Differences in Atherosclerotic Plaque Burden and Morphology Between Type 1 and 2 Diabetes as Assessed by Multislice Computed Tomography

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OBJECTIVE — It is unclear whether the coronary atherosclerotic plaque burden is similar in patients with type 1 and type 2 diabetes. By using multislice computed tomography (MSCT), the presence, degree, and morphology of coronary artery disease (CAD) in patients with type 1 and type 2 diabetes were compared.

RESEARCH DESIGN AND METHODS — Prospectively, coronary artery calcium (CAC) scoring and MSCT coronary angiography were performed in 135 asymptomatic patients (65 patients with type 1 diabetes and 70 patients with type 2 diabetes). The presence and extent of coronary atherosclerosis as well as plaque phenotype were assessed and compared between groups.

RESULTS — No difference was observed in average CAC score (217 ± 530 vs. 174 ± 361) or in the prevalence of coronary atherosclerosis (65% vs. 71%) in patients with type 1 and type 2 diabetes. However, the prevalence of obstructive atherosclerosis was higher in patients with type 2 diabetes ($n = 24$; 34%) compared with that in patients with type 1 diabetes ($n = 11$; 17%) ($P = 0.02$). In addition, a higher mean number of atherosclerotic and obstructive plaques was observed in patients with type 2 diabetes. In addition, the percentage of noncalcified plaques was higher in patients with type 2 (66%) versus type 1 diabetes (27%) ($P < 0.001$), resulting in a higher plaque burden for each CAC score compared with that in type 1 diabetic patients.

CONCLUSIONS — Although CAC scores and the prevalence of coronary atherosclerosis were similar between patients with type 1 and type 2 diabetes, CAD was more extensive in the latter. Also, a relatively higher proportion of noncalcified plaques was observed in patients with type 2 diabetes. These observations may be valuable in the development of targeted management strategies adapted to diabetes type.

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Cardiovascular disease and coronary artery disease (CAD) in particular constitute a major cause of morbidity and mortality in patients with diabetes (1). However, management of this patient population remains challenging. Current European guidelines regard type 2 diabetes as a CAD equivalent, whereas type 1 diabetes is considered a high-risk state only in presence of microalbuminuria (2). In contrast, U.S. guidelines in primary prevention recommend stringent phar-macological therapy with lipid and blood pressure goals comparable to those in secondary prevention for all diabetic patients regardless of type of diabetes (3). Notably, these guidelines are based on clinical trials in patients with type 2 diabetes. However, CAD in type 1 diabetes, which has been studied less extensively, may have a pathophysiology distinct from that in patients with type 2 diabetes. As a result, caution is indicated when clinical observations obtained in patients with type 2 diabetes are extrapolated to patients with type 1 diabetes. To date, it is unclear whether asymptomatic type 1 diabetic patients benefit equally from the current preventive treatment strategies.

To optimize guidelines for type 1 diabetic patients, more detailed understanding of coronary atherosclerosis in type 1 diabetes is required. Thus far, most studies have evaluated the complications and risk factors associated with microvascular disease in this population (4). Studies of CAD have focused mainly on type 1 diabetic patients with kidney failure undergoing coronary angiography before kidney transplantation (5). Limited information is available on the presence and morphology of CAD in asymptomatic patients with type 1 diabetes in daily clinical practice (6).

Multislice computed tomography (MSCT) allows evaluation of the coronary artery calcium (CAC) score and direct assessment of coronary artery integrity. Importantly, in diabetic patients the diagnostic accuracy of MSCT coronary angiography for the detection of significant stenoses has been shown to be similar to that for the general population (7). In addition, the technique provides information on atherosclerotic plaque burden and to some extent on plaque composition (8–10). Previous studies with MSCT revealed an increased prevalence of noncalcified coronary plaques, which have been linked to unstable CAD, in patients with type 2 diabetes (11,12). However, thus far no studies have addressed plaque morphology in patients with type 1 diabetes. To improve understanding of po-

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tential differences in pathophysiology and atherosclerotic patterns as well as for development of more targeted management strategies, the evaluation of differences in plaque composition on MSCT may provide valuable information. Therefore, the purpose of the present study was to explore and compare the extent, degree, and morphology of coronary atherosclerosis by MSCT in asymptomatic patients with type 1 and type 2 diabetes recruited from a regular diabetes clinic.

