European Journal of Vascular and Endovascular Surgery 43 (2012) 171–172

Contents lists available at SciVerse ScienceDirect

European Journal of Vascular and Endovascular Surgery

journal homepage: www.ejves.com

Short Report

Plasma Levels of Matrix Metalloproteinase-9: A Possible Diagnostic Marker of Successful Endovascular Aneurysm Repair

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ARTICLE INFO

Article history:
Received 15 April 2010
Accepted 18 October 2011
Available online 14 December 2011

Keywords:
Abdominal aortic aneurysm
Diagnosis
Endoleak
MMP-9

ABSTRACT

Objective: The aim of the study was evaluating the diagnostic value of plasma matrix metalloproteinase-(MMP)-2 and -9 and tissue inhibitor of MMP-1 (TIMP-1) for endoleak detection after endovascular aneurysm repair (EVAR).
Report: Consecutive EVAR patients ($n = 17$) with endoleak and matched controls without endoleak ($n = 20$) were prospectively enrolled. Increased levels of MMP-9 were observed in patients with endoleak ($P < 0.001$). Regression analysis showed no significant influence of age, sex or abdominal aortic aneurysm (AAA) size. The receiver operating characteristic (ROC) curve of plasma MMP-9 levels showed that a cut-off value of 55.18 ng ml^{-1} resulted in 100% sensitivity and 96% specificity with an AUC value of 0.988 ($P < 0.001$) to detect endoleak.
Conclusions: Plasma MMP-9 levels appear to discriminate between patients with and without an endoleak with high sensitivity and specificity.

Endoleak is the most common complication of endovascular aneurysm repair (EVAR) with a reported incidence varying from 2% to 45%.[1] Re-interventions are frequently required since endoleak may cause enlargement with eventual rupture of the aneurysm sac. Computed tomography angiography (CTA) is considered the gold standard for detection of these complications, despite known disadvantages such as cumulative radiation dose, nephrotoxic contrast agent and high costs.[2] Therefore, a less harmful and less costly alternative for follow-up after EVAR is desirable.

Increased circulating levels of plasma matrix metalloproteinase (MMP)-2 and -9 and tissue inhibitor of MMP-1 (TIMP-1) are associated with presence and size of abdominal aortic aneurysm (AAA).[3] It has been shown that decreased MMP levels during post-EVAR surveillance might indicate successful EVAR whereas an increase may help to identify patients with aneurysm sac growth and/or endoleakage.[4,5] However, reports on the diagnostic value of these biochemical assays are lacking and hence none of these assays are clinically applied. The objective of this study was to evaluate the potential clinical applicability of MMP-2 and -9 and TIMP-1 as a diagnostic tool for endoleakage presence.

Report

Thirty-seven patients who underwent routine CTA follow-up and blood sampling after EVAR were included in the study. Plasma levels of MMP-2 and -9 and TIMP-1 were determined using enzyme-linked immunosorbent assay (ELISA) (GE Healthcare/Life-sciences, Upssala, Sweden). Seventeen patients had an endoleak as detected on CTA, which included four type I, 12 type II and one type III endoleak. The other 20 patients were matched controls. Initial aneurysm diameter was larger in patients with endoleaks detected (Table 1). Patients and aneurysm characteristics as well as plasma levels of MMP-2 and -9 and TIMP-1 are listed in Table 1. Higher MMP-9 levels were observed in patients with an endoleak as

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doi:10.1016/j.ejvs.2011.10.014

Table 1
Patient and aneurysm characteristics.

