Vessel Shrinkage as a Sign of Atherosclerosis Progression in Type 2 Diabetes

A Serial Intravascular Ultrasound Analysis

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OBJECTIVE—The aim of this study was to determine the natural history of vascular remodeling of atherosclerotic plaques in patients with type 2 diabetes and the predictors of vessel shrinkage.

RESEARCH DESIGN AND METHODS—In this serial intracoronary ultrasound (IVUS) study, 237 coronary segments from 45 patients enrolled in the DIABETES I, II, and III trials were included. Quantitative volumetric IVUS analyses (motorized pullbacks at 0.5 mm/s) were performed in the same coronary segment after the index procedure and at the 9-month follow-up. Nontreated mild lesions (angiographic stenosis <25%) with ≥0.5 mm plaque thickening and length of ≥5 mm assessed by IVUS were included. Vessel shrinkage was defined as a Δexternal elastic membrane area/Δplaque area < 0. Statistical adjustment by multiple segments and multiple lesions per patient was performed.

RESULTS—Vessel shrinkage was identified in 37.1% of segments and was associated with a significant decrease in lumen area at 9 months (vessel shrinkage, 10 ± 4 mm^2 vs. non–vessel shrinkage, 11 ± 4 mm^2; $P = 0.04$). Independent predictors of vessel shrinkage were insulin requirements (odds ratio 4.6 [95% CI 1.40–15.10]; $P = 0.01$), glycated hemoglobin (1.5 [1.05–2.10]; $P = 0.02$), apolipoprotein B (0.96 [0.94–0.98]; $P < 0.001$), hypertension (3.7 [1.40–10.30]; $P = 0.009$), number of diseased vessels (5.6 [2.50–12.50]; $P < 0.001$), and prior revascularization (17.5 [6.50–46.90]; $P < 0.001$).

CONCLUSIONS—This serial IVUS study suggests that progression of coronary artery disease in patients with type 2 diabetes may be mainly attributed to vessel shrinkage. Besides, vessel shrinkage is influenced by insulin requirements and metabolic control and is associated with more advanced coronary atherosclerosis. ***Diabetes*** **58:209–214, 2009**

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Coronary artery remodeling is a phenomenon by which vessel dimension changes in response to atherosclerotic plaque accumulation. This concept was initially described by Glagov et al. (1) in a postmortem, histopathological study and confirmed by in vivo studies using intracoronary ultrasound (IVUS) analysis (2–7). Two different patterns of coronary remodeling have been described: a compensatory enlargement of the vessel in response to an increase of atherosclerotic plaque (positive remodeling) and a failure to enlarge or even vessel shrinkage (negative remodeling). The latter is a common finding in coronary stenosis of diabetic patients (8,9). In cross-sectional studies, negative remodeling has been associated with coronary risk factors, such as hypertension (5) and smoking (4), with the type of plaque (2,7) (calcified, hard plaques), and with metabolic control in diabetic patients (10–12). In most studies, remodeling has been evaluated only at a single time point. Therefore, the natural history of this process has not been properly addressed. In addition, remodeling index has been assessed by comparing vessel dimension at target site and that at the most normal-looking cross-section within 10 mm from the lesion taken as reference segment (2–7). However, reference segments are rarely disease free (9) and therefore may be also subject to the remodeling process. This may be especially true in diabetic patients (9). Nevertheless, no previous serial IVUS study has shown the factors associated with coronary remodeling in diabetic patients. Therefore, the aim of this study was to determine the natural history of vascular remodeling of atherosclerotic plaques in diabetic patients and the predictors of vessel shrinkage during time.

RESEARCH DESIGN AND METHODS

Study population. Type 2 diabetic patients enrolled in the DIABETES I, II, and III trials (13–15) in whom IVUS evaluation was performed were included in this study. The DIABETES I trial was a randomized, multicenter study that compared the safety and efficacy of sirolimus-eluting stent versus bare metal stent implantation in 160 type 2 diabetic patients. The DIABETES II and III trials were registries of 80 consecutive type 2 diabetic patients either treated with paclitaxel-eluting stent or tacrolimus-eluting stent, respectively. All of these trials have the same inclusion and exclusion criteria (13–15). In brief, type 2 diabetic patients treated with either insulin or oral agents at least for 1 month and one or more de novo lesions amenable for percutaneous revascularization were included. Per protocol, IVUS evaluation had to be attempted in at least one treated lesion both immediately after successful stent implantation and at the 9-month follow-up. For the purpose of the current serial IVUS study, nontreated mild lesions (angiographic stenosis <25% by visual assessment) with a plaque thickening at least ≥0.5 mm and length of ≥5 mm as assessed by IVUS were selected. The coronary segment eligible for serial

