The Diabetic Foot

Plantar forefoot ulcer, heel ulcer and minor amputation

Hedvig Örnehholm

DOCTORAL DISSERTATION
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Faculty opponent
Professor Michael Edmonds
King’s College, London
Abstract

Diabetes mellitus is increasing worldwide and is one of the most challenging healthcare dilemmas of the 21st century. Diabetes is associated with both micro- and macrovascular complications. These include neuropathy, retinopathy, nephropathy, cardiovascular and cerebrovascular complications, and peripheral vascular disease. These complications all contribute to an increased risk of foot ulcer, infection, delayed ulcer healing and amputation.

This thesis is based on four papers: Paper I on minor amputations, Paper II on plantar forefoot ulcers, Paper III on heel ulcers, and Paper IV on new foot ulcer development following healing of a plantar forefoot ulcer.

In Paper I 64% of all minor amputations healed at a level below the ankle. Re-amputation rate was 37% and almost one third of these healed below the ankle. The median healing time was 26 weeks. Vascular intervention (including endovascular and open methods) and pain as an indication for amputation were related to a lower healing rate below the ankle. Wagner grades 0–3 and age below 73 years at time of amputation were associated with a higher healing rate below the ankle.

In Paper II 79% of patients healed their plantar forefoot ulcer without amputation. Severe peripheral vascular disease (SPVD) was present in 26% of patients. Nine per cent healed after amputation (either minor or major) and 12% died unhealed. The median healing time was 17 weeks. Wagner grade 1 or 2 at inclusion, independent living and age below 67 years at inclusion were factors related to primary healing.

In Paper III 66% of patients healed their heel ulcer without amputation. SPVD was present in 31% of patients. The median healing time was 17 weeks. Vascular surgery after inclusion, nephropathy and oedema were factors related to primary healing.

In Paper IV 47% of patients developed a new foot ulcer within two years following healing of a plantar forefoot ulcer. Only eight per cent developed a recurrent foot ulcer (on the same foot and at the same site as the previously healed ulcer).

In summary, the major conclusions from this thesis are the following. Despite long healing time, it is possible for minor amputations to heal in a large proportion of patients with diabetes, although patients are elderly, with extensive co-morbidity and with severe foot ulcers including infection and/or gangrene in many cases. Four out of five patients with diabetes and a plantar forefoot ulcer heal without the need for an amputation. SPVD was present in one out of four patients with plantar forefoot ulcer, indicating the importance of vascular assessment in these patients. Two-thirds of patients with diabetes and a heel ulcer healed without amputation. Following a healed plantar forefoot ulcer the risk of developing a new foot ulcer is high. There is a lack of uniform terminology regarding new foot ulcer development. A concise definition for recurrent and other new foot ulcers is suggested. This may facilitate comparison and enhance scientific discussions.

Key words: diabetes, plantar forefoot ulcer, heel ulcer, minor amputation, outcome, recurrent ulcer

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Signature __________________________ Date __________________________
The Diabetic Foot

Plantar forefoot ulcer, heel ulcer and minor amputation

Hedvig Örneholm
To Peter, Idun, Tor and Sigrid

“For an obstinate ulcer, sweet wine and a lot of patience should be enough”
Hippocrates
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List of original papers

This thesis is based on the following papers, which are referred to in the text by their Roman numbers.


IV. Örneholm H, Apelqvist J, Larsson J, Eneroth M. Recurrent and other new foot ulcers after healed plantar forefoot diabetic ulcer (submitted)
### Definitions

<table>
<thead>
<tr>
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<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>Surgical removal of the whole or a part of the limb including its distal end</td>
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<tr>
<td>Assisted living</td>
<td>Any institutional living outside the patient’s own home</td>
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<tr>
<td>Cerebrovascular co-morbidity</td>
<td>History of neurological deficit</td>
</tr>
<tr>
<td>Concordance</td>
<td>The ability to keep 50% or more of appointments with the multidisciplinary foot care team</td>
</tr>
<tr>
<td>Critical limb ischaemia (CLI)</td>
<td>Toe pressure &lt;30 mmHg and/or ankle pressure &lt;50 mmHg</td>
</tr>
<tr>
<td>Deep ulcer</td>
<td>Full thickness lesion of the skin penetrating below the dermis to subcutaneous structures, such as fascia, muscle, tendon, or bone</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>Calculated from the year of diagnosis until presentation with an ulcer at the foot clinic</td>
</tr>
<tr>
<td>End-stage renal disease (ESRD)</td>
<td>Uraemia (creatinine level &gt;300 µmol/l), treatment in dialysis, or a previous renal transplantation</td>
</tr>
<tr>
<td>Foot</td>
<td>The structure below the malleoli</td>
</tr>
<tr>
<td>Foot ulcer</td>
<td>Full thickness lesion of the skin of the foot</td>
</tr>
<tr>
<td>Gangrene</td>
<td>Death of tissue in all tissue layers (cutis, tendon, fascia, muscle)</td>
</tr>
<tr>
<td>Healing</td>
<td>Macroscopically complete epithelialization which has to be reconfirmed after 6 months</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
<td>-------------------------------------------</td>
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<tr>
<td>Healing time</td>
<td>Number of weeks from arrival at the foot clinic until healing</td>
</tr>
<tr>
<td>Home care</td>
<td>Any assistance the patient had in his/her own home</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Blood pressure over 140/90 mmHg or treatment with antihypertensive agents</td>
</tr>
<tr>
<td>Index ulcer</td>
<td>The first ulcer in the studied time period</td>
</tr>
<tr>
<td>Infection</td>
<td>A pathological state caused by invasion and multiplication of microorganisms in tissues accompanied by tissue destruction or a host inflammatory response</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>Angina pectoris or myocardial infarction</td>
</tr>
<tr>
<td>Minor amputation</td>
<td>Any amputation through or distal to the ankle joint</td>
</tr>
<tr>
<td>Minor debridement</td>
<td>Removal of callosities and debris that can be performed in the outpatient clinic without anaesthesia</td>
</tr>
<tr>
<td>Major amputation</td>
<td>Any amputation proximal to the ankle joint</td>
</tr>
<tr>
<td>Major debridement</td>
<td>Surgical revision or resection of soft tissues and/or bone that requires anaesthesia and/or the use of an operating theatre</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Devitalized (dead) tissue</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>Persistent urine albumin &gt; 300 mg/L</td>
</tr>
<tr>
<td>Neuropathy (diabetic)</td>
<td>The presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes, after exclusion of other causes</td>
</tr>
<tr>
<td>Non-ischaemic heart disease</td>
<td>Other causes such as atrial fibrillation or valvular heart disease</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Infection of the bone, with involvement of the bone marrow</td>
</tr>
<tr>
<td>Other new foot ulcer</td>
<td>A foot ulcer developing after healing of a previous foot ulcer, located at any site on the contralateral foot, or on the same foot at any other site than the previously healed foot ulcer</td>
</tr>
<tr>
<td>Pain</td>
<td>Rest pain localized in the foot</td>
</tr>
<tr>
<td>Partial forefoot amputation</td>
<td>Resection of two, three or four rays. The partial forefoot amputations were divided into two groups: one group in which the first ray was included and one in which it was not.</td>
</tr>
<tr>
<td>Peripheral vascular disease (PVD)</td>
<td>Obstructive atherosclerotic vascular disease, outside the heart and brain, with clinical symptoms, signs or abnormalities on non-invasive vascular assessment, resulting in disturbed or impaired circulation in one or more extremities</td>
</tr>
<tr>
<td>Previous amputation</td>
<td>Amputation performed before the patient entered the study</td>
</tr>
<tr>
<td>Previous vascular surgery</td>
<td>Vascular surgery performed before the patient entered the study</td>
</tr>
<tr>
<td>Primary amputation</td>
<td>The first amputation in a sequence until a final outcome (healing or death)</td>
</tr>
<tr>
<td>Primary healing</td>
<td>Healing without major debridement or amputation</td>
</tr>
<tr>
<td>Re-amputation</td>
<td>An amputation performed on a previously amputated limb, due to non-healing of the previous amputation</td>
</tr>
<tr>
<td>Recurrent foot ulcer</td>
<td>An ulcer appearing on the same foot and at the same site as a previously healed ulcer</td>
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<tr>
<td>Term</td>
<td>Description</td>
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<td>-------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Classified as pre-proliferative or proliferative based on retinal photographs by an ophthalmologist</td>
</tr>
<tr>
<td>Severe peripheral vascular disease (SPVD)</td>
<td>Toe pressure &lt;45 mmHg or ankle pressure &lt;80 mmHg</td>
</tr>
<tr>
<td>Single ray amputation</td>
<td>Resection of one toe including part of the metatarsal bone. This group was subdivided in two: single first ray amputations and single ray amputations of any other toe (II, III, IV or V).</td>
</tr>
<tr>
<td>Smoker</td>
<td>Currently smoking or having stopped smoking for less than one year</td>
</tr>
<tr>
<td>Superficial ulcer</td>
<td>Full thickness lesion of the skin not penetrating any structure deeper than the dermis</td>
</tr>
<tr>
<td>Toe amputation</td>
<td>Resection of the toe through or distal to the metatarsophalangeal joint</td>
</tr>
<tr>
<td>Trans-metatarsal amputation</td>
<td>Resection of all toes through the metatarsal bones</td>
</tr>
<tr>
<td>Ulcer</td>
<td>A full thickness lesion through all the layers of the skin</td>
</tr>
<tr>
<td>Ulcer duration</td>
<td>Defined as number of weeks from onset until arrival at the foot clinic. When time of onset could not be established, ulcer duration was categorized as unknown.</td>
</tr>
</tbody>
</table>
Abstract

