Skin accumulation of advanced glycation end products is increased in patients with an abdominal aortic aneurysm

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ABSTRACT

Objective: Advanced glycation end products (AGEs) are implicated in the pathogenesis of cardiovascular disease. Accumulation of AGEs is driven by oxidative or glycemic stress and can be assessed by skin autofluorescence (SAF). SAF is increased in patients with peripheral artery disease (PAD) and independently associated with mortality and major adverse cardiovascular events in these patients. PAD and abdominal aortic aneurysm (AAA) share several risk factors. Inflammation is an important process in AAA formation and increases levels of oxidative stress. We therefore hypothesized that SAF would be increased in AAA patients compared with controls.

Methods: A case-control study was performed in 248 AAA patients and 124 controls without AAA or PAD matched for age and presence of diabetes mellitus. SAF was noninvasively assessed with the AGE Reader (Diagnoptics Technologies BV, Groningen, The Netherlands).

Results: SAF was higher in AAA patients than in controls: 2.89 ± 0.63 vs 2.68 ± 0.63 arbitrary units ($P = .003$). PAD comorbidity was associated with increased SAF within the AAA patient group ($P = .01$). After correction for known factors influencing SAF (age, current smoking, hypertension, and estimated glomerular filtration rate), PAD comorbidity remained an independent determinant of SAF. Logistic regression analysis of the total cohort showed an unadjusted odds ratio (OR) of 1.74 (95% confidence interval [CI], 1.20-2.51) for the presence of AAA with each unit increase of SAF and an adjusted OR of 1.78 (95% CI, 1.22-2.60) after correction for cardiovascular comorbidity (cerebrovascular disease and coronary artery disease). After additional correction for sex, current smoking, hypertension, and use of lipid-lowering drugs, this significance was lost (adjusted OR, 1.53; 95% CI, 0.94-2.48).

Conclusions: Skin accumulation of AGEs, measured by SAF, is increased in patients with AAA compared with controls without AAA or PAD, independent of the presence of coronary artery disease and cerebrovascular disease. In AAA patients, SAF is closely associated with the presence of PAD and cardiovascular risk factors. (J Vasc Surg 2017;■:1-8.)

An abdominal aortic aneurysm (AAA) is characterized by enlargement of the aorta as a consequence of pathophysiological changes in the aortic vascular wall, including inflammation, smooth muscle cell apoptosis, and proteolysis of elastin and collagen in the tunica media.[1] Most AAAs are discovered as an incidental finding because this disease is asymptomatic in most patients.[2] Rupture of the AAA is generally an emergency situation with an estimated mortality rate of 80%.[3]

Advanced glycation end products (AGEs) are formed by nonenzymatic reactions on reducing sugars and proteins and have two potentially harmful effects.[4] First, formation of cross-links contributes to stiffening of the myocardium and arteries.[5] Second, interaction with the receptor for AGEs induces inflammatory responses through activation of nuclear factor-κB and consecutive release of proinflammatory cytokines.[4]

Assessment of skin AGEs can be performed with a noninvasive technique called skin autofluorescence (SAF).[6] The estimated turnover time of skin collagen is 15 years; thus, skin AGEs and SAF represent a long-term metabolic memory.[7] In addition, SAF is positively related to AGE levels in cardiac tissue and venous bypass graft material, both vascular tissues with also a typical slow turnover.[8,9]

Although the formation and accumulation of AGEs in long-lived tissues occurs physiologically with aging, this formation is enhanced in conditions associated with hyperglycemia or oxidative stress such as diabetes mellitus (DM), autoimmune disease, renal insufficiency, and atherosclerosis.[4] As a result, SAF is increased in patients with these conditions compared with controls,[10-13] and increased SAF is also associated with major adverse

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cardiovascular events in patients with DM, myocardial infarction, and peripheral artery disease (PAD).[14-17]

PAD and AAA disease share several risk factors and are frequently found in the same patient. Inflammation is an important pathway of AAA formation, mediating elastin and collagen degradation by proteases derived from inflammatory cells.[18] This led us to hypothesize that SAF, as a measure of skin AGEs, would be increased in patients with an AAA; therefore, the aim of this study was to compare SAF levels in AAA patients and controls. We also investigated whether SAF is associated with the presence of AAA after correction for cardiovascular risk factors, such as smoking, and cardiovascular comorbidity, expressed by a history of cerebrovascular disease (CVD) or coronary artery disease (CAD).

