Lower atherosclerotic burden in familial abdominal aortic aneurysm

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Objective: **Despite the apparent familial tendency toward abdominal aortic aneurysm (AAA) formation, the genetic causes and underlying molecular mechanisms are still undefined. In this study, we investigated the association between familial AAA (fAAA) and atherosclerosis.**

Methods: **Data were collected from a prospective database including AAA patients between 2004 and 2012 in the Erasmus University Medical Center, Rotterdam, The Netherlands. Family history was obtained by written questionnaire (93.1% response rate). Patients were classified as fAAA when at least one affected first-degree relative with an aortic aneurysm was reported. Patients without an affected first-degree relative were classified as sporadic AAA (spAAA). A standardized ultrasound measurement of the common carotid intima-media thickness (CIMT), a marker for generalized atherosclerosis, was routinely performed and patients' clinical characteristics (demographics, aneurysm characteristics, cardiovascular comorbidities and risk factors, and medication use) were recorded. Multivariable linear regression analyses were used to assess the mean adjusted difference in CIMT and multivariable logistic regression analysis was used to calculate associations of increased CIMT and clinical characteristics between fAAA and spAAA.**

Results: **A total of 461 AAA patients (85% men, mean age, 70 years) were included in the study; 103 patients (22.3%) were classified as fAAA and 358 patients (77.7%) as spAAA. The mean (standard deviation) CIMT in patients with fAAA was 0.89 (0.24) mm and 1.00 (0.29) mm in patients with spAAA ($P = .001$). Adjustment for clinical characteristics showed a mean difference in CIMT of 0.09 mm (95% confidence interval, 0.02-0.15; $P = .011$) between both groups. Increased CIMT, smoking, hypertension, and diabetes mellitus were all less associated with fAAA compared with spAAA.**

Conclusions: **The current study shows a lower atherosclerotic burden, as reflected by a lower CIMT, in patients with fAAA compared with patients with spAAA, independent of common atherosclerotic risk factors. These results support the hypothesis that although atherosclerosis is a common underlying feature in patients with aneurysms, atherosclerosis is not the primary driving factor in the development of fAAA (J Vasc Surg 2014;59:589-93.)**

Abdominal aortic aneurysm (AAA) is characterized by infiltration of inflammatory cells, loss of vascular smooth muscle cells, and extracellular matrix degeneration in the aortic wall.[1] While the causality has been challenged, AAA is associated with atherosclerosis.[2,3] Approximately 20% of patients with an AAA have a first-degree relative diagnosed with an aortic aneurysm.[4] Despite the apparent familial tendency toward AAA formation, the genetic causes and underlying molecular mechanisms are still undefined.[5]

In this study, we investigated the association between familial AAA (fAAA) and atherosclerosis. To this end, we assessed the common carotid intima-media thickness (CIMT) in patients with AAA using B-mode ultrasonography. Thickening of the intimal and medial layers of the common carotid artery is an early expression of generalized atherosclerosis.[6,7] We evaluated the difference in CIMT between patients with a genetic predisposition to AAA (ie, patients with fAAA) and patients with sporadic AAA (spAAA), correcting for clinical characteristics. Furthermore, we investigated whether CIMT could serve as a clinical marker to identify patients with fAAA in our population.

METHODS

Study population. The study population consisted of patients with an AAA, defined as an external maximum transverse abdominal aortic diameter ≥30 mm,[8] who underwent either elective open or endovascular repair or remained under surveillance between 2004 and 2012 at the Erasmus University Medical Center in Rotterdam, The Netherlands. The database included a total of 780 patients with AAA. Between 2009 and 2012, all AAA patients were

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contacted when visiting the outpatient clinic or by mail and asked to complete a semistructured questionnaire, to collect personal data and family histories, and return the questionnaire by mail. Patients who did not respond after one reminder, were contacted and interviewed by telephone (K.vdL.). In families with multiple AAA patients, only one index patient (ie, first family member diagnosed with AAA) was included in the study. Patients diagnosed with a known genetic aortic aneurysm syndrome (eg, Marfan, Loeys-Dietz, or vascular Ehlers-Danlos syndrome) were excluded. The study complied with the declaration of Helsinki and was approved by the Institutional Review Board.

Questionnaire and classification of fAAA. The questionnaire requested information on demographics and the medical history of the index patient. Furthermore, structured questions were included on the occurrence of aortic aneurysms and cardiovascular disease for all known relatives of the index patient. Patients were classified as fAAA when at least one first-degree relative (parents, siblings, or children) was reported to have an aortic aneurysm. Patients who did not report a first-degree relative affected with AAA were classified as spAAA. Patients reporting only second- or third-degree relatives were also classified as spAAA because the reporting of medical information of second- or third-degree relatives was considered less reliable.