analysis had to be located at least 10 mm distal or proximal from the previously stented segment and thus not subject to balloon injury during the index procedure. We excluded from the analysis those lesions with artifacts related to IVUS, such as nonuniform rotational distortion. In addition, patients with multiple balloon inflations during complex procedures were also excluded when doubts remained concerning the exact location of the inflated balloon. Study protocols were approved by the ethics medical committee of the participating institutions, and all patients gave written informed consent.

IVUS imaging and analysis. IVUS imaging was carried out at the index procedure and at 9-month follow-up. The probe was placed at least 10 mm distal from the stent and was retrieved by means of a motorized pullback up to the aorto-ostial junction. IVUS pullbacks were performed at a constant speed of 0.5 mm/s. In all cases, the IVUS system used was the ClearView console (CVIS, Sunnyvale, CA) with the Atlantis-Pro 40-MHz catheter (CVIS). From the motorized pullback, angiographically nonsignificant plaques not related to the treatment site were serially analyzed. Furthermore, because different types of plaques and different patterns of coronary remodeling may be encountered throughout a given coronary lesions, each study lesion was divided into three segments for serial quantitative and qualitative analyses. This serial IVUS analysis was performed by an independent corelab (University of Florida Health Science Center at Shands Jacksonville, Jacksonville, FL), blinded to the clinical and laboratory data. The analyses followed a previously described methodology (16). From the digitized images, lumen, plaque, and external elastic membrane (EEM) areas were measured at intervals of 0.5 mm in each coronary segment. Mean lumen, plaque, and EEM areas and changes from baseline to 9-month follow-up were calculated. In addition, segments were qualitatively categorized into four types: soft, mixed, fibrous, and calcified following current definitions (17) with the agreement of two independent observers.

Definitions. Serial vascular changes were categorized as vessel shrinkage or vessel enlargement. Vessel shrinkage was identified in those lesions in which a decrease in the mean vessel area was observed during the 9-month follow-up. It was defined as the ratio of Δvessel area to Δatheroma area <0 (18). Conversely, serial vessel enlargement was defined as a ratio >0. The type of plaque was defined (17) as soft tissue when at least 80% area was constituted by material showing less echo reflectivity than the adventitia, with an arc of calcium $<10°$; fibrous plaque when echo reflectivity of at least 80% of the material was as bright as or brighter than the adventitia without acoustic shadowing; diffuse calcified plaque when it contained material brighter than adventitia showing acoustic shadowing in $>90°$; and mixed when plaque did not match the 80% criterion.

Biochemical parameters. At the index procedure and at the 9-month follow-up, total serum cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, apolipoprotein (apo)A, apoB, A1C, and high-sensitivity C-reactive protein (hs–C-reactive protein) were measured after overnight fasting, following prespecified protocol. Serum total cholesterol, triglyceride, and HDL were measured by automated enzymatic procedures, and serum apoA and apoB were measured by immunochemical methods. LDL cholesterol was calculated by Friedewald formula (19): LDL cholesterol = total cholesterol − HDL cholesterol − (triglyceride/5). All of the lipid profiles were assessed at the central laboratory of our hospital. hs–C-reactive protein levels were measured from frozen serum samples by immunonephelometry using a commercially available kit (Beckman Coulter, Fullerton, CA).

Statistical analysis. Statistical analysis was performed by the SPSS 12.0 and SAS 9.1 version. Quantitative data are presented as means ± SD and qualitative as percentages. To take into account the intraindividual variability (repeated assessments), all comparisons (univariable and multivariable) were adjusted by means of a generalized estimating equations (GEE) model stratifying per patient, lesion, and segments (20). The association between IVUS measurement and laboratory data was performed by linear regression analysis to obtain the regression coefficient (B). To evaluate the association between clinical and laboratory data with vessel shrinkage, a multivariable logistic regression model was performed. In this analysis, those variables with P value <0.1 on univariable analysis or clinically relevant were included: insulin-dependent diabetes, hypertension, previous revascularization, unstable angina, number of diseased vessels, statin use, ACE inhibitors use, triglycerides, apoB, and glycated hemoglobin levels. A two-tailed value of $P < 0.05$ was considered significant.