Diabetes mellitus is increasing worldwide and is one of the most challenging healthcare dilemmas of the 21st century. Diabetes is associated with both micro- and macrovascular complications. These include neuropathy, retinopathy, nephropathy, cardiovascular and cerebrovascular complications, and peripheral vascular disease. These complications all contribute to an increased risk of foot ulcer, infection, delayed ulcer healing and amputation.

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In Paper II 79% of patients healed their plantar forefoot ulcer without amputation. Severe peripheral vascular disease (SPVD) was present in 26% of patients. Nine per cent healed after amputation (either minor or major) and 12% died unhealed. The median healing time was 17 weeks. Wagner grade 1 or 2 at inclusion, independent living and age below 67 years at inclusion were factors related to primary healing.

In Paper III 66% of patients healed their heel ulcer without amputation. SPVD was present in 31% of patients. The median healing time was 17 weeks. Vascular surgery after inclusion, nephropathy and oedema were factors related to primary healing.

In Paper IV 47% of patients developed a new foot ulcer within two years following healing of a plantar forefoot ulcer. Only eight per cent developed a recurrent foot ulcer (on the same foot and at the same site as the previously healed ulcer).
In summary, the major conclusions from this thesis are the following. Despite long healing time, it is possible for minor amputations to heal in a large proportion of patients with diabetes, although patients are elderly, with extensive co-morbidity and with severe foot ulcers including infection and/or gangrene in many cases. Four out of five patients with diabetes and a plantar forefoot ulcer heal without the need for an amputation. SPVD was present in one out of four patients with plantar forefoot ulcer, indicating the importance of vascular assessment in these patients. Two-thirds of patients with diabetes and a heel ulcer healed without amputation. Following a healed plantar forefoot ulcer the risk of developing a new foot ulcer is high. There is a lack of uniform terminology regarding new foot ulcer development. A concise definition for recurrent and other new foot ulcers is suggested. This may facilitate comparison and enhance scientific discussions.
Introduction

Diabetes Mellitus

Diabetes mellitus is increasing worldwide and it is one of the most challenging health care dilemmas in the 21st century. In 2015, 415 million people over the world were estimated to have diabetes, and this number is projected to rise to 642 million by the year 2040. Two of the main types of diabetes are type 1 and type 2. Type 1 diabetes is caused by an autoimmune reaction, in which the body’s defence system attacks the insulin-producing beta cells in the pancreas. Type 1 diabetes accounts for a small percentage of the total burden of diabetes in the population. Type 2 diabetes is the most common type of diabetes. In type 2 diabetes, the body is able to produce insulin but becomes resistant so that the insulin is ineffective. Over time, insulin levels may subsequently become insufficient. Type 2 diabetes constitutes about 85–90% of all diabetes in developed countries and accounts for an even higher percentage in developing countries. The economic consequences, for both patient and society, are very large and every effort to improve care of these patients is worthwhile. Diabetes mellitus is characterized by hyperglycaemia due to defects in insulin secretion, insulin action, or both. Diabetes-related complications are frequently grouped into micro- and macrovascular diseases.

Macrovascular complications

Cardiovascular disease

Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes and risk factors for cardiovascular disease, such as hypertension, dyslipidaemia, smoking, albuminuria, and a family history of cardiovascular events, should be assessed once a year in patients with diabetes. Prevention strategies, as well as treatment of manifest complications, can be beneficial and elimination of risk factors to prevent cardiovascular events is an important part of treatment. Both lifestyle changes and pharmacological agents may be used to treat risk factors.

In a 30-year follow-up of the Diabetes Control and Complications Trial (DCCT), the cumulative incidence of cardiovascular disease was 14% in the conventional
therapy group and 9% in the intensive therapy group. In the follow-up of the same study, intensive treatment of blood glucose levels in patients with type 1 diabetes was shown to reduce the risk of long-term complications.

