

**EXTRACELLULAR MATRIX REMODELLING PROTEASES IN ACUTE APPENDICITIS
AND THEIR IMPACT ON APPENDICEAL PERFORATIONS**

AKADEMISK AVHANDLING

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av

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Avhandlingen baseras på följande delarbeten:

- I. A local imbalance between MMP and TIMP may have an implication on the severity and course of appendicitis.
Solberg A, Holmdahl L, Falk P, Palmgren I, Ivarsson ML.
Int J Colorectal Dis. 2008 Jun;23(6):611-8
- II. Progress of tissue injury in appendicitis involves the serine proteases uPA and PAI-1.
Solberg A, Holmdahl L, Falk P, Willén R, Palmgren I, Ivarsson ML.
Scand J Gastroenterol. 2009;44(5):579-84.
- III. Tissue proteolysis in appendicitis with perforation
Solberg A, Holmdahl L, Falk P, Willén R, Palmgren I, Ivarsson ML.
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- IV Plasma MMP-9, PAI-1 and TIMP-1 as diagnostic markers for the severity of acute appendicitis
Solberg A, Holmdahl L, Falk P, Wolving M, Palmgren I, Ivarsson M-L
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BACKGROUND

Appendicitis is associated with varying degradation of extracellular matrix (ECM) involved in tissue injury. The principal aim of this study was to investigate whether immunoreactive techniques could illustrate the course and severity of appendicitis and separate the different inflammatory grades, phlegmonous, gangrenous and perforated appendicitis, from each other and from uninflamed appendix. This could lead to early identification of patients with appendicitis that have or are at risk of a perforation, thereby improving their treatment and outcome.

MATERIALS AND METHODS

In Papers I-II, tissue biopsies were taken from 40 appendectomized patients. Ten patients who had a hemicolectomy served as controls. In paper III, proteolysis from tissue biopsies at and adjacent to the perforation was studied in 15 patients operated on for perforated appendicitis. In paper IV, biopsies from the appendix and plasma samples taken prior to surgery and 4 weeks postoperatively were taken in 57 patients operated on for suspected appendicitis. Protein levels of matrix metalloproteinase (MMP) -1, -2, -3, -9 and tissue inhibitor of metalloproteinase (TIMP-1) (Papers I, III and IV), urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1) (Papers II, III and IV) were determined by ELISA and localised by immunohistochemistry.

RESULTS

MMP-9 was the most abundant protease in all groups of appendicitis compared with controls. The expression of MMP-1 and PAI-1 was significantly higher in perforated appendicitis compared with phlegmonous appendicitis and controls while MMP-2 showed an opposite pattern. uPA was twice as high in all groups of appendicitis compared with controls while no differences were found in MMP-3 and TIMP-1 expression between the groups. Immunohistochemically, a scattered distribution of MMP-9 and TIMP-1 was demonstrated in the appendiceal wall in gangrenous and perforated appendicitis. When investigating the proteases in relation to the sites of perforation, MMP-9 and PAI-1 was found to be highest at the perforation sites while MMP-1 was higher close to them and MMP-2 decreased gradually away from them. No difference was seen in TIMP-1 and uPA. The individual differences in plasma for TIMP-1 were higher in patients with perforated appendicitis than in them who had phlegmonous and gangrenous appendicitis.

CONCLUSIONS

ECM remodelling proteases and anti-proteases could be demonstrated in appendicitis. A local imbalance between MMP-9 and TIMP-1 in combination with an over-expression of PAI-1 participated in the ECM degradation, leading to tissue injury in appendiceal perforation. TIMP-1 in plasma could be an inflammatory diagnostic marker for patients at risk for appendiceal perforation.

Keywords; Appendicitis, Perforation, Extracellular matrix, MMP-9, TIMP-1, uPA, PAI-1