RESULTS

Baseline characteristics. Overall, 244 arteries studied by IVUS from 222 patients were reviewed (Fig. 1). One hundred and ninety-two pullbacks were not amenable for this serial study. Main reasons included absence of lesion that met inclusion criteria (n = 183, 95.3%) and artifacts related to IVUS (n = 4, 2%). Thus, serial IVUS analyses were available in 79 lesions from 45 patients. From these lesions, a total of 237 matched atherosclerotic segments were finally defined and serially analyzed for a 9-month period. Baseline clinical and metabolic characteristics of the overall population are presented in Table 1. Mean length of the entire lesions were 10.3 ± 4.4 mm, and each segment measured on average 3.4 ± 1.5 mm. The type of plaque most frequently observed in each segments was mixed (39.2%) followed by calcified (31.2%).

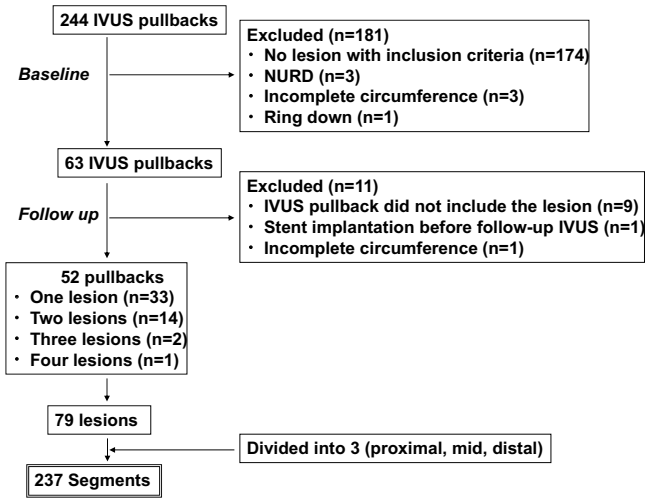

FIG. 1. Flow chart of the study.

Serial quantitative and qualitative IVUS analyses. Overall, a significant increase in EEM (20.3 ± 4.9 vs. 21.4 ± 4.9; $P < 0.001$), plaque (10.1 ± 3.4 vs. 10.6 ± 3.5, $P < 0.001$), and lumen (10.1 ± 3.6 vs. 10.7 ± 3.8, $P < 0.001$) areas were observed during follow-up. There were strong positive lineal relationships between ΔEEM and Δlumen areas and between ΔEEM and Δplaque areas (Fig. 2). Conversely, correlation between Δlumen and Δplaque areas was weak, although it maintained statistical significance.

TABLE 1
Baseline characteristics

Clinical characteristics (n = 45)	
Age (years)	67.4 ± 9.1
Male	35 (77.8)
Type 1 diabetic	13 (28.9)
BMI	29.3 ± 3.9
Hyperlipidemia	29 (64.4)
Hypertension	30 (66.7)
Smoke	26 (57.8)
Peripheral arterial disease	2 (4.4)
Previous myocardial infarction	19 (42.2)
Previous revascularization	8 (17.8)
Unstable angina	31 (68.9)
Multivessel disease	30 (66.7)
LVEF (%)	66.6 ± 14.1
A1C	7.2 ± 1.4
Subsegments (n = 237)	
Vessel area	20.3 ± 4.9
Plaque area	10.1 ± 3.4
Lumen area	10.1 ± 3.6
Vessel shrinkage	88 (37.1)

Data are means ± SD or n (%). LVEF, left ventricular ejection fraction.