**Cerebrovascular disease**

The risk of death due to cerebrovascular disease is increased in patients with diabetes (both type 1 and type 2). Hyperglycaemia at hospital admission for a stroke has been shown to be a predictor of worse neurological outcome. In a large study on more than 13,000 patients, the presence of diabetes led to a two- to threefold increase in the risk of stroke. The same study also showed that women had a higher risk of stroke than men. In patients with diabetes there is also an increased risk and rate of dementia and cognitive decline. Cerebrovascular disease has been shown to be more common in patients with diabetes and a foot ulcer than in patients without a foot ulcer.

**Microvascular complications**

**Diabetic peripheral neuropathy**

Diabetic peripheral neuropathy affects up to 30–50% of patients with diabetes and is a serious complication in patients with diabetes. Diabetic neuropathy is one major risk factor for development of diabetic foot ulcer.

The nervous system is divided into three main parts: sensory, motor and autonomic. The sensory nerves are important to feel the surroundings, and loss of the sensory nerves leads to a loss of protective sensation. A sensory neuropathy is associated with the loss of pain, pressure awareness, temperature sensation and proprioception. The ability to feel pain, for example stepping on a pin and feeling it, is an important protective sensation. It was first described by the late Dr Paul Brand and summarized by Dr Andrew Boulton. The motor nerves are responsible for maintaining posture and balance. Loss of function in these nerves affects the muscles in the leg and foot, altering the biomechanics and foot anatomy, leading to foot deformities and increased pressure within the foot in an effort to maintain balance. The autonomic nerves work to maintain normal organ function and homeostasis, and are subdivided into the sympathetic and parasympathetic system. Loss of the autonomic nerves in the lower limb leads to loss of normal sweating leading to dry skin which may crack, and loss of the ability to control vascular blood flow which may play a part in impaired wound healing.
Diabetic retinopathy

Diabetic retinopathy is a specific vascular complication to diabetes, is related to the duration of diabetes, and is the leading cause of new blindness in patients under 75 years. After 15 years’ diabetes duration almost all patients with type 1 diabetes will have diabetic retinopathy. In patients with type 2 diabetes and duration of diabetes of more than 15 years the corresponding number is 85% of patients receiving insulin treatment and 58% in patients not receiving insulin treatment. Presence of retinopathy and loss of vision have been associated with an increased risk of foot ulcers.

Diabetic nephropathy

Diabetic nephropathy is present in 20–40% of patients with diabetes and is the leading cause of end-stage renal disease (ESRD), dialysis and/or renal transplantation. Nephropathy has been described as a marker for worse outcome in diabetic foot ulcers. ESRD seems to have a stronger negative impact in patients who also have peripheral artery disease.

The diabetic foot

The definition of the diabetic foot has been described as infection, ulceration and/or destruction of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular disease. As indicated by this description, one or more of these conditions may coincide, and they often do. A diabetic foot ulcer is the general term to describe a full-thickness wound below the ankle in a patient with diabetes. The major adverse outcomes of diabetic foot problems are foot ulcers and amputations, and foot problems account for more hospital admissions than any other long-term complications of diabetes, and also result in increasing morbidity and mortality.
Diabetic foot ulcer

Prevalence and incidence

The prevalence of diabetic foot ulcers is described to be between 4% and 10% of the diabetic population, with a lifetime risk of up to 25%. The incidence of foot ulcers in diabetic patients varies between 2 and 6% in Western Europe and North America, and between 19% and 29% in the Middle East. The EURODIALE study showed that there are marked regional differences throughout Europe regarding diabetic foot ulcer and amputation incidence.

Aetiology

Peripheral neuropathy and PVD are the two factors most commonly attributed to diabetic foot ulcer. Diabetic foot ulcers are therefore often described as of neuropathic, ischaemic, or neuro-ischaemic origin. The cause of diabetic foot ulcers is often multifactorial. Sensory loss, foot deformities, repetitive pressures and skin breakdown are considered to be the key aetipathogenetic pathways to neuropathic foot ulcers in diabetes, as first described by Paul Brand in the mid-20th century, and addressing these issues is today a cornerstone in the management of plantar diabetic foot ulcers. Visual impairment, reduced joint mobility, callosities, present or previous foot ulceration, and previous amputation have also been described as factors contributing to the development of diabetic foot ulcers.

Classification

There are several classification systems for diabetic foot ulcers, three being the most commonly used, each with their advantages and limitations. The Wagner classification system for foot ulcers is widely used, and was the only one of these three that was available when the study databases were started. It includes the following grades.
Wagner grade 0  No ulcer
Wagner grade 1  Superficial ulcer (up to but not through dermis)
Wagner grade 2  Ulcer extension involving ligament, tendon, joint capsule or fascia (no abscess or osteomyelitis)
Wagner grade 3  Deep ulcer with abscess and/or osteomyelitis
Wagner grade 4  Gangrene of portion of the foot
Wagner grade 5  Extensive gangrene of the foot

The first three grades (grades 0–2) are based on the physical depth of the lesion only, grade 3 on the physical depth and infection and grades 4–5 on the extent of gangrene in the foot. Shown below are examples of ulcers in different Wagner stages.
The Texas Diabetic Wound Classification System\textsuperscript{34} includes wound depth, the presence of infection and PVD in every category of the wound assessment.

The PEDIS classification system\textsuperscript{35} includes the categories: Perfusion, Extent/size, Depth/tissue loss, Infection and Sensation, with a grading system for each category. These two classifications are mainly used for research purposes. In 2010 a review of scoring systems for diabetic foot ulcer was published.\textsuperscript{36} In summary, this review showed that many scoring systems exist for classification of diabetic foot ulcer, but few of these have been validated. Detailed scoring systems may be useful in comparing data from different centres, while simpler scoring systems may be more easily used in clinical practice.

**Infection**

Although infection is seldom the direct cause of a diabetic foot ulcer, in the EURODIALE study, 25–75\% of patients at various centres were considered to have a wound infection at the time of admission.\textsuperscript{37} Infection in the diabetic foot increases the risk of hospitalization and of a subsequent amputation, especially in combination with PVD.\textsuperscript{25,37-39}
Treatment

Prevention of diabetic foot ulcers includes regular inspection and examination of feet at risk, education of patients and relatives, and off-loading with custom-made insoles and individually adjusted footwear.\textsuperscript{1,40}

The basis for management of the diabetic foot ulcer is the multidisciplinary team, which includes medical and surgical treatment, podiatry, nursing and orthotic support.\textsuperscript{1,19} The multidisciplinary team treatment of diabetic patients with foot ulcer has been shown to be cost-effective, improves healing rate, and reduces amputation rate and ulcer recurrence.\textsuperscript{41-47} Treatment of metabolic disturbances, malnutrition, peripheral vascular disease, infection, pain, and oedema as well as topical treatment with ulcer dressings, off-loading, vascular assessment and surgery, and orthopaedic surgery (major debridement, minor and major amputation) are all important parts of the multidisciplinary team approach.\textsuperscript{19}

Excision of the ulcer, metatarsal head resection, Achilles tendon lengthening, and local skin flap have all been described as surgical treatment of diabetic foot ulcers. The results seem good but adequate perfusion of the foot is needed.\textsuperscript{19} Amputations (both minor and major) are also part of the surgical procedures used for treatment of diabetic foot ulcers. Indication for amputation is often multifactorial. A non-healing ulcer should not be used as an indication for amputation.\textsuperscript{19}
Table 1. Multifactorial treatment of diabetic foot ulcers (adapted from Apelqvist 2012).