	Endoleak − ($n = 20$)	Endoleak + ($n = 17$)	P value
Male gender (%)	19 (95)	16 (94)	ns
Age—years (mean (SD))	74 (9.5)	73 (7.0)	ns
Smoking history (%)	20 (100)	17 (100)	ns
Current smokers (%)	5 (25)	4 (24)	
Ex smokers (%)	15 (75)	13 (76)	
Statin use (%)	7 (35)	11 (65)	ns
Months between EVAR and CTA (mean (SD))	18 (15)	21 (15)	ns
Initial AP AAA diameter − mm (mean (SD))	57 (17)	72 (19)	0.038
Right groin introduction of main device (%)	18 (90)	17 (100)	ns
Neck diameter − mm (mean (SD))	24 (4.2)	24 (3.7)	ns
Neck length − mm (mean (SD))	35 (14)	37 (16)	ns
Unfavorable angulation of neck (%)	3 (15)	2 (12)	ns
Diameter ipsilateral CIA − mm (mean (SD))	17 (6.1)	15 (3.2)	ns
Diameter contralateral CIA − mm (mean (SD))	18 (7.3)	17 (4.5)	ns
Tortuosity of iliac axis	3 (15)	4 (24)	ns
Patent IMA (%)	5 (25)	4 (24)	ns
MMP-2 (ng/mL)	1006.58 (285.76)	1110.37 (370.23)	ns
MMP-9 (ng/mL)	25.02 (13.40)	89.54 (26.46)	<0.001[a]
TIMP-1 (ng/mL)	138.14 (69.08)	142.51 (63.29)	ns

AP = Anterior–posterior, mm = millimeter, SD = standard deviation, CIA = common iliac artery, IMA = inferior mesenteric artery, MMP-2 = matrix metalloproteinase -2, MMP-9 = matrix metalloproteinase-9, TIMP-1 = tissue inhibitor of the matrix metalloproteinase type 1.
[a] Additional regression analysis showed that sex, age and AAA size (Dmax) do not influence the significant effect of MMP-9 on predicting endoleak.

compared with patients without endoleak ($P < 0.001$) (Table 1). The receiver operating characteristic (ROC) curve represents the relationship between the specificity and the sensitivity of plasma MMP-9 levels in detecting endoleak presence. The area under the curve (AUC) was 0.99 with a sensitivity of 100% (95% confidence interval (CI) 80.5–100) and a specificity of 96% (95% CI 75.1–99.9) using a cut-off value of 55.18 ng ml^{-1}. Plasma MMP-9 levels cannot differentiate between different endoleak types. Anterior–posterior aneurysmal diameter (Dmax) was significantly larger in the endoleak group (72 vs. 57 mm; $P = 0.038$); however, plasma MMP-9 levels were not associated with Dmax or intraluminal thrombus (ILT) volume. Two patients who underwent intervention to eliminate type II endoleak showed at 1 month post-intervention a decrease in plasma MMP-9 levels (102.95–16.23 ng ml^{-1} and 121.97 to 20.28 ng ml^{-1}). Furthermore, we determined MMP-9 levels in fluid aspirated from the aneurysm sac of these patients, showing greatly increased levels of MMP-9, 386.34 and 343.78 ng ml^{-1}, respectively.

Discussion

The present study showed that plasma MMP-9 levels can accurately discriminate between patients with and without an endoleak with both high sensitivity and specificity. The ROC and the AUC demonstrated that plasma MMP-9 is an excellent test to determine endoleak presence. Implementing a blood test to differentiate between patients with and without an endoleak is clinically important. Patients without an endoleak could be spared to undergo CTA with the aforementioned additional hazards and cost.

Sangiorgi et al. and Lorelli et al. previously suggested that plasma MMP-9 levels can be used to monitor the success of EVAR procedures and showed proof of concept.[4,5] The current study is the first to report the diagnostic value of the MMP-9 assay in post-EVAR surveillance. We also showed that MMP-9 levels were associated with endoleak presence and not with Dmax or ILT. Although this case control study has a limited number of patients, sensitivity and specificity rates are impressive and the confidence intervals are reassuring. Nevertheless, an adequately powered prospective clinical trial is necessary to validate the applicability of plasma MMP-9 levels to differentiate between patients with and without endoleak in clinical practice and the potential role of plasma MMP-9 levels in selecting EVAR patients requiring CTA. Furthermore, standardisation of the assay (e.g., monoclonal antibody and calibrators) will be necessary for the application of one standard cut-off value.

In conclusion, the present study suggests that plasma levels of MMP-9 can accurately discriminate between patients with and without an endoleak with both high sensitivity and specificity. A prospective clinical trial to validate the clinical applicability of this assay is in progress.

Funding Sources

None.

Disclosures

No conflicts to disclose.

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