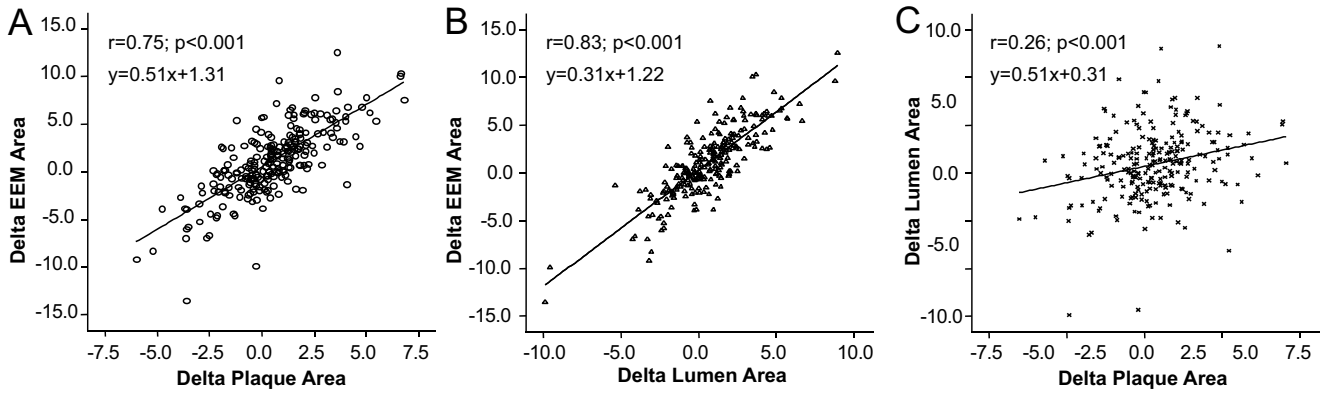

FIG. 2. ***A*****: Relationship between Δplaque area and ΔEEM area.** ***B*****: Relationship between Δlumen area and ΔEEM area.** ***C*****: Relationship between Δplaque area and Δlumen area.**

Predictors of vessel shrinkage. Vessel shrinkage was identified in 88 segments (37.1%), whereas some degree of vessel enlargement was observed in the remaining segments. At follow-up, vessel shrinkage was associated with a significant decrease in lumen area at 9 months (vessel shrinkage, 10 ± 4 mm^2, vs. non–vessel shrinkage, 11 ± 4 mm^2; $P = 0.04$). These two differential patterns of vascular remodeling are depicted in Fig. 3. Segments that, on average, shrank during follow-up presented a significant decrease in mean lumen dimension as a result of mean EEM reduction. In this scenario, mean plaque area was also reduced during follow-up. Conversely, segments that, on average, enlarged presented an increase in the mean lumen area secondary to an enlargement in both mean EEM and plaque areas. Factors associated with vessel shrinkage at the univariable analysis are depicted in Table 2. There were not significant differences between the type of plaque and the development of vessel shrinkage (Table 3). By multivariate analysis, independent predictors of vessel shrinkage were insulin-dependent diabetes, glycated hemoglobin, apoB level, hypertension, number of diseased vessels, and prior revascularization (Fig. 4). Results of this multivariate analysis remained basically unchanged after excluding those patients with prior revascularization. In addition, a significant inverse correlation between mean lumen area at follow-up and glycated hemoglobin levels were observed: lumen area (mm^2) = 13.83–0.39 (glycated hemoglobin, %) + 3.8 intrastate variable.

DISCUSSION

As described by Glagov et al. (1), the coronary vessel develops an adaptive response (remodeling) to compensate for plaque accumulation. An increase in vessel dimen-