RESEARCH DESIGN AND METHODS

A total of 135 consecutive asymptomatic patients with diabetes were prospectively included from an ongoing registry of new patients at the diabetes outpatient clinic. Diabetic patients were referred to the cardiology outpatient clinic for cardiovascular screening. Patients were stratified as having type 1 or type 2 diabetes according to the American Diabetes Association criteria (13). Plasma levels of C-peptide and autoantibodies to islet cells, insulin, and GAD were determined to distinguish between primary insulinopenia and immune destruction of pancreas β-cells (type 1 diabetes) and insulin resistance (type 2 diabetes).

Asymptomatic status was confirmed using the Rose questionnaire for angina (14). A structured interview, physical examination, and laboratory analysis were obtained for all patients. Cardiovascular risk factors were assessed according to the following criteria: *1*) positive family history of CAD (CAD in first-degree family members aged <55 (men) or <65 (women) years), *2*) smoking (current smoking or smoking in the past 2 years), *3*) hypertension (blood pressure >140/90 mmHg or treatment with antihypertensive medication), *4*) hypercholesterolemia (total cholesterol level >5.0 mmol/l or use of cholesterol-lowering medication), 5) obesity (estimated by BMI [weight in kilograms divided by the square of height in meters]), *6*) level of glycemic control defined by plasma A1C (millimoles per liter), *7*) diabetic nephropathy (urinary albumin-to-creatinine ratio ≥35 mg/mmol), and *8*) renal function (estimated by glomerular filtration rate [GFR]).

Noninvasive MSCT coronary angiography was performed in all patients as part of a clinical protocol. Exclusion criteria were ventricular and supraventricular arrhythmia and contraindications for the use of iodinated contrast media.

MSCT data acquisition

Imaging was performed with a 64-slice MSCT scanner (Toshiba Medical Systems, Tokyo, Japan). For patients with heart rate ≥65 bpm, oral β-blocking medication (50 or 100 mg metoprolol) was provided 1 h preceding the scan, if tolerated. First, a prospective CAC scan without contrast enhancement was performed, followed by MSCT coronary angiography according to protocols described previously (15).

Assessment of CAD by MSCT

CAC score. The CAC score was assessed using dedicated software (Vitrea2; Vital Images, Minnetonka, MN). CAC was identified as a dense area in the coronary artery exceeding the threshold of 130 Hounsfield units. A total Agatston score was determined for each patient.

Coronary atherosclerosis. All MSCT coronary angiograms were interpreted by two experienced observers blinded to the patient's characteristics. Discrepancies in interpretation were immediately resolved by consensus. The presence of coronary atherosclerosis was evaluated by scrolling through axial images, followed by visual assessment of curved multiplanar reconstructions in at least two orthogonal planes. Coronary plaques were defined as structures >1 mm^2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding pericardial tissue (10).

First, the presence of any atherosclerosis (≥1 plaque in the coronary tree) or multivessel atherosclerosis (≥1 plaque in minimum two coronary arteries) and that of obstructive atherosclerosis (luminal narrowing ≥50%) were evaluated at the patient level in type 1 and type 2 diabetic patients. Thereafter, a more extensive analysis of plaque burden was obtained by registering the total number of atherosclerotic plaques and obstructive plaques for each patient (10). In addition, plaques were classified according to phenotype: *1*) noncalcified plaques (plaques with lower density than contrast-enhanced lumen), *2*) calcified plaques (plaques with higher density than contrast-enhanced lumen), and *3*) mixed plaques (plaques with components of low- and high-density plaques) (8–10).

Statistical analysis

Continuous variables were expressed as means ± SD and compared between the groups of patients with type 1 and type 2 diabetes by using a two-tailed independent *t* test. Categorical variables were expressed as numbers (percentages) or medians (lower quartile, upper quartile) and compared with a χ^2 test. Separate multivariate regression analyses with backward elimination were performed, correcting for all baseline clinical characteristics including age, male sex, BMI, smoking, positive family history of CAD, hypercholesterolemia, hypertension, A1C, GFR, and type of diabetes to identify independent predictors of each coronary atherosclerosis variable on MSCT.

The relationship between CAC scores and extent of coronary atherosclerosis was compared in patients with type 1 and type 2 diabetes. Patients were further classified according to CAC scores: *1*) patients without coronary calcium, *2*) patients with a CAC score in the range of 1–100, and *3*) patients with a CAC score >100. The mean number of atherosclerotic lesions was determined for each CAC score category.

