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Dual Treatment Strategy by Venous Ulcers: Pilot Study to Dual-Frequency Ultrasound Application

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ABSTRACT

We propose a new dual treatment strategy for venous ulcer, consisting in simultaneous modulation of matrix metalloproteinases (*MMPs*) *and heat shock proteins* (*HSPs*) *in the wound. One treatment method which can efficiently modulate both these substances is based on the application of dual-frequency ultrasound* (*LDM*). *This strategy was checked in a pilot study on 10 patients with chronic venous ulcers and demonstrated excellent healing rate.*

Keywords*: *Venous Ulcer, Dual-Frequency Ultrasound, Matrix Metalloproteinases, Heat Shock Proteins

1. Introduction

Chronic wounds (CWs) are the wounds which show no healing tendency during the first 12 weeks of the treatment or do not heal in 12 months. CWs belong to the worldwide most severe health problems not only because of their broad therapy resistance but rather because of permanently increasing costs for the healthcare. Such wounds are usually associated with some severe diseases (e.g. diabetes) and heal very slow even under optimal treatment conditions.

CWs can be subdivided into three groups: pressure sores, diabetic and venous ulcers (the last represents up to 84% of leg ulcers). Although these wounds have different pathophysiology their healing shows some similar features: local inflammation, building-up of granulation tissue, re-epithelisation of the wound and remodeling of extracellular matrix. These processes are tightly connected with collagen turnover as well as with a shifting of the equilibrium between the processes of production (controlled by mesenchymal cells) and decomposition (controlled primarily by different enzymes from the family of matrix metalloproteinases—MMPs) in the involved connective tissue.

Different theories were developed to explain the pathophysiology of CWs, especially of diabetic and venous ulcers; among them the "fibrin cuff hypothesis" [1], "white cell trapping hypothesis" [2] as well as some others. No of these theories could really explain the difference between normal wounds and CWs.

Recently two new ideas were proposed. One is based on the over-expression of MMPs in the wound bed (see e.g. [3-5]), another is connected with the under-expression of heat shock proteins (HSPs) in the wound under some attendant circumstances [6-9]. Several treatment strategies based on these theories were developed during the last years, among them the local suppression of the MMPs-production through application of the MMP-antagonists as well as the local production of the HSPs in the wound.

Presently the MMP- and HSP-theories exist separately of each other and consequently the corresponding treatment strategies for MMP-suppression do not take into account the HSP-production in the wound and vice versa. Different treatment methods based on these theories demonstrate more or less good healing by some patients but show also a significant group of therapy resistant patients. This means the single treatment strategy may be sub-optimal and has to be replaced through the dual-strategy which takes into account both the processes of MMP- and HSP-production within a CW.

2. MMPs in Wound Healing

Different MMPs as well as their antagonists (TIMPs) are believed to be involved in the wound healing processes [4,5]. Initially it was strongly believed that MMPs in the wound are active only during the resolution phase, mainly during the scar resorption. The newest results show however that these enzymes are also active during the inflammation and re-epithelisation phases [5], which

