetic	Diabetic	Nondiabetic	Diabetic	Nondiabetic
Global severity index	17 (7, 3)	46 (31, 58)	7 (1, 17)	23 (14, 31)	4 (1, 11)	16 (10, 26)	20 (10, 32)	21 (12, 34)	7 (2, 17)	14 (7, 26)	30 (17, 43)	15 (8, 33)	34 (20, 49)	24 (5, 32)	64	64	64	64

TABLE 2 Quantitative Coronary Angiographic Results

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Nondiabetic women had significantly milder CAD than nondiabetic men: global severity index, 17 (7, 3) vs 46 (31, 58), $p < 0.001$; global extent index, 7 (1, 17) vs 23 (14, 31), $p < 0.001$; global atheroma burden index, 4 (1, 11) vs 16 (10, 26), $p < 0.001$. This sex difference was consistent across all parts of the coronary tree (data not shown). In sharp contrast, there were no differences between the sexes among type 1 diabetic patients in global atheroma burden index: women, 20 (10, 32); men, 21 (12, 34); $p = 0.494$, or in any other indexes (not shown).

As expected, patients with serum creatinine value $< 100 \mu\text{mol/L}$ had milder CAD than subjects with $> 100 \mu\text{mol/L}$, in both diabetic (global atheroma burden, 15 [8, 31] vs 24 [18, 35]; $p = 0.016$) and nondiabetic (7 [2, 17] vs 14 [7, 26]; $p = 0.033$) groups, respectively.

Correlations between angiographic scores and risk variables: In the diabetic group, the known duration of diabetes was a consistent predictor of CAD severity and extent in the midsegments (severity index, $r = 0.585$, $p < 0.001$; extent index, $r = 0.482$, $p < 0.001$; atheroma burden index, $r = 0.392$, $p < 0.005$), in the distal segments (severity index, $r = 0.428$, $p < 0.002$; extent index, $r = 0.447$, $p < 0.001$; atheroma burden index, $r = 0.430$, $p < 0.002$), and globally (severity index, $r = 0.453$, $p < 0.001$; extent index, $r = 0.510$, $p < 0.001$), but not in the proximal segments.

We found an inverse correlation in the diabetic group between high-density lipoprotein cholesterol concentration and midsegment severity ($r = -0.365$, $p < 0.01$) and atheroma burden ($r = -0.361$, $p < 0.01$) indexes, proximal-segment extent ($r = -0.278$, $p < 0.05$) and atheroma burden ($r = -0.270$, $p < 0.05$) indexes, and global atheroma burden index ($r = -0.370$, $p < 0.01$). In the nondiabetic group, a consistent significant inverse relation between high-density lipoprotein and the angiographic scores was observed in all 15 segments and vessel territories analyzed.

Serum cholesterol and triglyceride concentrations and a history of hypertension were unrelated to the angiographic scores in both groups. The angiographic indexes also did not correlate with glycosylated hemoglobin A_{1c} or a history of smoking in the diabetic group. In the nondiabetic group current or former smokers had significantly more severe (30 [17, 43] vs 15 [8, 33], $p = 0.014$) and extensive (34 [20, 49] vs 24 [5, 32], $p = 0.037$) proximal-segment CAD than subjects who had never smoked.

Left ventricular systolic function: Left ventricular global ejection fractions were, on average, 64% in both groups. Regional ejection fractions were also similar among the groups and sexes.

DISCUSSION

The main finding of this study was that type 1 diabetic patients had a more severe, extensive, and distal type of CAD than individually matched control patients. QCA-derived indexes of

CAD were on average 1.4- to 4.3-fold higher in diabetic than in nondiabetic patients. These differences were particularly marked in women, suggesting a loss of sex difference for CAD among type 1 diabetic patients. The greater impact of type 1 diabetes in women is not explained by the established risk factors; diabetes may impair the mechanisms by which premenopausal women are usually protected against CAD. These findings are consistent with earlier studies.[7-9](#)

Some limitations must be acknowledged. The diabetic status of a patient may have accounted for the likelihood of reaching invasive examinations. Furthermore, this was a retrospective study with 64 matched pairs, and the clinical data were retrieved from medical records.

Hyperglycemia is the hallmark of type 1 diabetes and a major determinant of atherosclerosis.[10](#) It is also a strong factor in explaining extensive CAD in the diabetic group in this study. We found the duration of diabetes to be an important determinant of CAD in type 1 diabetes, similar to a previous study in type 2 diabetic patients.[11](#) Hyperglycemia induces glycosylation of proteins and accumulation of advanced glycosylation end products in the extracellular matrix of the arterial wall.[12,13](#) High levels of these end products also occur in end-stage renal disease.[14](#) Accordingly, the presence of renal failure aggravated the severity of CAD in our study.

Because the age of diabetes onset has not been shown to contribute to the risk of CAD,[15](#) it has been suggested that diabetes merely accelerates atherosclerosis rather than initiates the process. The first deaths due to CAD in type 1 diabetic patients occur in their early thirties but during the following 25 years, one third of diabetic patients die of CAD.[15,16](#) In patients without diabetic nephropathy, cardiovascular events begin 12 to 13 years after the diagnosis of diabetes, and in the presence of nephropathy, on average, 4 years earlier.[17](#) In the present study coronary angiography was performed, on average, 14 years after onset of diabetes.

Previously, we found no association between apolipoprotein B-containing lipoproteins and CAD in the type 2 diabetic group [11](#); in the present study, serum cholesterol or triglyceride concentrations were not determinants of CAD severity in type 1 diabetic patients. These findings, however, provide no evidence against the atherogenicity of apolipoprotein B-containing particles. Hyperglycemia leads to glycosylation of apolipoproteins, which renders them more atherogenic.[18](#) Accordingly, even normal levels of these lipoproteins may be deleterious in diabetes, which in turn may negate a quantitative relation between lipid concentrations and CAD severity.

High-density lipoprotein cholesterol, by contrast, was protective against CAD in type 1 diabetic patients. This is in line with our earlier type 2 diabetes data.[11](#) Type 1 diabetic patients with CAD had lower levels of HDL cholesterol than patients without CAD.[19](#) However, even normal levels of high-density lipoprotein cholesterol may have a diminished protective power in diabetes because of changes in reverse cholesterol transport and endothelial function.

Previous studies of the severity and extent of CAD in diabetic patients have yielded conflicting results.[20-24](#) Studies restricted to type 1 diabetes [1,2](#) are in agreement with the present one. In a small autopsy study, Crall and Roberts [2](#) found that type 1 diabetic patients had more extramural coronary luminal narrowing by atherosclerotic plaques than nondiabetic control subjects. In a visual analysis of coronary angiograms, Valsania and coworkers [1](#) found that diffuse multivessel disease was more prevalent in the diabetic than in the nondiabetic

group. Thus, existing data agree that CAD in type 1 diabetes is what is often considered "diabetic" CAD (i.e., more extensive, diffuse, and distally located). In type 2 diabetes the issue is more controversial.[3,20-24](#)

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