Statistical analyses were performed using SPSS software (version 12.0.1; SPSS, Chicago, IL) and SAS software (version 6.12; SAS Institute, Cary, NC). $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics. A total of 135 asymptomatic diabetic patients were included in the study. Mean age was 48 ± 10 years, and 79 patients (59%) were male. The study population consisted of 65 patients with type 1 and 70 patients with type 2 diabetes. Baseline characteristics are provided in Table 1. Importantly, age and sex distribution were comparable in patients with type 1 and type 2 diabetes. However, patients with type 2 diabetes had a significantly higher BMI and A1C and a shorter duration of diagnosed diabetes. Other baseline cardiovascular risk factors were similar in the two groups.

Assessment of CAD by MSCT

CAD at patient level. Results of CAD assessment by MSCT are illustrated in Table 2. The mean CAC score and prevalence of atherosclerosis were similar among patients with type 1 and type 2 diabetes. However, the prevalence of multivessel atherosclerosis was higher in patients with type 2 ($n = 41$; 59%) than in patients with type 1 ($n = 19$; 29%) diabetes ($P = 0.001$). Finally, obstructive stenosis was more prevalent in patients with type 2 di-

Table 1—Characteristics of the study population

	Type 1 diabetes	Type 2 diabetes	P
n	65	70	
Age (years)	46.0 (38.0, 54.5)	49.5 (45.0, 57.0)	0.08
Men	42 (65)	37 (53)	0.17
BMI (kg/m^2)	23.8 (22.2, 26.6)	28.2 (24.9, 33.4)	<0.001
Smokers	17 (26)	14 (20)	0.40
Family history of CAD	30 (46)	37 (53)	0.44
Hypercholesterolemia	41 (63)	50 (71)	0.30
Hypertension	32 (49)	43 (61)	0.22
Duration of diabetes (years)	23.0 (9.5, 33.0)	7.5 (2.0, 13.0)	<0.001
A1C (mmol/l)	7.6 (6.6, 8.6)	8.3 (7.0, 9.5)	0.04
GFR (ml/min per 1.73m^2)	101.6 (84.7, 122.8)	98.4 (81.8, 124.8)	0.88
Albuminuria*	1 (2)	4 (6)	0.20

Data are medians (lower quartile, upper quartile) or number of patients (%). n = 135. *Albuminuria was defined by a urine albumin-to-creatinine ratio ≥35 mg/mmol.

abetes (n = 24; 34%) than in patients with type 1 diabetes (n = 11; 17%) (P = 0.02).

Plaque analysis. Quantification of the total number of atherosclerotic plaques for each patient revealed a significantly higher mean number of lesions in patients with type 2 diabetes (9.9 ± 11.9) compared with that in patients with type 1 diabetes (3.4 ± 4.8) (P < 0.001) (Fig. 1A). In addition, the mean number of obstructive plaques was significantly higher in patients with type 2 diabetes (1.7 ± 3.9) than in patients with type 1 diabetes (0.5 ± 1.4) (P = 0.02) (Fig. 1A).

Analysis of plaque phenotype showed a higher mean number of noncalcified plaques in patients with type 2 diabetes (6.5 ± 9.5) versus patients with type 1 diabetes (1.0 ± 1.3) (P < 0.001), whereas the mean number of mixed and calcified plaques was not significantly different. Accordingly, a higher proportion of non-calcified plaques was observed in patients with type 2 diabetes (66%) compared with patients with type 1 diabetes (27%) (P < 0.001) (Fig. 1B).

Relation between type of diabetes and the presence and extent of CAD

To correct for baseline characteristics, the relation between type 2 diabetes (compared with type 1 diabetes) and the presence and extent of CAD were evaluated using multivariate regression analyses (Table 3). Although type of diabetes was not related to the presence of any atherosclerosis, type 2 diabetes was strongly related to the extent and degree of coronary atherosclerosis after correction for all other risk factors. In addition, an independent association was observed between the presence of type 2 diabetes and number of noncalcified coronary plaques.

Relation between CAC scores and atherosclerosis

Comparison of the CAC score versus coronary angiography findings showed that the number of atherosclerotic lesions paralleled the increase in coronary calcium (Fig. 1C). However, for each CAC score category the mean number of atherosclerotic lesions was significantly higher in patients with type 2 diabetes (Fig. 1C).

Similarly, the prevalence of obstructive atherosclerosis increased per CAC score category (Fig. 1D). Importantly, absence of coronary calcium excluded the presence of obstructive atherosclerosis in patients with type 1 diabetes, whereas obstructive atherosclerosis was identified in three patients with type 2 diabetes (9%). In patients with a CAC score ≤100, obstructive atherosclerosis was found in only 2 (4%) type 1 diabetic patients, whereas 10 (19%) type 2 diabetic patients showed obstructive CAD.

