

# Patients with diabetes differ in atherosclerotic plaque characteristics and have worse clinical outcome after iliofemoral endarterectomy compared with patients without diabetes

Steven T. W. van Haelst, MD,<sup>a</sup> Saskia Haitjema, MD,<sup>b</sup> Jean-Paul P. M. de Vries, MD, PhD,<sup>c</sup> Frans L. Moll, MD, PhD,<sup>a</sup> Gerard Pasterkamp, MD, PhD,<sup>b,d</sup> Hester M. den Ruijter, PhD,<sup>b</sup> and Gert J. de Borst, MD, PhD,<sup>a</sup> *Utrecht and Nieuwegein, The Netherlands*

## ABSTRACT

**Objective:** Diabetes mellitus (DM) is associated with peripheral arterial disease (PAD) and leads to worse clinical outcome compared with patients without DM. The objective of this study was to determine the impact of DM on iliofemoral artery plaque characteristics and to examine secondary clinical outcomes in patients with DM and PAD undergoing surgical revascularization.

**Methods:** We analyzed 198 patients with and 453 patients without DM from the Athero-Express biobank, a prospective ongoing biobank study, who underwent endarterectomy of the femoral or iliac artery between 2002 and 2013. Seven histologic plaque characteristics (calcification, collagen, lipid core, intraplaque hemorrhage, macrophages, microvessels, and smooth muscle cells) and secondary clinical outcome were compared. Composite outcome consisted of any of the following secondary manifestations of cardiovascular disease: stroke, myocardial infarction, cardiovascular death, or peripheral intervention. In addition, target vessel revascularization (TVR) was examined. The follow-up period was standardized at 3 years after the procedure.

**Results:** Patients with DM were more likely to have calcified plaques compared with patients without DM (odds ratio, 2.11; 95% confidence interval, 1.43-3.12;  $P < .01$ ). No other plaque characteristic differed significantly between the two groups. In total, 112 (57.1%) patients with DM and 198 (45.1%) patients without DM reached a composite end point during follow-up, of whom 21 (10.7%) and 27 (6.2%) died of cardiovascular causes, respectively. DM was an independent predictor of composite cardiovascular events (hazard ratio, 1.36; 95% confidence interval, 1.020-1.801;  $P = .01$ ) during follow-up. No difference in the incidence of TVR was observed between patients with and without DM (31.5% and 30%, respectively; difference in survival time,  $P = .86$ ) or in longer duration of DM with composite event-free survival (difference in survival time,  $P = .57$ ).

**Conclusions:** Patients with DM who undergo surgical revascularization for PAD with the use of thromboendarterectomy or remote endarterectomy have a more calcified atherosclerotic plaque and an increased incidence in composite cardiovascular events but no increase in TVR. (J Vasc Surg 2016;■:1-8.)

The prevalence of diabetes mellitus (DM) is increasing across the world.<sup>1</sup> DM is a known risk factor for atherosclerosis and thus for peripheral arterial disease (PAD).<sup>2</sup>

The ways in which DM influences vascular disease are multifold. DM is associated with increased inflammatory activity and endothelial cell activation, causing constrictive remodeling.<sup>3-5</sup> Moreover, DM causes hypercoagulability, which plays a role in plaque growth and plaque rupture and increases the risk of sudden intravascular occlusion or thrombosis.<sup>6</sup> Patients with DM and PAD have a more than twofold higher risk of cardiovascular morbidity and mortality compared with DM patients without PAD.<sup>7,8</sup> In addition, the duration of DM is associated with higher prevalence of PAD.<sup>9</sup> As the prevalence of DM is expanding dramatically and the disease occurs at an increasingly younger age,<sup>10</sup> the number of patients with DM affected by PAD in later life will rise, consequently increasing the financial burden on health care systems worldwide.<sup>3,11</sup>

Plaque characteristics of patients with DM have previously been histologically examined, predominantly in carotid and coronary arteries, but conflicting results have been obtained, presumably because of the small

From the Department of Vascular Surgery,<sup>a</sup> Laboratory of Experimental Cardiology,<sup>b</sup> and Laboratory of Clinical Chemistry and Haematology,<sup>d</sup> University Medical Center Utrecht, Utrecht; and the Department of Vascular Surgery, St. Antonius Hospital, Nieuwegein.<sup>c</sup>

S.H. is supported by the FP7 EU project CVgenes@target (HEALTH-F2-2013-601456).

Author conflict of interest: none.

Additional material for this article may be found online at [www.jvascsurg.org](http://www.jvascsurg.org).

Correspondence: Gert Jan de Borst, MD, PhD, Department of Vascular Surgery, Heidelberglaan 100, Utrecht 3584 CX, The Netherlands (e-mail: [g.j.deborst-2@umcutrecht.nl](mailto:g.j.deborst-2@umcutrecht.nl)).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

Copyright © 2016 by the Society for Vascular Surgery. Published by Elsevier Inc.