<table>
<thead>
<tr>
<th>Goal</th>
<th>Investigation/evaluation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve circulation</td>
<td>Non-invasive vascular testing:</td>
<td>Percutaneous angiography (PTA)</td>
</tr>
<tr>
<td></td>
<td>Systolic toe/ankle blood pressure, transcutaneous oxygen pressure, duplex (ultrasound)</td>
<td>Sub intimal angioplasty</td>
</tr>
<tr>
<td></td>
<td>Invasive vascular testing:</td>
<td>Reconstructive vascular surgery</td>
</tr>
<tr>
<td></td>
<td>Angiography, MR angiography, CT angiography, CO₂ angiography</td>
<td>Vascular agents</td>
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<tr>
<td></td>
<td></td>
<td>Remove oedema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperbaric oxygen</td>
</tr>
<tr>
<td>Treat infection</td>
<td>Superficial or deep infection, osteomyelitis, abscess</td>
<td>Antibiotics (oral/parenteral)</td>
</tr>
<tr>
<td></td>
<td>ESR, CRP, white blood cell count, bacterial culture, bone biopsy, X-ray, CT-bone scan, MRI</td>
<td>Incision/drainage</td>
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<td>Resection</td>
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<td></td>
<td>Amputation</td>
</tr>
<tr>
<td>Remove oedema</td>
<td>Evaluate the cause of oedema</td>
<td>External compression therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Analgesic agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immobilization/off-loading</td>
</tr>
<tr>
<td>Pain control</td>
<td>Cause/type of pain</td>
<td>Analgesic agents</td>
</tr>
<tr>
<td></td>
<td>Pain evaluation protocol/diary</td>
<td>Insulin treatment often necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nutritional support</td>
</tr>
<tr>
<td>Improve metabolic control</td>
<td>HbA1c self-monitoring of glucose</td>
<td>Therapeutic/protective footwear, insoles, orthosis, total contact cast, crutches, wheelchair, bed rest</td>
</tr>
<tr>
<td>Off-loading</td>
<td>Type and site of ulcer, biomechanical evaluation, walking capacity</td>
<td>Topical treatment and dressings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Debridement</td>
</tr>
<tr>
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<td></td>
<td>Control of exudation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moist wound healing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NWPT</td>
</tr>
<tr>
<td>Wound bed preparation</td>
<td>Type, site, and condition of the ulcer, necrosis, exudation, peri-ulcer maceration, signs of inflammation, granulation</td>
<td></td>
</tr>
<tr>
<td>Removal of dead tissue</td>
<td>Extent of tissue destruction, infection, ischaemia</td>
<td>Minor debridement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drainage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amputation</td>
</tr>
<tr>
<td>Correction of foot deformities</td>
<td>Evaluation of foot deformities</td>
<td>Corrective foot surgery</td>
</tr>
<tr>
<td>Improve general condition</td>
<td>Dehydration, malnutrition, intercurrent disease, congestive heart failure, nephropathy, metabolic syndrome, smoking habits</td>
<td>Fluid and nutrition replacement therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aggressive treatment of intercurrent disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antiplatelet drugs, antihypertensive agents, lipid decreasing agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cessation of smoking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physiotherapy</td>
</tr>
</tbody>
</table>

Complications and outcome

Occasionally, a diabetic foot ulcer may be considered an underlying, even if not an immediate, cause of death, and not infrequently it may be a contributing factor by starting a deteriorating chain of events. Diabetic foot ulcer patients have a greater than twofold increase in mortality compared with non-ulcerated diabetic patients, and Chammas et al concluded that ischaemic heart disease is the major cause of premature mortality. Up to 70% mortality after 5 to 10 years has been
reported.\textsuperscript{49,50} Evaluating outcome for more than five years, around half of the patients will have died, making analysis more difficult due to small numbers.\textsuperscript{49,51-53} The high mortality rate among these patients deserves attention and further underlines the general morbidity of this patient group. Mortality, specifically related to foot ulcer location, is rarely reported on. A report from 2012 showed that patients with depressive symptoms and a new diabetic foot ulcer had a higher mortality than patients who did not exhibit signs of depression.\textsuperscript{54}

Apart from increased mortality, the most serious immediate adverse outcome is a lower limb amputation. It has been claimed that every 30 seconds a lower limb is amputated due to diabetes.\textsuperscript{1} Up to 70\% of all lower extremity amputations are performed in people with diabetes and 85\% of these amputations are preceded by a foot ulcer.\textsuperscript{1,2,55}

**Factors related to healing**

The main outcomes of a diabetic foot ulcer are primary healing, healing after debridement, healing after amputation (either minor or major), and death unhealed. Most seem to agree that neuropathy, PVD, minor foot trauma and foot deformity contribute to the development of diabetic foot ulcers.\textsuperscript{1,42} When it comes to factors which influence outcome of foot ulcers and minor amputations there are no unanimous results. This is mostly due to confounding factors such as differences in study design, patients included, follow-up time, definitions (or lack thereof), and treatment strategies.

The number of large cohort studies with factors related to healing of foot ulcers is limited. In most mixed cohort studies primary healing rates of 60 to 74\% and amputation rates of 8 to 23\% have been reported.\textsuperscript{24,25,56-59} Multiple factors have been described to be predictors of non-healing of various types of diabetic foot ulcers, such as PVD\textsuperscript{25,60}, infection\textsuperscript{24}, cardiovascular disease\textsuperscript{25,61}, end-stage renal disease\textsuperscript{25,62}, severe retinopathy\textsuperscript{63}, tissue involvement\textsuperscript{24,25,57,64}, peripheral oedema\textsuperscript{24,25}, ulcer location\textsuperscript{65}, male gender\textsuperscript{63,66}, age\textsuperscript{67}, diabetes duration, metabolic control\textsuperscript{63,66}, and socio-economic status.\textsuperscript{66,67} Depression has been found to be associated with amputation.\textsuperscript{68} Most of these studies have small numbers of patients and there are differences in study design, patient selection, definitions and follow-up, making comparisons difficult. In a prospective study of 575 patients with an infected diabetic foot ulcer presenting to 14 different diabetic foot clinics in ten European countries, periwound oedema, foul smell, (non-)purulent exudate, deep ulcer, positive probe-to-bone test, pretibial oedema, fever, and elevated C-reactive protein were all found to be independent risk factors for amputation.\textsuperscript{69} However, there does not seem to be any consensus with regard to factors related to outcome.
Table 2. Factors related to outcome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Extremity</th>
<th>Ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors related to outcome (non-healing)</td>
<td>Cardiovascular disease\textsuperscript{25,61}, ESRD\textsuperscript{25,62}, retinopathy\textsuperscript{63}, male gender\textsuperscript{25,64}, age\textsuperscript{65}, diabetes duration\textsuperscript{25}, metabolic control\textsuperscript{63,66}, socio-economic status\textsuperscript{66,67}</td>
<td>PVD\textsuperscript{25,60}</td>
</tr>
<tr>
<td>Factors related to amputation</td>
<td>Fever\textsuperscript{68}, elevated CRP\textsuperscript{69} (C-reactive protein), depression\textsuperscript{68}</td>
<td>PVD\textsuperscript{60}</td>
</tr>
</tbody>
</table>