CONCLUSIONS — In the present study, no significant difference was observed in the prevalence of atherosclerosis in asymptomatic patients with type 1 and type 2 diabetes. However, in patients with type 1 diabetes, multivessel disease was less prevalent and a lower atherosclerotic plaque burden was observed. Moreover, the number of obstructive coronary lesions was significantly lower in patients with type 1 diabetes. The presence of type 2 diabetes (as opposed to type 1 diabetes) was shown to be an independent predictor of extent and degree of coronary atherosclerosis on MSCT angiography. Second, for each CAC score category a higher atherosclerotic plaque burden was observed in patients with type 2 diabetes. This observation was explained by the high proportion of noncalcified plaques in asymptomatic patients with type 2 diabetes compared with a high proportion of calcified plaques in patients with type 1 diabetes.

Plaque burden

Most previous studies on the prevalence of coronary atherosclerosis have used conventional coronary angiography to examine patients with a clinical suspicion of CAD and observed more extensive CAD in diabetic patients than in their nondiabetic counterparts (16,17). Limited studies have been performed in asymptomatic diabetic patients. MSCT provides accurate noninvasive evaluation of the extent and degree of coronary atherosclerosis and may be used in patients with a lower

Table 2—Results of MSCT coronary angiography

	Type 1 diabetes	Type 2 diabetes	P
Patients			
Coronary artery calcium scores	217 ± 530	174 ± 361	0.59
Atherosclerosis	42 (65)	50 (71)	0.40
Atherosclerosis, multivessel	19 (29)	41 (59)	0.001
Obstructive atherosclerosis*	11 (17)	24 (34)	0.02
Plaques			
No. of plaques	3.4 ± 4.8	9.9 ± 11.9	<0.001
No. of obstructive plaques	0.5 ± 1.4	1.7 ± 3.9	0.02
No. of noncalcified plaques	1.0 ± 1.3	6.5 ± 9.5	<0.001
No. of mixed plaques	0.7 ± 1.3	1.1 ± 1.9	0.25
No. of calcified plaques	1.8 ± 3.6	2.2 ± 3.9	0.52

