UMEÅ UNIVERSITET

Vascular remodelling and circulating basement membrane fragments in abdominal aortic aneurysm

Mari Holsti

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i hörsal B, byggnad 1B, 9 trappor, Norrlands universitetssjukhus, fredagen den 15 mars, kl. 13.00.

Avhandlingen kommer att försvaras på svenska.

Fakultetsopponent: Docent Joakim Nordanstig,
Institutionen för molekylär och klinisk medicin, Sahlgrenska akademin, Göteborgs universitet, Sverige.

Institutionen för kirurgisk och perioperativ vetenskap
Umeå Universitet
Umeå 2019

Organization
Umeå University
Dept. of Surgical and Perioperative Sciences

Document type
Doctoral thesis

Date of publication
20190221

Author Mari Holsti

Title Vascular remodelling and circulating basement membrane fragments in abdominal aortic aneurysm

Abstract An abdominal aortic aneurysm (AAA) is a degenerative disease, characterized by advanced inflammation and extracellular matrix (ECM) remodelling. Enhanced protease activity mediated by cytokines results in the degradation of ECM proteins, leading to the generation of different bioactive fragments. Some of these generated fragments are released from the vascular basement membrane (VBM), a highly specialized ECM. VBM provides mechanical and structural stability and regulates many important cellular functions of the vascular system. Type IV and XVIII collagens are two structural proteins in VBM, with crucial roles in maintaining the VBM integrity and vascular architecture. Circulating levels of type IV and XVIII collagen fragments are found physiologically, but have also been associated with many diseases. Remodelling of VBM and expression of its components has not been as well studied in AAA as that of the interstitial ECM. Here we investigate these VBM collagens, their expression and possible association with aortic diameter and expansion rate in individuals with an AAA in comparison with different control groups. Further we study whether there is a link between the circulating VBM collagen fragments and several inflammatory markers, all highly involved in AAA pathogenesis. Lastly, we study the impact of surgical intervention on plasma levels of VBM collagens in patients treated by either open surgical repair (OSR) or endovascular aortic aneurysm repair (EVAR).

Methods Circulating levels of type IV and XVIII collagen fragments were analysed in individuals with an AAA compared with healthy controls and patients with peripheral artery disease (PAD), (**paper I**). A possible association between VBM collagen fragments and the aortic diameter and expansion rate was studied in a large population-based cohort of 615 men stratified into three aortic diameter groups based on initial maximum aortic diameter (**paper II**). Furthermore, 159 individuals were followed up over time with repeated measurements of aortic diameter and blood samples. The follow up cohort were divided into two subgroups based on expansion rate of AAA. Moreover, the location of VBM collagens in tissue from aortic wall in individuals with an AAA was characterized and the expression pattern was compared with normal aorta (**paper II**). In **paper III**, the association between the plasma levels of VBM collagens and inflammatory markers; IL-1 (IL-1α and IL-1β), IL-6, IL-8, TNF-α INF-γ and hs-CRP were studied in the same cohort as used in paper II. Finally, the effect of surgical intervention on circulating levels of VBM collagen fragments was investigated in AAA patients who had undergone either OSR or EVAR with comparison of plasma levels before and after AAA repair. Ultrasound technique was used for measurements of aortic diameter (**paper I, II, III and IV**). Analysis of circulating VBM collagens and inflammatory markers were performed by ELISA-assay (**Paper I, II, III and IV**) and Multiplex-assays (**paper III**), respectively. Aortic wall tissues were analysed by haematoxylin and eosin (H&E) and immunofluorescence staining (**Paper II**).

Results There were significantly increased plasma levels of VBM collagen fragments in individuals with an AAA, compared with healthy controls and those with PAD. The levels of type IV collagen in AAA patients did not differ from the group with PAD, and there were no significant differences between the control groups regarding plasma levels of both VBM collagen fragments (**Paper I**). The increased levels of VBM collagen fragments were significantly associated with aortic diameter with highest levels in the group with an AAA. Altered expression of the VBM collagens and fragmentation of elastic fibres were observed in tissue from AAA patients (**Paper II**). A significant association between the levels of pro-inflammatory cytokines IL-6 and IL-8, and VBM collagens was found. Additionally, there was a significant association between the plasma levels of IL-8, TNF-α and hs-CRP and an AAA. Aneurysms with faster expansion rate had significantly higher levels of IL-6, IL-1β, and type XVIII collagen/endostatin. Additionally, IL-6, type XVIII collagen/endostatin and baseline-aortic diameter were significantly associated with expansion rate (**Paper III**). AAA repair was associated with changes in plasma levels of both VBM collagens (**Paper IV**).

Conclusion Circulating levels of VBM collagens were increased in patients with an AAA, and significantly associated with aortic diameter and expansion rate. The expression of VBM collagens was altered in AAA tissue compared with normal aorta. In addition, plasma levels of several inflammatory markers were associated with VBM collagens, aortic diameter and expansion rate. The levels of both VBM collagens were altered at short- and long-term follow-up after AAA repair.

Keywords AAA, extracellular matrix, vascular remodelling, collagen, inflammation

Language	**ISBN**	**ISSN**	**Number of pages**
English	978-91-7855-028-9	0346-6612	77 + 4 papers