

Insights into Healing Response in Severe Sepsis from a Connective Tissue Perspective:

A Longitudinal Case-control Study on Wound Healing, Collagen Synthesis and Degradation, and Matrix Metalloproteinases in Patients with Severe Sepsis

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Fia Gäddnäs, MD, defended her PhD thesis in Oulu (Uleåborg), on September 3rd 2010. The thesis was supervised by Professor Tero Ala-Kokko, Department of Anesthesiology, and Docent Vesa Koivukangas, Department of Surgery, University of Oulu, Finland. The opponent was Professor Leena Lindgren from Tampere. The thesis used suction blister technique developed by Finnish dermatologist Urpo Kiistala and collagen turnover measurements developed in the University of Oulu and Oulu University Hospital. These techniques have been widely used in dermatology but can, as seen in this thesis, be utilized to study other disease entities as well. This thesis can be found at: <http://herkules.oulu.fi/isbn9789514262548/isbn9789514262548.pdf>.

Sepsis is a major challenge for healing responses maintaining homeostasis. Coagulation and inflammation are activated at the whole-body level, even in undamaged tissues. Despite constantly growing knowledge and advances in care, high mortality in severe sepsis remains. It was hypothesised that tissue regeneration processes may also be altered in severe sepsis.

The study population consisted of 44 patients with severe sepsis and 15 healthy controls. Serum samples were obtained during ten days of severe sepsis and twice again, three months and six months later. Experimental suction blisters were performed twice during severe sepsis and at 3 and 6 months. Serum samples were obtained and suction blisters were induced once in controls. Biochemical analyses were performed to assess the level of procollagen I and III aminoterminal propeptides (PINP, PIIINP), reflecting the synthesis of corresponding collagens; in serum and suction blister fluid. In addition collagen I degradation product in serum was measured. Physiological measurements of transepidermal water loss and blood flow were done in order to evaluate the re-epithelisation rate and blood flow in an experimental wound. Levels of matrix metalloproteinases (MMPs) 2, 8 and 9 were measured from serum and suction blister fluid.

Decrease in water evaporation from an experimental blister wound was slower in sepsis than in controls. On the fourth day the sepsis patients had higher blood flow in the blister wound than the controls (both in the healing wound and in the newly induced wound). The procollagen III aminoterminal propeptide (PIIINP) levels were increased in serum in severe sepsis, whereas procollagen I aminoterminal propeptide (PINP) levels were not, making up a pronounced PIIINP/PINP ratio. PIIINP and PINP levels were associated with disease severity and



Fig. 1. Fia Gäddnäs (right) defended her thesis in Oulu, Finland on September 2010. Opponent was Leena Lindgren (middle) and Tero Ala-Kokko acted as supervisor.

outcome. In addition, collagen I degradation measured with ICTP assay was increased in severe sepsis and PINP/ICTP ratio was lower. Furthermore, the overall protein concentration and PINP and PIIINP levels were low in suction blister fluid, which implies that the balance of the extracellular matrix consistence is disturbed in uninjured skin in severe sepsis. Then again in survivors the levels of PINP and PIIINP were up-regulated at three months but returned to normal by six months. MMP-9 levels in serum and skin blister fluid were lower in severe sepsis than in controls during the ten days studied. The MMP-2 levels

were found to be increased both in serum and in skin blister fluid in severe sepsis in comparison to the controls and MMP-2 was associated with disease severity and outcome. MMP-8 was increased in serum and in skin blister fluid.

In conclusion, the balance of collagen turnover is altered in severe sepsis in serum and skin and epidermal re-epithelisation is delayed. The levels of MMP-2 and MMP-8 are increased whereas levels of MMP-9 are depressed.