Data are means ± SD or number of patients (%). *Obstructive atherosclerosis was defined as luminal narrowing ≥50%.
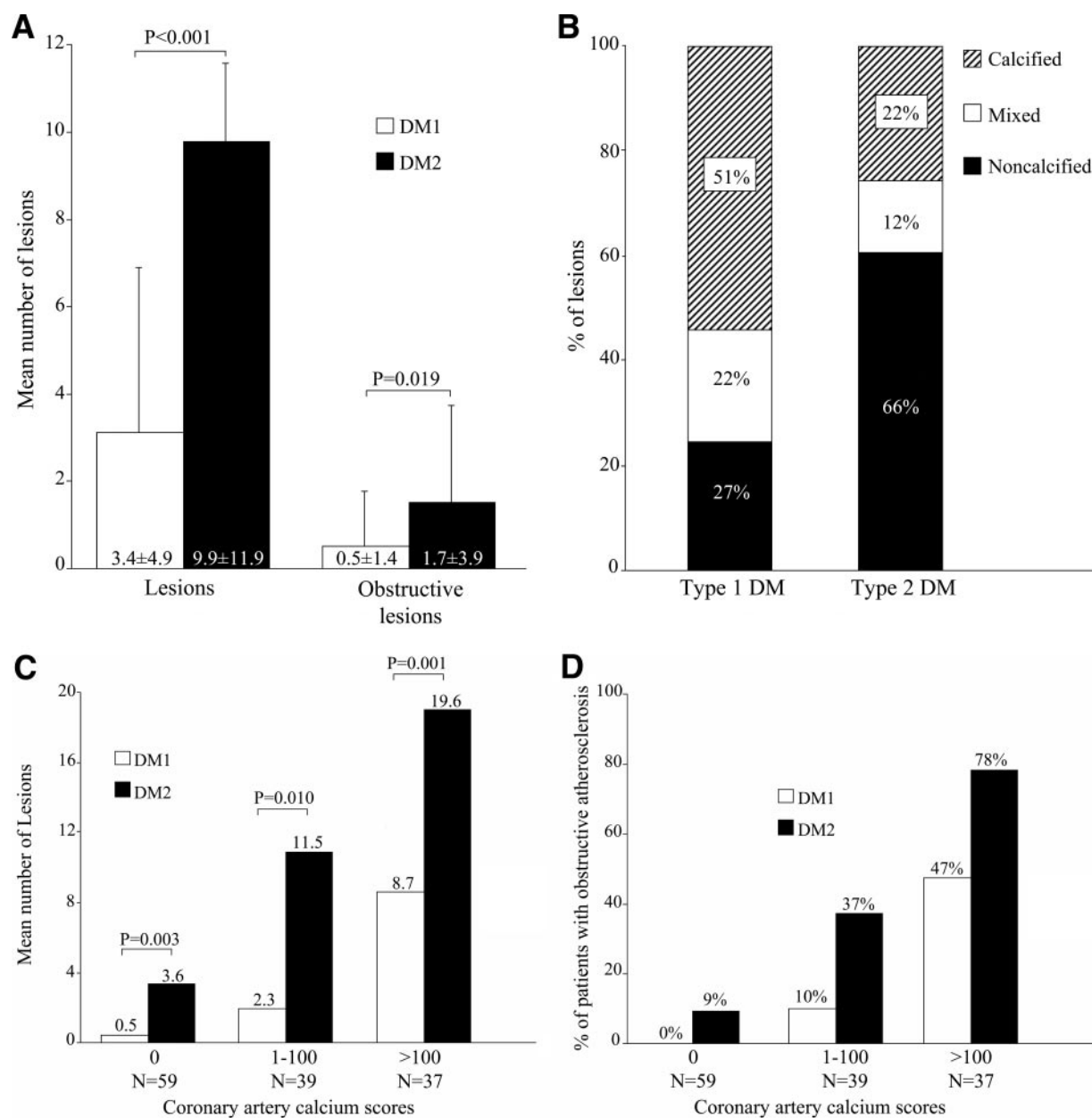
Figure 1—*A: Clustered columns demonstrating average number of lesions and obstructive lesions in type 1 (DM1) and type 2 (DM2) diabetes. A significantly higher mean number of lesions and obstructive lesions were observed in type 2 diabetes. B: Bar graph illustrating plaque phenotype in type 1 and type 2 diabetes. A higher percentage of noncalcified plaques was observed in type 2 diabetes. C: Clustered bar graph illustrating the increase in number of lesions for each CAC score category among patients with type 1 and type 2 diabetes. The plaque burden was significantly higher in type 2 diabetes for each CAC score category. D: Clustered bar graph demonstrating the increase in prevalence of obstructive atherosclerosis for each CAC score category among patients with type 1 and type 2 diabetes. An absence of coronary calcium excluded obstructive atherosclerosis in type 1 diabetes, but not in type 2 diabetes. The prevalence of obstructive atherosclerosis was higher in type 2 diabetes for each CAC score category.*

likelihood of CAD. Importantly, excellent sensitivity, specificity, and negative predictive values for detection of significant stenosis have also been shown in diabetic patients (7). Thus far, the technique has been used in several studies to explore the presence and extent of CAD in patients with type 2 diabetes. Scholte et al. (12) observed a high prevalence of coronary atherosclerosis (80%), which predominantly involved more than one coronary artery (74%), in asymptomatic type 2 diabetic patients. Obstructive CAD was observed in 26% of patients, similar to observations in the current study. Thus far, no MSCT studies have reported on the presence of CAD in asymptomatic type 1 diabetic patients.

However, using magnetic resonance imaging, Kim et al. (6) previously evaluated CAD in asymptomatic patients with type 1 diabetes and observed a higher atherosclerotic plaque burden in the presence of diabetic nephropathy compared with that in normoalbuminuria. In that particular study, an absence of diabetic nephropathy excluded the presence of subclinical obstructive CAD. In our current study, the prevalence of nephropathy was low (1%) in type 1 diabetic patients,

Table 3—*Presence of type 2 diabetes (not type 1 diabetes) as a predictor of MSCT variables: results of multivariate analysis in a backward regression model*

	Hazard ratio β (95% CI)	*P*
Patients		
Coronary artery calcium scores*	—	NS
Atherosclerosis†	—	NS
Atherosclerosis, multivessel†	4.16 (1.76–9.93)	0.001
Obstructive atherosclerosis†‡	4.01 (1.38–11.60)	0.01
Plaques		
No. of plaques*	6.82 (3.51–10.13)	<0.001
No. of obstructive plaques*	1.40 (1.32–2.48)	0.01
No. of noncalcified plaques*	6.27 (3.60–8.94)	<0.001
No. of mixed plaques*	—	NS
No. of calcified plaques*	—	NS