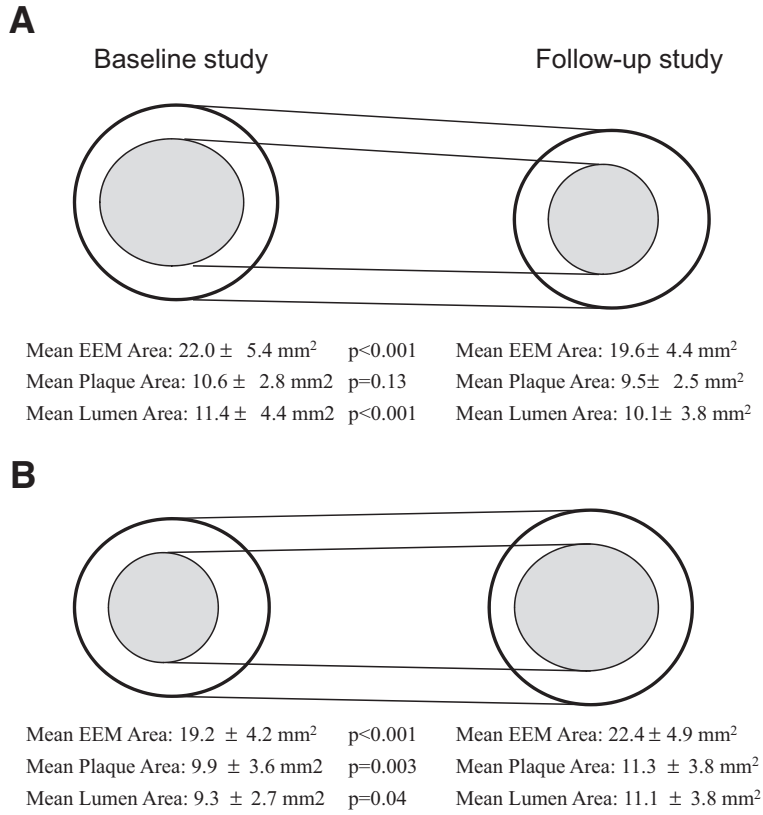

FIG. 3. Patterns of coronary remodeling. ***A*****: Vessel shrinkage (*n* = 88).** ***B*****: Vessel enlargement (*n* = 149).**

TABLE 2
Stratified univariable analysis

Clinical characteristics	Vessel shrinkage	Nonvessel shrinkage	*P* value
Age (years)	66.4 ± 10.7	67.5 ± 8.4	0.35
Male	70 (79.3)	119 (79.7)	0.91
Type 1 diabetic	27 (31)	24 (16)	0.009
BMI	29.1 ± 1.4	29.8 ± 3.9	0.16
Hyperlipidemia	61 (69.3)	98 (65.8)	0.57
Hypertension	67 (76.1)	92 (61.3)	0.02
Smoke	53 (60.2)	100 (67.1)	0.28
Peripheral vasculopathy	2 (2.3)	4 (2.7)	0.84
Previous myocardial infarction	40 (45.5)	56 (37.6)	0.23
Previous revascularization	25 (28.4)	11 (7.4)	<0.001
Unstable angina	50 (56.8)	109 (73.2)	0.01
Number of vessels disease	2.2 ± 0.8	1.8 ± 0.7	0.001
LVEF	65.1 ± 15.6	65.8 ± 17.2	0.73
Statin	67 (76.1)	137 (91.9)	0.001
ACE inhibitors	40 (45.5)	104 (69.8)	0.0003
Laboratory test			
Total cholesterol (mg/dl)	166.6 ± 40.1	169.2 ± 32.9	0.59
Triglycerides (mg/dl)	124.1 ± 46.6	145.8 ± 64.7	0.008
HDL cholesterol (mg/dl)	43.5 ± 13.9	41.6 ± 10.5	0.26
LDL cholesterol (mg/dl)	97.7 ± 39.2	97.9 ± 34.6	0.95
ApoA (mg/dl)	117.6 ± 30.2	119.9 ± 20.7	0.54
ApoB (mg/dl)	89.6 ± 27.5	97.9 ± 21.3	0.03
A1C (%)	7.7 ± 1.4	7.4 ± 1.3	0.06
hs–C-reactive protein	1.0 ± 1.9	1.0 ± 1.2	0.87

Data are means ± SD or *n* (%). LVEF, left ventricular ejection fraction. *All statistics were calculated with the GEE method stratifying by patients, vessel, and segment.

sions may be able to accommodate the plaque growth (vessel enlargement or positive remodeling). However, this compensatory vascular enlargement has a limit and lumen dimension may be preserved up to 40% of plaque accumulation. Beyond that limit, any further increase in plaque will decrease lumen dimensions. On the other hand, some plaques lack this adaptive behavior, and vessel shrinkage (or negative remodeling) appears as the main contributor to lumen reduction. Previous studies have shown that type 2 diabetic patients develop more frequently negative remodeling than the general population (9,10); however, the factors associated with this phenomenon were unknown.

This is the first report on the natural history of coronary wall structures from diabetic patients by the use of serial IVUS evaluation. This study demonstrates a bidirectional pattern of vascular remodeling in diabetic patients over time. An overall vascular shrinkage (i.e., EEM, plaque, and lumen reductions) was shown in more than one-third of the analyzed plaques. On the other side of the spectrum is the pattern of overall vascular enlargement (i.e., EEM, plaque, and lumen increases) observed in the remaining two-thirds of plaques. Thus, according to our findings, vessel shrinkage appeared as the major determinant of lumen reduction during follow-up in nonsignificant stenotic plaques.