<http://dx.doi.org/10.1016/j.jvs.2016.06.110>

numbers of patients.<sup>3</sup> A large study performed in carotid patients suffering from DM showed no difference in plaque characterization between patients with and without DM.<sup>12</sup> Imaging of plaques in PAD patients revealed that DM-induced atherosclerosis is mainly located in below-the-knee arteries instead of the iliofemoral segments.<sup>13,14</sup> Furthermore, it is associated with calcification of the medial layer instead of the intimal layer of the arteries, known as Mönckeberg sclerosis.<sup>15,16</sup> Histologic characteristics of peripheral plaques have, to our knowledge, never been investigated in a large cohort of PAD patients with DM, a prevalent comorbidity. Moreover, it is unclear whether DM is an independent and causative predictor for secondary cardiovascular disease or decreased patency rates in PAD patients undergoing surgical revascularization.<sup>5,17-20</sup>

For this study, we analyzed a large cohort of patients undergoing plaque removal from the iliofemoral arteries to determine the impact of DM on plaque characteristics. In addition, the clinical outcome in patients with DM and PAD after endarterectomy was assessed. We hypothesized that plaque composition of iliofemoral arteries in patients with DM would be different compared with patients without DM and that patients with DM would have worse clinical outcomes and an increased need for target vessel revascularization (TVR).

## METHODS

**Patient population.** The Athero-Express biobank is a prospective ongoing biobank study that includes blood and plaque specimens of patients undergoing carotid or iliofemoral endarterectomy surgery in two large tertiary referral hospitals in the Netherlands: the St. Antonius Hospital in Nieuwegein and the University Medical Center in Utrecht.<sup>21</sup> Plaque removal is conducted according to local and international guidelines, by either direct thromboendarterectomy or remote endarterectomy.<sup>22</sup> The use of a patch was at the clinician's discretion. Clinical data were prospectively collected from patient files and standardized questionnaires.

For this study, the first entry of iliac and femoral endarterectomy for each unique patient was included, without any exclusion criteria. This enabled us to investigate the effect of one of the most prevalent comorbidities in PAD on plaque histology and to compare this with existing literature on other plaque domains, such as carotid and coronary plaques.

Presence of DM was defined as presence of one of the following: (1) DM in medical history extracted from the patient file, (2) use of either insulin or oral glucose inhibitors extracted from the patient file, or (3) self-reported DM in the patient questionnaire. Duration of the disease was extracted from the patient questionnaire. A restenotic artery at baseline was defined as surgery on an artery already treated in the past, either by percutaneous intervention or by surgery.

Follow-up data during a 3-year period were obtained through questionnaires sent to patients. Secondary cardiovascular events were validated using health records kept by general practitioners. Composite secondary cardiovascular events were defined as myocardial infarction (MI), stroke, cardiovascular death, or peripheral intervention. Cardiovascular death was defined as one of the following: fatal MI, fatal stroke (either bleeding or ischemic), fatal ruptured abdominal aneurysm, fatal heart failure, or sudden death. Stroke was defined as neurologic symptoms lasting >24 hours and diagnosed by a neurologist as a stroke. A history of coronary artery disease was defined as either one of the following: MI or percutaneous coronary intervention or coronary artery bypass graft surgery. Peripheral interventions consisted of either surgery or percutaneous events, including thrombolysis, in any artery other than the coronary arteries or the aorta. Patients could have had more than one event, but only the first occurrence of any of the secondary end points was used for the survival analyses on composite end points. To determine a measure of patency, TVR was defined during a 3-year follow-up as peripheral reintervention on the same operation side and artery as in the entry surgery. If patients suffered from more than one TVR, the first was used as an end point for the survival analysis of TVR-free survival.

The study was approved by the respective medical ethics boards of both hospitals. The study was conducted in accordance with the declaration of Helsinki. All patients provided written informed consent before participation in this study.

**Sample collection.** A detailed description of the sample collection within the Athero-Express biobank can be found elsewhere.<sup>21</sup> In short, blood is collected preoperatively from the radial artery and subsequently stored at  $-80^{\circ}$ . The plaque is processed immediately after surgical removal. The culprit lesion is identified, stored in 4% formaldehyde, decalcified (softening the calcification in the plaque for handling purposes without fully dissolving it), and embedded in paraffin for histologic analysis. The rest of the plaque is cut into pieces of 5 mm and stored at  $-80^{\circ}$ .

**Histologic assessment.** The transverse cross sections of plaque are used for histologic assessment.<sup>23</sup> Plaque specimens were stained for macrophages (CD68), smooth muscle cells ( $\alpha$ -actin), collagen (picosirius red), extent of calcification (hematoxylin-eosin), and microvessels (CD34). The presence of plaque thrombosis was determined using a combination of luminal thrombi, intraplaque hemorrhage, hematoxylin-eosin staining, and presence of fibrin by Mallory phosphotungstic acid-hematoxylin staining. The presence of luminal thrombosis, intraplaque hemorrhage, or both was considered positive plaque thrombosis. Computerized analyses were used to quantify macrophages and smooth muscle cells

Download English Version:

<https://daneshyari.com/en/article/5617407>

Download Persian Version:

<https://daneshyari.com/article/5617407>

[Daneshyari.com](https://daneshyari.com)