1. INTRODUCTION

Non-healing foot ulcers are serious complications in diabetes mellitus, and the pathogenesis are multifactorial. One of the pathological contributing factors is peripheral arterial disease, which is characterized by narrowing of the peripheral arteries, and impairment in the ability to regulate blood flow and adapt to the oxygen and nutrient demand of the tissue, i.e. vascular function. A final stage of peripheral arterial disease is critical limb ischemia and by the fact that treatment options often are limited, the risk of ending up with an amputation is high. Both critical limb ischemia and diabetes are associated with impaired angiogenesis, and this reduced capability of the tissue to create a sufficient capillary network in the regeneration of tissue loss or damage, decreases wound healing.

Exercise training increases blood flow to the exercised limb and improves vascular function and initiates angiogenesis in healthy individuals. In long term adaptations to training, both aerobic, anaerobic and resistance training induce beneficial effects such as increased capillarization. However, some patients may not be able to conduct regular exercise training, and therefore alternative movement interventions are needed to address this patient cohort.

The underlying hypothesis of this thesis was, that improved vascular function and capillarization in the skeletal muscles leads to increased blood flow, oxygen and nutrient supply to the entire limb, including removal of waste products, potentially enhancing wound healing. To test this hypothesis, we applied a novel passive movement model as the intervention to induce a temporary elevation in blood flow in patients with non-healing diabetic foot ulcers. We investigated several selected angiogenic proteins and proteins related to vascular function in skeletal muscles, in the patients included in the passive movement trial and, to assess the effect of severe ischemia, also in muscle from patients that underwent transfemoral amputation due to critical limb ischemia. In addition, a study was conducted on the interobserver agreement of diabetic foot ulcer classification and treatment recommendation, among clinicians and nurses. This thesis has the structure of a summary and discussion of the 3 manuscripts, in order to guide the reader through the translational aspects between fundamental research physiology and a clinical health outcome.