Healing time after a diabetic foot ulcer or a minor amputation is not always reported. Reported healing times in the literature for plantar ulcers range from 6 to 12 weeks.\textsuperscript{56,57,70,71} Most data in the literature are from randomized controlled trials with less than 20 weeks’ follow-up, which means that many ulcers are not given enough time to heal. To further complicate scientific discussion and comparison, healing is not always defined. In the studies which make up this thesis, healing was defined as intact skin for 6 months or intact skin at time of death.

The long healing times and costs attributed to minor amputations have been mentioned as reasons to perform a major amputation instead. However, the functional outcome of a major amputation is worse even if it heals better. Furthermore, the costs of a major amputation by far exceed the cost of a minor amputation, even with the long healing times.\textsuperscript{2,72}
Peripheral vascular disease

Peripheral vascular disease (PVD) refers to diseases of blood vessels outside the heart and brain, with a narrowing of the vessels that carry blood to the extremities, stomach or kidneys. Symptoms or signs of PVD can be observed in up to 50% of the patients with a diabetic foot ulcer and is a risk factor for poor healing and amputation.\textsuperscript{25,37,56,60,73} Identifying PVD is important because its presence is associated with worse outcomes.\textsuperscript{24,74} In a systematic review of which measures of PVD predict healing of diabetic foot ulcers, skin perfusion pressure $\geq 40$ mmHg, toe pressure $\geq 30$ mmHg and transcutaneous pressure of oxygen (TcPO2 ) $\geq 25$ mmHg were associated with at least a 25% higher chance of healing.\textsuperscript{60} Among patients with diabetic foot ulceration, the measurement of skin perfusion pressures, toe pressures and TcPO2 appears to be more useful in predicting ulcer healing than ankle pressures or the ABI.\textsuperscript{60} An ankle pressure of $<50$ mmHg or an ABI $<0.5$ is associated with a significant increase in the incidence of major amputation.\textsuperscript{60} In a systematic review on the effectiveness of therapies to revascularize the ulcerated foot in patients with diabetes and PVD, improved rates of limb salvage were found associated with revascularization compared with the results of conservatively treated patients.\textsuperscript{73}

The most important factors related to development of foot ulcers in individuals with diabetes are peripheral neuropathy, minor foot trauma, foot deformity and decreased tissue perfusion.\textsuperscript{1,75} Diabetic foot ulcers are frequently presented as neuropathic or neuroischaemic/ischaemic, according to above-mentioned classification system, related to its aetiology or pathogenesis, or to site of ulcer. Diabetic foot ulcers are frequently seen in patients with a combination of two or more risk factors occurring together.\textsuperscript{24,25} With regard to the aetiology of foot ulceration, peripheral vascular disease and neuropathy are frequently present in the same patient. Although traditionally it is stated that the majority of foot ulcers are purely neuropathic an increase has been found in the incidence of neuroischaemic and/or ischaemic foot ulcers. Ulcers frequently result from external trauma to the insensitive foot, such as ill-fitting shoes, burns, walking barefoot and foreign objects in shoes.\textsuperscript{25,42} However, an ulcer caused by increased mechanical stress due to disturbed biomechanics is usually localized in the metatarsal heads or the plantar area of the first digit, whereas decubitus ulcers are located in the heel.
Plantar forefoot ulcer

Prevalence, incidence and aetiology

Plantar ulcers are usually localized under the metatarsal heads or plantar surface of the first digit, and constitute 22–25% of all diabetic foot ulcers in large Western cohort studies. These ulcers are usually considered purely neuropathic and caused by mechanical stress, but a large share of these patients also have PVD.

Treatment

The main aim of treatment is to achieve healing of the wound and avoid minor and major amputation as well as ulcer recurrence. The basis for treatment of plantar forefoot ulcers is the same as for all diabetic foot ulcers, and described in Table 1.

Off-loading

Off-loading is the most important treatment strategy in plantar forefoot ulcers, especially Wagner grades 1–2. It can be achieved by non-surgical or surgical methods. Total contact casting is currently considered the gold standard to off-load plantar foot ulcers. By using the total contact cast, healing rates of 90% in neuropathic and 69% in non-infected ulcers with PVD can be achieved. Bus and colleagues showed in a systematic review that there is sufficient evidence in the literature to support the recommendation of non-removable off-loading devices to heal a plantar forefoot ulcer.

Surgical treatment

The most important part of the treatment for control of a deep infection with or without minor gangrene in the diabetic foot (Wagner grades 3–4), is urgent incision and drainage and radical debridement of all infected, non-viable tissue.

Various elective surgical procedures have been described to off-load plantar forefoot ulcers, such as flexor tenotomy, Achilles tendon lengthening, plantar fascia release and multiple metatarsal head resections, to name some. A review by Scott and colleagues discusses the evidence that flexor tenotomy can heal and prevent toe ulcers in diabetic patients. This review concludes that while most studies report high healing rates (92–100%) and low recurrence rates (0–18%), these are case series studies, which undermines the validity of the procedure studied. Colen et al investigated whether Achilles tendon lengthening in combination with total contact cast and wound surgery would be effective in
healing midfoot and forefoot ulcers in 287 diabetic patients. The results of this study showed that patients with Achilles tendon lengthening had a lower ulcer recurrence rate and fewer transfer lesions than patients receiving total contact cast and wound surgery alone. Kim et al showed that 60 diabetic patients who had a selective plantar fascia release healed their neuropathic forefoot ulcer in 56% of cases. Armstrong and colleagues evaluated 92 diabetic patients with a plantar forefoot ulcer treated with multiple metatarsal head resection. The authors concluded that patients with surgery healed faster and had fewer recurrent ulcers than patients not having surgery. Since the evidence of the effect of surgical procedures on off-loading is weak, and since surgical procedures were not specifically evaluated in the present thesis, no detailed description of surgical procedures is given.