Clinical characteristics. Patients were prospectively enrolled and the following characteristics were recorded for all patients as part of routine clinical practice, including sex, age, body mass index, as well as aneurysm characteristics and the cardiovascular comorbidities and risk factors. Aneurysm characteristics included maximal aneurysm diameter and rupture rate. Cardiovascular comorbidities included congestive heart failure, ischemic heart disease (history of myocardial infarction, angina pectoris, coronary revascularization or pathologic Q-waves on the electrocardiogram), and cerebrovascular disease (history of ischemic/hemorrhagic stroke or transient ischemic attack). Cardiovascular risk factors included kidney disease (serum creatinine $\geq$2.0 mg/dL), diabetes mellitus (fasting plasma glucose $\geq$7.0 mmol/L, non-fasting glucose $\geq$11.1 mmol/L or use of antidiabetic medication), hypertension (blood pressure $\geq$140/90 mm Hg in nondiabetics, $\geq$130/80 mm Hg in diabetics or use of antihypertensive medication), and hypercholesterolemia (low-density lipoprotein cholesterol $\geq$3.5 mmol/L or use of lipid lowering medication). Smoking status was obtained and included current smoking and ever smoking (ie, patients who are currently smoking OR patients with a history of smoking). Prescription medication was recorded, including statins, beta-blockers, renin-angiotensin system inhibitors, diuretics, and antiplatelet drugs. Serum concentrations of the inflammatory biomarker high-sensitivity C-reactive protein were measured using immunochemistry (Beckman Coulter, Woerden, The Netherlands).

Atherosclerotic marker. The severity of atherosclerotic disease was assessed by measurements of the CIMT using B-mode ultrasonography according to the guidelines from the "Mannheim Carotid Intima-Media Thickness Consensus."[9,10] Patients were examined in the supine position with the head turned 45° away from the side being scanned and the neck extended slightly. A longitudinal view of the right and left common carotid artery was obtained by a portable Sonosite Titan Ultrasound System (Sonosite Inc, Bothell, Wash) with a L38-10-5 MHz linear ultrasound transducer or a portable Vivid-I Ultrasound System (Vivid-I; GE Healthcare, Solingen, Germany) with an 8L-RS transducer. Several measurements were made along a minimum of 10 mm at the posterior wall of the right and left common carotid artery. The intima-media thickness was calculated online by built-in software of the ultrasound system from the interface between lumen and intima to the interface between media and adventitia. The maximum CIMT value of both common carotid arteries was used for the analysis. Atherosclerotic plaques, defined as focal structures of at least 0.5 mm encroaching into the arterial lumen, were excluded from analysis.[10] The sonographers who performed the measurements were blinded for the clinical characteristics of the patients and had an interobserver correlation of 96.2%.[9]

Statistical analysis. Dichotomous data are presented as numbers and percentages. Continuous variables are presented as mean (standard deviation) or median (interquartile range) when not normally distributed. Categorical data were analyzed with chi-square test, and continuous variables with analysis of variance or Kruskal-Wallis test, as appropriate. Multivariable linear regression analysis was performed to assess the mean adjusted difference in CIMT between fAAA and spAAA. The CIMT was used as dependent variable and we adjusted for age $\leq$65 years at diagnosis, sex, body mass index, congestive heart failure, ischemic heart disease, cerebrovascular disease, kidney disease, diabetes mellitus, hypercholesterolemia, hypertension, ever smoking, and high-sensitivity C-reactive protein. Additional analysis was performed using previous adjustments plus medication. Covariates were chosen on the basis of biological plausibility. Multivariable binary logistic regression analysis was used to calculate the associations of increased CIMT (per mm) and clinical characteristics between fAAA and spAAA. Covariates in the model were the same clinical characteristics as used in the multivariable linear regression analysis. To assess any selection bias, baseline characteristics for patients with and without (ie, those excluded from the study) CIMT measurement were analyzed with χ^2 tests. For all tests, a P value of $< .05$ (two-sided) was considered significant. All analyses were performed using IBM SPSS Statistics v. 20.0 (SPSS Inc, Chicago, Ill).

RESULTS

The questionnaire was presented to 610 AAA patients, and 482 patients (79.0%) responded after one reminder. Of the remaining 128 patients who did not return the questionnaire, 10 patients were deceased, 108 were interviewed by telephone, and 10 could not be reached. Twenty-two AAA patients were related to other AAA patients participating in the study and were excluded. In this way, family