The predictive value of type 2 diabetes was tested in a separate multivariate regression model for each MSCT variable. *Results of analysis in a multivariate linear regression model. †Results of analysis in a multivariate binary logistic regression model. ‡Obstructive atherosclerosis was defined as luminal narrowing ≥50%.

suggesting that these patients were at relatively low risk. Interestingly, however, the absence of nephropathy did not exclude subclinical obstructive CAD on MSCT. Nevertheless, compared with type 2 diabetes, the extent of atherosclerosis was less severe with a lower prevalence of multivessel disease and fewer lesions. Moreover, a smaller proportion of patients with type 1 diabetes had obstructive atherosclerosis. Importantly, in this study, the presence of type 2 diabetes remained a significant predictor of the severity of atherosclerosis after correction for traditional cardiovascular risk factors including obesity, glycemic control, and renal function. Accordingly, the higher atherosclerotic plaque burden in patients with type 2 diabetes may warrant more aggressive antiatherosclerotic treatment. On the other hand, MSCT coronary angiography excluded atherosclerosis in ~30% of both type 1 and type 2 diabetic patients. This finding raises the question of whether antiatherosclerotic medical therapy should be initiated in all asymptomatic diabetic patients and to what extent. It is possible that MSCT may be used to identify or exclude the presence of atherosclerosis and provide a basis for individually tailored therapy.

Plaque morphology and relation with CAC
In addition to increased severity of atherosclerosis, we also observed differences in relative plaque composition in patients with type 2 diabetes with a higher percentage of noncalcified plaques. This finding is in line with a previous study in which noncalcified plaques comprised 41% of atherosclerotic plaques in asymptomatic patients with type 2 diabetes (12). In retrospective studies, a higher proportion of noncalcified plaques has been associated with unstable CAD. Preliminary prognostic data also suggest that the presence of substantial noncalcified plaque indeed confers a worse outcome (18). Accordingly, it has been suggested that these plaques represent more active stages of CAD and may be more prone to rupture (15,19). Notably, the distribution of coronary plaque phenotype has not been examined previously in type 1 diabetes. In contrast with patients with type 2 diabetes, we found a higher proportion of calcified plaques and a lower proportion of noncalcified plaques in patients with type 1 diabetes, despite similar CAC scores. As a result, plaque burden was higher for each CAC score category in type 2 compared with type 1 diabetic patients.

Assessment of CAC score has been suggested as a primary step in cardiovascular risk stratification and screening of asymptomatic diabetic patients (20) because the presence of elevated CAC scores has been associated with a higher likelihood of myocardial ischemia (21). However, our current observations suggest that CAC score assessment may be more effective in identifying CAD in patients with type 1 diabetes. Indeed, the absence of coronary calcium accurately excluded the presence of obstructive coronary atherosclerosis in patients with type 1 diabetes. In contrast, this relation was distorted in patients with type 2 diabetes with a higher prevalence of obstructive CAD in patients without or only minor calcium. As both the prevalence of obstructive CAD and extent of CAD per CAC category were higher, it appears that CAC scores may underestimate CAD in patients with type 2 diabetes, in line with previous comparisons with nondiabetic patients (22). Accordingly, strategies using CAC scores to identify diabetic patients at higher risk should be developed with caution and should potentially be adjusted for type of diabetes.

Study limitations
Several limitations need to be acknowledged. The current analysis was restricted to evaluation of coronary atherosclerosis in patients with type 1 and type 2 diabetes, and the proatherogenic processes involved in each form of diabetes were not investigated. In addition, the lack of a control group without diabetes should be acknowledged. Because MSCT coronary angiography involves radiation exposure, it is not feasible to perform a similar assessment in asymptomatic subjects free of cardiovascular risk. Furthermore, MSCT coronary angiography requires administration of potentially nephrotoxic contrast media, rendering the technique unsuitable for use in asymptomatic diabetic patients with severe renal dysfunction. Finally, no follow-up data were available. Indeed, the prognostic implications of our observations should be evaluated in prospective follow-up studies.

In summary, although CAC scores and the prevalence of coronary atherosclerosis were similar between patients with type 1 and type 2 diabetes, CAD was more extensive in the latter. In addition, a relatively higher proportion of noncalcified plaques was observed in patients with type 2 diabetes. These observations may be valuable in the development of targeted management strategies adapted to diabetes type. It is possible that MSCT angiography may be useful to identify or exclude the presence of atherosclerosis and provide a basis for individually tailored therapy.

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