**Outcome**

There are few studies on larger cohorts who specifically discuss the characteristics and outcome of plantar forefoot ulcers in diabetic patients, and in most studies there is a combination of various types of ulcer and ulcer locations. In mixed cohort studies regarding short-term outcome, primary healing rates of 64–85%, amputation rates of 8–23% (irrespective of level), and mortality rates of 10–20%, have been described. In randomized controlled trials of neuropathic diabetic foot ulcers (mostly, but not exclusively, plantar) healing rates over 12–20 weeks of 36–60% have been reported.

**Factors related to outcome**

There are not many published studies specifically focusing on long-term outcome of plantar forefoot ulcer. In reports on cohorts with mixed ulcer locations, extent of tissue involvement, PVD, neuropathy, age, male gender, and co-morbidity have been reported as factors influencing outcome.

In studies with plantar and mixed ulcer location, poor glycaemic control, neuropathy, poor compliance with footwear and foot care, non-attendance, delay in reporting new symptoms, PVD, insulin treatment, plantar ulcer location, osteomyelitis, and cumulative duration of past foot ulcers have been reported as factors negatively influencing long-term outcome. A Cochrane review from 2013 found that non-removable off-loading devices were more effective in healing plantar foot ulcers than removable ones.
Plantar ulcer recurrence

There are very few large cohort studies about the risk of new foot ulcers following healing of a diabetic foot ulcer, particularly after healing of a plantar forefoot ulcer. In available reports, rates of new foot ulceration following healing of a foot ulcer of various aetiologies in subjects with diabetes vary widely, from 8% in a study on percutaneous Achilles tendon lengthening in 52 patients to 70% in a study of all types of diabetic foot ulcers. Bus et al found evidence to support the claim that therapeutic footwear worn by the patient can prevent foot ulcer recurrence, while there is not enough evidence regarding the efficacy of surgical off-loading to prevent and heal plantar forefoot ulcers. There is no consensus regarding the terminology of foot ulcers appearing after an initial foot ulcer has healed. In the literature these foot ulcers are termed recurrent ulcer, reulceration, new ulcer, and transfer ulcer. Often the term ulcer recurrence is used without any definition. To be able to compare treatment strategies and to identify risk factors and prevent new foot ulcers, there is a need for more uniform definitions of new foot ulcers.

Heel ulcer

Prevalence, incidence and aetiology

In the EURODIALE study heel ulcers were reported as 10% of all diabetic foot ulcers, and Gershater et al found heel ulcers to be 15% of diabetic foot ulcers. Most studies with regard to ulcers located in the heel in patients with diabetes have small numbers or a selected category of patients. An ulcer located to the heel often has decubitus origin, but it may also be caused by repetitive trauma and mechanical stress.

Treatment

The main aim of treatment of a diabetic heel ulcer is to heal the ulcer, to avoid major amputation as well as new ulcer development. The basis for treatment of heel ulcers is the same as for all diabetic foot ulcers, and is described in Table 1.
Off-loading

Irremovable off-loading devices have been shown to be effective in healing plantar foot ulcers\(^79\) and off-loading is thought to be an important part of the treatment strategy in heel ulcers although there are no published studies on heel ulcers. Jeffcoate and colleagues\(^114\) have published a study protocol for investigating a removable device to off-load and heal heel ulcers. As yet there are no published results available on PubMed.

Surgical treatment

As in all other ulcer localizations in the diabetic foot, the most important treatment for control of a deep infection of heel ulcers is drainage and radical debridement of all infected, non-viable tissue.\(^115\) Other surgical procedures, such as partial calcanectomy\(^116\), distal bypass surgery and partial calcanectomy combined\(^108\), and free flap transfer and revascularization combined\(^115,117\), have been described as improving the healing of heel ulcers. There are no large studies evaluating different surgical procedures to improve the healing of diabetic heel ulcers. Surgical procedures were not specifically evaluated in the present thesis and thus no detailed description of these procedures is given.

Complications and outcome

Avoiding major amputation is the main goal in treating a heel ulcer. However, studies focusing specifically on heel ulcers in patients with diabetes are scarce in the literature. In sixteen studies on heel ulcers\(^65,107-113,115-122\), seven include a mixture of diabetic and non-diabetic subjects\(^107,110,112,118-121\), Table 3. The remaining nine studies on diabetic patients with heel ulcers comprise in total 508 patients. The median age spans from 53 to 73 years and reported healing rates vary from 51 to 95% .\(^65,108,109,111,113,115-117,122\)
Table 3. Overview of studies of heel ulcers and factors related to outcome