METHODS

Study population. We performed a case-control study. AAA patients were recruited from the vascular surgery outpatient clinic at the University Medical Center Groningen (UMCG), The Netherlands, between 2007 and 2011. Patients at least 18 years of age with a confirmed AAA were eligible to participate. AAA was ascertained by evidence of an enlarged diameter of the aorta of ≥30 mm on ultrasound imaging, magnetic resonance angiography, or computed tomography angiography. In case of an emergency or elective repair without available medical imaging reports, surgical reports or referral letters were used to confirm the diagnosis.

AAA patients and controls were matched 2:1 by age and presence of DM (Fig 1). Controls were selected from earlier studies. Diabetic controls were selected from a cohort (n = 973) from the diabetes outpatient clinic, Zwolle, The Netherlands.[11] The nondiabetic control group consisted of patients admitted to the UMCG for surgical interventions (n = 231) unrelated to cardiovascular disease and of patients who visited the vascular surgery outpatient clinic in the UMCG (n = 121), mostly because of varicose veins or carotid artery stenosis, who had no history or symptoms of AAA or PAD.[12,13]

Exclusion criteria for AAA patients and controls were sepsis, recent myocardial infarction or stroke, defined as an event ≤3 months before recruitment, renal replacement therapy or end-stage renal disease (estimated glomerular filtration rate [eGFR] <15 mL/min/1.73m^2), solid organ transplantation, or active cancer. AAA patients with a mycotic or inflammatory aneurysm or a history of connective tissue disease were excluded. Control patients with a history or symptoms of AAA or PAD were also excluded.

All participating patients gave informed consent. The study was approved by the local Institutional Review Board and complied with the principles of the Declaration of Helsinki.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center prospective case-controlled study
- **Take Home Message:** Skin accumulation of advanced glycation end products as measured by skin autofluorescence was increased in 248 patients with abdominal aortic aneurysm compared with 124 matched controls.
- **Recommendation:** This study suggests that using skin autofluorescence to measure advanced glycation end products may be a useful in the detection of patients with abdominal aortic aneurysm.

Data collection. Traditional cardiovascular risk factors were prospectively assessed, including current smoking status, body mass index, presence of DM, hypertension, eGFR, and use of lipid-lowering, glucose-lowering, or anticoagulant drugs. eGFR was calculated from the serum creatinine level using the Modification of Diet in Renal Disease formula.[19] Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or the use of blood pressure-lowering drugs. Lipid-lowering therapy was defined as the use of statins, ezetimibe, or fibrates. For glucose-lowering therapy, the use of metformin, dipeptidyl peptidase 4 inhibitors, repaglinide, sulfonylurea derivatives, pioglitazone, glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter 2 inhibitors, and insulin was assessed. Anticoagulant therapy was defined as the use of anticoagulant or antiplatelet therapy.

History of cardiovascular comorbidity was retrieved from medical records and divided into CAD, CVD, and PAD. CAD was defined as a history of angina pectoris, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft. CVD was defined as a history of stroke, transient ischemic attack, carotid endarterectomy, or carotid stenting. PAD was defined as a resting ankle-brachial index ≤0.90 combined with confirmation of obstructive disease on computed tomography angiography, magnetic resonance angiography, catheter angiography, or duplex ultrasound imaging.

For AAA patients, data on the diameter, surgical repair, and rupture of the aneurysm were obtained. The presence of aneurysms in other locations in addition to the abdominal aorta was assessed. Rupture of the AAA was confirmed using ultrasound imaging or during surgical repair of the aneurysm.

SAF assessment. SAF as a noninvasive measure of skin AGEs was assessed using the AGE Reader (Diagnoptics Technologies BV, Groningen, the Netherlands). This device uses ultraviolet A light to measure the dermal content of certain AGEs using their fluorescent properties.