TABLE 3
Relationship between baseline type of plaque and the development of negative remodeling at follow-up

	Vessel shrinkage	Nonvessel shrinkage	*P* value
Soft	10 (11.5)	21 (14.0)	>0.05
Mixed	36 (41.4)	57 (38.0)	>0.05
Fibrose	15 (17.2)	24 (16.0)	>0.05
Calcified	26 (29.9)	48 (32.0)	>0.05

Data are *n* (%).

Independent factors associated with vessel shrinkage included insulin requirements, the association with other cardiac risk factors, advanced coronary artery disease (CAD) (i.e., patients with previous revascularization or with multivessel disease), and the metabolic control.

In our study, only mild, and thus not previously revascularized, stenoses were studied. Of interest, we found a strong association between vessel shrinkage and previous revascularization. This revascularization was mainly performed by angioplasty (seven of eight) in different segments or arteries remote from the studied segment. The remaining patient underwent prior coronary artery bypass in another artery. Thus, all analyzed segments were not affected by competitive flow or even turbulences induced by the presence of surgical anastomoses proximal to any studied segment. Both vessel shrinkage and prior revascularization may represent markers of the duration of the atherosclerotic disease. Vessel shrinkage may appear as a late event in the development of atherosclerosis as a consequence of the maturation of atherosclerotic plaque that consists of a reduction in the lipid content and an increase in fibrosis and calcification (2).

At the time of the diagnosis of CAD, the presence of multivessel disease is a sign of an accelerated atherosclerosis in type 2 diabetic patients. In our study, we have found a relationship between multivessel disease and negative remodeling that may have resulted from a common underlying mechanism: endothelial dysfunction. It is well-documented that diabetic patients have an impairment of endothelial-dependent relaxation (21,22), and this

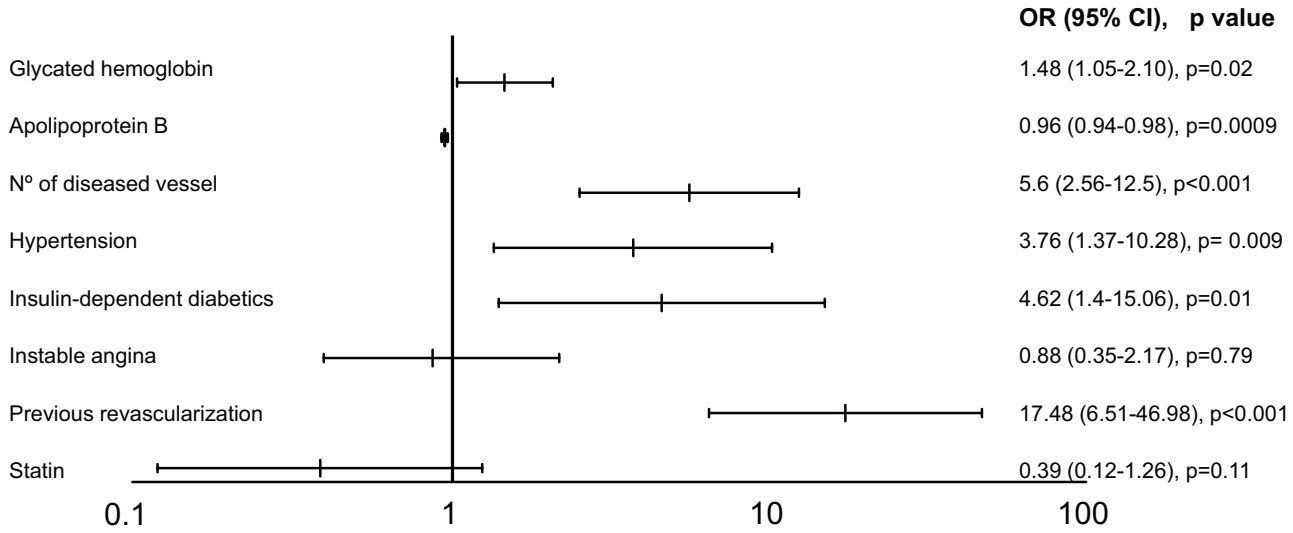

FIG. 4. Independent predictors of vessel shrinkage. Data in the *y*-axis are presented on a logarithmic scale. *All statistics were calculated with the GEE method stratifying by patients, vessel, and segment.

is associated with the extent of CAD (23). Furthermore, the dysfunctional endothelium can only offer a poor vasomotor response to a local increase in the shear stress caused by plaque deposition (24). As a result, the diseased coronary segment may lose the capacity to carry out an adaptive vascular remodeling (i.e., vessel enlargement) and to delay the atherosclerotic stenosis formation.