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Number of patients</th>
<th>Age</th>
<th>Patient selection</th>
<th>Definition of healing</th>
<th>Healing rate</th>
<th>Healing time</th>
<th>Follow-up</th>
<th>Factors related to outcome</th>
<th>Mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baumhauer et al 1998⁵⁵</td>
<td>8</td>
<td>52 (33-71)</td>
<td>Diabetes + non diabetes</td>
<td>No</td>
<td>88%</td>
<td>Not reported</td>
<td>27 (6-57) months</td>
<td>Not reported</td>
<td>25%</td>
<td>Primary closure in 5 cases. Retrospective review of total calcaneectomy. 1/8 amputation.</td>
</tr>
<tr>
<td>Baravarian et al 1999⁶⁶</td>
<td>12</td>
<td>65 (39-89)</td>
<td>Diabetes</td>
<td>Yes</td>
<td>83%</td>
<td>6 (2-20) weeks</td>
<td>13 months</td>
<td>Not reported</td>
<td>17%</td>
<td>Long surgical description. No amputation during follow-up.</td>
</tr>
<tr>
<td>Treiman et al 2000⁷⁷</td>
<td>91</td>
<td>67 (38-88)</td>
<td>Diabetes + non diabetes</td>
<td>No</td>
<td>73%</td>
<td>3.2 (1-6) months</td>
<td>21 (1-60) months</td>
<td>Normal renal function, palpable pedal pulse, patent posterior tibial artery had positive influence on outcome</td>
<td>15%</td>
<td>11% major amputation.</td>
</tr>
<tr>
<td>Bollinger et al 2002⁷⁷</td>
<td>22</td>
<td>57 (32-83)</td>
<td>Diabetes + non diabetes</td>
<td>No</td>
<td>100%</td>
<td>Not reported</td>
<td>27 (2-80) months</td>
<td>Not reported</td>
<td>18%</td>
<td>Primary wound closure. No major amputation.</td>
</tr>
<tr>
<td>Chipchase et al 2003⁸⁸</td>
<td>97 (157 heel ulcers)</td>
<td>69±13</td>
<td>Diabetes</td>
<td>Yes</td>
<td>61%</td>
<td>200 (24-1225) days</td>
<td>minimum 4 months</td>
<td>Larger ulcer, PVD showed worse outcome</td>
<td>20%</td>
<td>7% major amputation</td>
</tr>
<tr>
<td>Bakheit et al 2012⁹⁹</td>
<td>100</td>
<td>55±14</td>
<td>Diabetes</td>
<td>No</td>
<td>51%</td>
<td>180 (90-204) days</td>
<td>3 years</td>
<td>Shorter DM duration, adequate lower limb perfusion, superficial ulcer associated with better healing</td>
<td>8%</td>
<td>22% lower extremity amputation</td>
</tr>
<tr>
<td>Fraccalvieri et al 2012⁹⁹</td>
<td>7</td>
<td>74 (60-87)</td>
<td>Diabetes + non diabetes</td>
<td>No</td>
<td>100%</td>
<td>Not reported</td>
<td>22 (6-36) months</td>
<td>Not reported</td>
<td>14%</td>
<td>No amputation</td>
</tr>
<tr>
<td>Goudie et al 2012⁶⁶</td>
<td>21</td>
<td>61 (39-84)</td>
<td>Diabetes</td>
<td>No</td>
<td>95%</td>
<td>99 (79-133) days</td>
<td>24-48 months</td>
<td>Small sample, no conclusive factors found</td>
<td>5%</td>
<td>4/21 (19%) major amputation</td>
</tr>
<tr>
<td>Van Riet 2012⁹⁹</td>
<td>24</td>
<td>54 (20-81)</td>
<td>Diabetes + non diabetes</td>
<td>Yes</td>
<td>92%</td>
<td>129 (67-321) days</td>
<td>37 (3-91) months</td>
<td>Not reported</td>
<td>21%</td>
<td>4% major amputation (1/24)</td>
</tr>
<tr>
<td>Pickwell et al 2013⁸⁵</td>
<td>116 (cohort of &gt;1000 patients)</td>
<td>65±14</td>
<td>Diabetes</td>
<td>Yes</td>
<td>65%</td>
<td>237 (205-269) days</td>
<td>1 year</td>
<td>Longer duration of DM and ulcer, heart failure, PVD predicted time to healing</td>
<td>11%</td>
<td>Subgroup analysis of the EURODIALE cohort</td>
</tr>
<tr>
<td>Author/year</td>
<td>Number of patients</td>
<td>Age</td>
<td>Patient selection</td>
<td>Definition of healing</td>
<td>Healing rate</td>
<td>Healing time</td>
<td>Follow-up</td>
<td>Factors related to outcome</td>
<td>Mortality</td>
<td>Comments</td>
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<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Walsh et al 2013&lt;sup&gt;13&lt;/sup&gt;</td>
<td>10</td>
<td>64 (50-83) (DM) 77 (50-87) (non DM)</td>
<td>Diabetes + non diabetes</td>
<td>Yes</td>
<td>8/10 (5/7 in DM patients)</td>
<td>64 days (mean)</td>
<td>3 years</td>
<td>Not reported</td>
<td>0%</td>
<td>Case series of efficacy of calcanectomy. Small patient sample.</td>
</tr>
<tr>
<td>Shojaiefard et al 2013&lt;sup&gt;11&lt;/sup&gt;</td>
<td>37</td>
<td>62 ±14</td>
<td>Diabetes</td>
<td>No</td>
<td>89%</td>
<td>6 (4-7) months</td>
<td>Minimum 1 year</td>
<td>Not reported</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Oliver et al 2015&lt;sup&gt;12&lt;/sup&gt;</td>
<td>42</td>
<td>61±16.6 64±16</td>
<td>Diabetes + non diabetes</td>
<td>No</td>
<td>Not reported</td>
<td>Not reported</td>
<td>41±26 months</td>
<td>Not reported</td>
<td>12%</td>
<td>Study on partial calcanectomy for heel ulcers. Question is whether resection of more or less than 50% of calcaneus has an influence on outcome. It does not. 29% major amputation.</td>
</tr>
<tr>
<td>Yousuf et al 2015&lt;sup&gt;12&lt;/sup&gt;</td>
<td>50 (cohort 100 patients)</td>
<td>52.9±11</td>
<td>Diabetes</td>
<td>Yes</td>
<td>54%</td>
<td>20 weeks</td>
<td>Not specified</td>
<td>Not reported</td>
<td>0%</td>
<td>Study from Sudan. Compares outcome of forefoot ulcers vs heel ulcers.</td>
</tr>
<tr>
<td>Kallio et al 2015&lt;sup&gt;13&lt;/sup&gt;</td>
<td>63</td>
<td>56 (range 21)</td>
<td>Diabetes</td>
<td>Yes</td>
<td>84% 56% 33%</td>
<td>1991-2003</td>
<td>6 years</td>
<td>Smoking, heel ulcer, nephropathy, ulcer diameter &gt;10 cm associated with increased amputation risk</td>
<td>3% (30 day mortality)</td>
<td>Studies free flap transfer for heel ulcers. Amputation rate 11% (30 day amp rate). 30% major amputation during follow-up.</td>
</tr>
<tr>
<td>Lin et al 2016&lt;sup&gt;16&lt;/sup&gt;</td>
<td>12</td>
<td>73 (65-79)</td>
<td>Diabetes</td>
<td>No</td>
<td>75%</td>
<td>Not reported</td>
<td>2 weeks to 3 years</td>
<td>Not reported</td>
<td>8%</td>
<td>Included patients with near total occlusive PVD. Primary wound closure in all cases.</td>
</tr>
<tr>
<td>Örneholm et al 2016&lt;sup&gt;10&lt;/sup&gt;</td>
<td>768</td>
<td>73 (17-98)</td>
<td>Diabetes</td>
<td>Yes</td>
<td>66%</td>
<td>17 (1-416) weeks</td>
<td>Until healing or death</td>
<td>Vascular surgery, nephropathy, oedema, creatinine &lt;91 µmol/L</td>
<td>25%</td>
<td>12% major amputation</td>
</tr>
</tbody>
</table>
Chipchase et al were the first to describe a large number of diabetic patients with heel ulcers.\textsuperscript{111} They found a healing rate of 61\%. In studies where healing time is reported the healing time was 6–33 weeks.\textsuperscript{65,108,109,111,113,122}

In available reports on heel ulcers, in mixed cohorts of diabetic and non-diabetic subjects, the major amputation rate is reported to be between 0\% and 30\%.\textsuperscript{107-113,115,117,121,122} In more than half of these studies there are less than 50 study participants.

