Circulating biomarkers are not associated with endoleaks after endovascular repair of abdominal aortic aneurysms

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ABSTRACT

Objective: Endoleak is a common complication of endovascular aneurysm repair (EVAR) for abdominal aortic aneurysm (AAA) but can be detected only through prolonged follow-up with repeated aortic imaging. This study examined the potential for circulating matrix metalloproteinase 9 (MMP9), osteoprotegerin (OPG), D-dimer, homocysteine (HCY), and C-reactive protein (CRP) to act as diagnostic markers for endoleak in AAA patients undergoing elective EVAR.

Methods: Linear mixed-effects models were constructed to assess differences in AAA diameter after EVAR between groups of patients who did and did not develop endoleak during follow-up, adjusting for potential confounders. Circulating MMP9, OPG, D-dimer, HCY, and CRP concentrations were measured in preoperative and postoperative plasma samples. The association of these markers with endoleak diagnosis was assessed using linear mixed effects adjusted as before. The potential for each marker to diagnose endoleak was assessed using receiver operating characteristic curves.

Results: Seventy-five patients were included in the study, 24 of whom developed an endoleak during follow-up. Patients with an endoleak had significantly larger AAA sac diameters than those who did not have an endoleak. None of the assessed markers showed a significant association with endoleak. This was confirmed through receiver operating characteristic curve analyses indicating poor diagnostic ability for all markers.

Conclusions: Circulating concentrations of MMP9, OPG, D-dimer, HCY, and CRP were not associated with endoleak in patients undergoing EVAR in this study. (J Vasc Surg 2018;67:770-7.)

Abdominal aortic aneurysm (AAA) affects ~2% of men older than 65 years and is a leading cause of mortality in the elderly.[1-5] The main current treatment for AAA is endovascular aneurysm repair (EVAR). This involves the endovascular placement of stent grafts to isolate the AAA wall from the main aortic blood flow.[6] Despite low perioperative morbidity and mortality, the durability of EVAR is of concern as a high proportion of patients have continued perfusion of the AAA sac or endoleak.[7-9] Endoleak is the most common complication of EVAR and may be due to incomplete seal of the proximal or distal end of the graft (type I endoleak), reverse flow through collateral arteries (type II endoleak), or stent defects (types III-V).[10,11] Patients undergoing EVAR require long-term monitoring involving computed tomography or ultrasound to detect endoleak.[12] This has several disadvantages, including repeated exposure of the patient to ionizing radiation and the requirement for specialist infrastructure and trained staff, which has a negative impact on the cost-effectiveness of EVAR.[10]

It has been suggested that the current disadvantages associated with imaging-based monitoring may be overcome through the discovery of blood-borne markers to diagnose endoleak, which may ultimately reduce the need for post-EVAR imaging.[10] This is based on the theory that successful EVAR will place a physical barrier between the aneurysmal wall and the bloodstream, thereby reducing the circulating concentrations of AAA-secreted proteins. Continued perfusion of the AAA sac due to endoleak would therefore be reflected by persistent elevations or spikes in the circulating concentration of AAA biomarkers during follow-up. Aortic inflammation, excessive extracellular matrix remodeling, and thrombosis are implicated in AAA pathogenesis, suggesting that circulating markers of these processes may be useful in diagnosing endoleak.[4,13-15] To date, relatively few studies have specifically investigated the association of blood-borne markers with the presence of endoleak, and the potential value of a blood marker-based approach for EVAR surveillance remains unclear.

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The aim of this study was therefore to assess the association of circulating concentrations of three putative biomarkers previously associated with AAA presence (matrix metalloproteinase 9 [MMP9], osteoprotegerin [OPG], and D-dimer) and two routinely assessed blood parameters (homocysteine [HCY] and C-reactive protein [CRP]) with endoleak in a cohort of patients undergoing elective EVAR.

ARTICLE HIGHLIGHTS

- **Type of Research:** Prospective review of a subset of a national registry
- **Take Home Message:** In 75 patients who underwent elective endovascular aortic aneurysm repair, circulating biomarkers, including matrix metalloproteinase 9, osteoprotegerin, D-dimer, homocysteine, and C-reactive protein, were not associated with the presence of an endoleak that developed in 24 patients during follow-up.
- **Recommendation:** This study suggests that the measurements of circulating biomarkers cannot identify patients with endoleaks after endovascular aneurysm repair and have no role in postoperative surveillance.

METHODS

Patient recruitment and follow-up. This study analyzed a subset of patients recruited to the Australian EVAR outcomes modeling trial that has been described in detail in previous publications.[16-18] For the purposes of this study, patients undergoing EVAR were observed prospectively to monitor outcome. To be eligible for inclusion in the study, patients were required to have undergone elective EVAR to repair an AAA, to have had at least one infrarenal aortic computed tomography angiography examination before and after EVAR, and to have provided a fasting blood sample before and at least 3 months after EVAR. All patients provided written informed consent on recruitment, and the study was conducted under institutional ethics approval in accordance with the guidelines of the Declaration of Helsinki. Follow-up was conducted according to institutional guidelines. All patients underwent imaging at 1 month and 6 months after EVAR, followed by repeated scans at 12, 24, and 36 months.

Diagnosis of endoleak. This was performed through assessment of computed tomography angiography as a contrast blush inside the AAA sac after EVAR. To be included in the study, this endoleak needed to have been confirmed on at least two occasions during follow-up.

Data collection and definitions used. Characteristics collected from each patient included age at the time of operation (referred to as age), sex, history of smoking, hypertension, diabetes mellitus, ischemic heart disease, and prescribed medications. Height and weight were measured and were used to calculate body mass index (calculated as weight in kilograms/height in square meters). For the purposes of this study, patients were classified as having never or ever smoked. Diabetes mellitus and hypertension were defined by a history of diagnosis or treatment for these conditions. Serum lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), HCY, CRP, and creatinine were measured in hospital pathology laboratories using previously described methods.[19]

Assessment of circulating AAA biomarkers. Commercial enzyme-linked immunosorbent assays were used to measure plasma concentrations of MMP9 and OPG (both using plasma collected in ethylenediaminetetraacetic acid-coated tubes [R&D Systems, Minneapolis, Minn]) and D-dimer (using plasma collected in sodium citrate-coated tubes [Technozym; Technoclone, Vienna, Austria]) according to the manufacturer's directions. We have previously used these kits to analyze clinical samples with excellent reproducibility.[20-22]

Statistical analyses. Demographic differences between groups of patients were compared by univariate statistics using the SPSS software (version 23.0; IBM, Armonk, NY). Continuous demographic variables were compared using the Mann-Whitney *U* test and were presented as median and interquartile range. Nominal variables were presented as count and percentage and were compared using the χ^2 test. Longitudinal comparisons to assess changes in AAA diameter and circulating biomarker concentrations were performed using random intercept linear mixed-effects models with the freely available R statistical package as previously described.[23] This was initially assessed in unadjusted analyses including endoleak presence and time as fixed effects and variation between individual patients as a random effect (unadjusted models). Time was treated as a factorial variable in models assessing AAA diameter as images were acquired at set intervals after EVAR. For models assessing biomarker concentrations, time was considered a continuous variable owing to variations in blood collection intervals after EVAR. For these analyses, MMP9, D-dimer, OPG, and CRP concentrations were log transformed to conform to model assumptions. We then assessed the association of biomarkers with endoleak presence in multivariable linear mixed-effects models including age, prescription for statins, and hypertension as additional fixed effects based on observations of significant differences for these variables between groups on univariate comparisons (adjusted models). Model fit was assessed by examining the distribution of residuals using q-q normal plots and scatter plots of the fitted