The use of insulin in type 2 diabetic patients is a marker for disease duration, as well as the presence of multivessel disease, and previous revascularization. The need for insulin treatment increases risk of cardiovascular events in the diabetic population (25). In a previous cross-sectional study (3), a smaller vessel size, less atherosclerotic plaque burden, and less positive remodeling were evident in type 1 diabetic patients compared with type 2 diabetic patients. Likewise, the presence of hypertension was also associated with vascular shrinkage. The association between negative remodeling and hypertension has been described previously in the general population (5). Hypertension substantially increases the risk of both macrovascular and microvascular complications due to a synergistic effect in the development of cardiovascular disease (26). Because hypertension is an extremely common comorbid condition in diabetes, there is a major need for careful control of other coronary risk factors in this high-risk population.

Another important factor associated with atherosclerosis progression is the metabolic control. Hyperglycemia is one of the main mechanisms involved in the development of complications in diabetic patients. Previous studies (27–29) demonstrated the association of high glycated hemoglobin levels with the severity of the CAD and with poorer outcome after percutaneous coronary angioplasty. Recently, Anand et al. (30) showed that suboptimal glycemic control is a risk factor for coronary artery calcification progression. In this regard, this is the first study that demonstrates an association between glycated hemoglobin levels and vessel shrinkage over time. One mechanism that may be proposed is the formation of advanced glycation end products (AGEs) (31,32) during hyperglycemia. Furthermore, AGEs may be involved in blood vessel interaction and triggering an inflammatory-proliferative process that may contribute to accelerating atherosclerosis. Lipid metabolism is commonly impaired in diabetic patients. LDL levels had been the traditional lipid measurement in the prediction of cardiac events. Other parameters, such as apoB levels, which reflect the concentration of proatherogenic lipoproteins (VLDL and LDL), may be used as well. Whether apoB is more predictive of the development of CAD than LDL levels is controversial. Ingelsson et al. (33) evidenced that apoB levels and other traditional lipid measurement were comparable in the prediction of cardiac events. In our study, the apoB serum levels were negatively associated with vessel shrinkage. Although no specific studies addressed the influence of apoB levels on vascular changes, we may compare our results with those reported with LDL levels. In this regard, previous studies performed in the general population have demonstrated an association between a decrease in LDL levels (after statin treatment) and a decrease in the plaque and vessel volume during follow-up (34,35). In the present study, the type of plaque was not associated with the development of vessel shrinkage. These results are in agreement with previous static IVUS studies performed in diabetic patients (10,11). Conversely, other investigations (2,7) showed inconsistent evidence, which revealed the relationship between plaque characterization and vessel remodeling. However, these studies only investigated nondiabetic patients. Thus, no extrapolation can be performed from that study to the diabetic population. The relationship between metabolic disorder and atherosclerosis progression observed in our study stresses the importance of accurate glycemic, lipid, and blood pressure control in diabetic patients to prevent them from accelerating CAD.

Study limitations. This is an observational study with two main limitations: the relatively small number of patients and the selection bias inherent to IVUS studies. In this regard, there are two important sources of bias. First, the arteries or lesions unsuitable for IVUS (very small vessel or heavily calcified lesions) were excluded. For this reason, the results cannot be extrapolated to those kinds of lesions and arteries. Second, we have studied only mild lesions that are more prone to progress or regress. Therefore, our findings cannot be applicable to more severely stenotic coronary segments that might require immediate revascularization. In our study, measurement of EEM area of plaques containing deposits of calcium was obtained by interpolating the adventitial border, and thus, some inac-

curacy of this measurement cannot be completely ruled out.

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No potential conflicts of interest relevant to this article were reported.

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