ABSTRACT

The presence non-healing diabetic foot ulcers is a serious complication in diabetes mellitus and the amputation risk is high. Treatments tend to focus on the wound itself, and not on the pathophysiology behind the wounds. There are several factors believed to influence the development of foot ulcers in diabetes, and two important factors are poor perfusion and a reduction in the microvascular network. Previous studies have shown that passive movement training can increase leg blood flow and promote angiogenesis in healthy individuals, but the effect of this intervention on the healing of diabetic foot ulcers has not been examined. The primary aim of this thesis was to investigate the effect of passive leg movement on wound healing, leg blood flow and proteins in muscle of importance for angiogenesis and vascular function in patients with non-healing diabetic foot ulcers. Secondly, to obtain an insight into skeletal muscle proteins related to vascular function and angiogenesis in critical limb ischemia. Thirdly, a study was conducted to validate the interobserver agreement of Meggitt-Wagner ulcer classification and treatment recommendations, given by clinicians and nurses.

A randomized controlled trial was conducted, to study the effect of 8-weeks of passive movement sessions on: 1) wound healing, measured by digital planimetry software image J, 2) femoral blood flow, assessed by ultrasound doppler, 3) skeletal muscle proteins of relevance for vascular function and angiogenesis by western blotting and multiplate assay. For the study of vascular and angiogenic proteins in critical limb ischemia, muscle biopsies were taken at the vascularized proximal part and distal ischemic part of the amputated leg. Muscle cells were also cultured from the biopsies and growth factor release were studied in an in vitro cell study. For the study on wound classification and treatment recommendations, a survey Xact questionnaire was given to medical doctors and nurses to evaluate interobserver agreement.

Passive movement training lead to a clinically relevant (40%; p=0,062) greater wound healing compared to controls but did not affect resting femoral blood flow or the level of proteins related to vascular function and pro-or antiangiogenic factors. In the muscle samples from the amputation study, the levels of vascular and angiogenic protein were similar in the distal ischemic muscle compared to age matched healthy controls. Vascular endothelial growth factor release, a key function in angiogenesis, was similar between muscle cells cultured from proximal and distal parts in the amputated leg. The interobserver agreement was substantial (Krippendorffs alpha coefficient = 0,67) in respect of Meggitt-Wagners ulcer classification, but not in terms of treatment recommendations.
A key finding in the present thesis was that a period of passive movement training has a clinically relevant effect on wound healing in non-healing diabetic foot ulcers. The mechanism underlying this effect may be the increase in blood flow to the limb during the passive movement sessions, however, there was no support of an improved vascular function or angiogenic potential in the skeletal muscle samples after the intervention. Moreover, the results from the amputation study, indicates that there is similar angiogenic potential in ischemic muscle as in healthy muscle ischemic. Finally, the conducted survey has shown that the evaluation and treatment of foot ulcers should not be based on just a pictorial material.