For heel ulcers in diabetic patients reports of mortality range from 0\% to 20\%.\textsuperscript{65,108,109,111,113,115-117,122}

**Factors related to healing**

Due to the small number of studies on diabetic patients with heel ulcers it is not easy to find definitive evidence of factors related to outcome of heel ulcers, Table 3. A study of 91 diabetic and non-diabetic patients showed that normal renal function, a palpable pedal pulse, and adequate perfusion to the foot had a positive influence on outcome.\textsuperscript{112} Chipchase and colleagues, in a study on 97 diabetic patients, showed that a larger ulcer and the presence of PVD led to worse outcome.\textsuperscript{111} Bakheit and colleagues, in a study on 100 diabetic patients, showed that shorter diabetes duration, adequate lower limb perfusion, and a superficial ulcer were factors associated with better healing.\textsuperscript{113} In a study on a subgroup from the EURODIALE study, Pickwell and colleagues showed that longer duration of diabetes and ulcer, heart failure, and PVD predicted time to healing.\textsuperscript{65} Yosuf and colleagues, in a study comprising 50 heel ulcers, showed that a larger ulcer had a longer healing time.\textsuperscript{122} Kallio and colleagues, in a study on 63 diabetic patients with free flap transfer for heel ulcer, showed that smoking, nephropathy, and ulcer diameter >10 cm were factors associated with increased risk of major amputation.\textsuperscript{117}
Lower limb amputations

Prevalence and incidence

The prevalence of amputation in patients with diabetes varies globally (1/1,000 inhabitants in Madrid and Japan to up to 20/1,000 in some Indian tribes in North America).123,124

For many years the incidence of minor amputation was unknown and little was known about the outcome.125,126 In recent years several studies have described the incidence and/or prevalence of minor amputations.55,127-130 Both Larsson and Krishnan described a fall in incidence of major amputations, but described an increase in minor amputations.127,128 Spanish national data show a decrease in the incidence of both minor and major amputations in patients with diabetes.129 Ahmad found that the prevalence of major amputations in diabetics in England 2003–2013 was reduced, whereas minor amputations increased.55 Wang et al described a decrease in both major and minor amputations between the years 2004 and 2013 although minor amputations increased during the last two years of the period.130

Indications

The most common indications for amputation described in the literature are gangrene, infection, and a non-healing ulcer.1,86,131-147 Although frequently reported as such, a non-healing ulcer should not necessarily be considered an indication for amputation since the duration of an ulcer is not an unfavourable factor with regard to amputation.42

The immediate objective of a minor amputation is often to control infection and halt the progression of gangrene, thereby minimizing the risk of major amputation and thus optimizing ambulatory function. Infection is often present when a minor amputation becomes necessary in patients with diabetes and the blood supply to a smaller or larger extent compromised. This may often require open treatment in order to preserve all viable tissue, and this means long healing times.

There is no randomized controlled study regarding amputation level selection in diabetic foot ulcer. The basic consideration is to choose the lowest amputation level where healing is deemed possible. However, sometimes functional aspect may modify this, e.g. in the presence of a marked contracture of the knee, which can make a knee disarticulation more favourable than a transtibial amputation. The main objectives for major amputation are to relieve pain, to restore ambulation
and/or to save the patient’s life. However, non-ambulation and mortality rate after a major amputation in diabetes are high since many diabetic patients are older and many have extensive co-morbidity. Walking with a prosthesis requires more energy than walking on an intact limb. A major amputation therefore often results in non-ambulation. To improve ambulation is the main reason why it is important to try to avoid a major amputation in patients with diabetic foot ulcers.

**Complications and outcome**

Reported healing rates at minor amputation levels, in studies with diabetes patients and mixed cohorts of diabetes and non-diabetes patients, range from 12% to 100%. These variations might be explained by differences in patient selection, definitions, included patients/procedures, and length of follow-up. The long healing times after a minor amputation have sometimes been used as an argument for performing a primary major amputation. However, the high complication rate after a major amputation and the long-term costs of a major amputation by far exceed the negative consequences of a minor amputation. Furthermore, minor amputation was not associated with a negative impact on health-related quality of life (HRQoL) in patients with a diabetic foot ulcer and it may therefore not be considered treatment failure in terms of HRQoL, but rather a viable treatment option.

Re-amputation was defined as an amputation at the same or at a more proximal level after a primary amputation on the same extremity that had not yet healed. Reported re-amputation rates for minor amputations in patients with or without diabetes vary from 8% to 60%. These variations might also be explained by differences in patient selection, definitions, included patients/procedures, and length of follow-up.

**Factors related to healing**

There is limited information from larger studies regarding factors related to outcome of minor amputation, in patients with diabetes specifically (Table 4). Peripheral vascular disease, end-stage renal disease, transmetatarsal amputation, unsuccessful revascularization, depth of ulcer, infection, renal insufficiency and male sex, less than 100% attendance, poor glycaemic control, hypertension, insulin-dependent diabetes, and gangrene have all been suggested as leading to less healing and increased risk of major amputation. Hosch et al found that presence of ischaemia and patient less likely to
have been prescribed shoes/insoles were risk factors for re-amputation to major amputation.\textsuperscript{154} Palpable distal pulses, osteomyelitis, infection limited to the digit, and higher toe pressure have been suggested as factors having a positive impact on outcome after a minor amputation.\textsuperscript{152,155,157}
### Table 4.
Overview of studies on minor amputation and factors related to outcome

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Number of patients</th>
<th>Patient selection</th>
<th>Outcome</th>
<th>Amputation level</th>
<th>Follow-up</th>
<th>Factors related to outcome</th>
<th>Age</th>
<th>Re-amputation rate</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sizer et al 1972</td>
<td>557</td>
<td>Diabetes</td>
<td>94% healing rate (patients with emergency surgery excluded)</td>
<td>Minor only</td>
<td>1960-1971</td>
<td>Not reported</td>
<td>56.8</td>
<td>Not reported</td>
<td>Specifically. Overall limb salvage 95%. Chart review of digital amputations during a 12-year period.</td>
</tr>
<tr>
<td>Boeckstyns et al 1984</td>
<td>63</td>
<td>Diabetes + non diabetes</td>
<td>17/63 primary wound healing</td>
<td>Minor only (transmetatarsal + transartsal)</td>
<td>1976-1981</td>
<td>Ankle blood pressure &lt;60 mmHg related to failure.</td>
<td>70 (41-91)</td>
<td>25/63 major re-amputation within 1 year</td>
<td></td>
</tr>
<tr>
<td>Pinczur et al 1984</td>
<td>25</td>
<td>Diabetes + non diabetes</td>
<td>12 % healed in DM patients.</td>
<td>Minor only (ray resections)</td>
<td>2 years</td>
<td>Not reported</td>
<td>All patients &gt; 50 years old</td>
<td>9/17 DM patients had proximal re-amputation</td>
<td></td>
</tr>
<tr>
<td>Turnbull et al 1988</td>
<td>68</td>
<td>Diabetes</td>
<td>69% healed</td>
<td>Minor only (partial foot amputations)</td>
<td>5 years</td>
<td>Patients with palpable distal pulses were more likely to heal.</td>
<td>Mean 69 (range 32-87)</td>
<td>30%</td>
<td>Mortality 7%</td>
</tr>
<tr>
<td>Hoeh et al 1997</td>
<td>35</td>
<td>Diabetes</td>
<td>37% healed after first surgery. 68.6 % healed at transmetatarsal level</td>
<td>Minor (transmetatarsal)</td>
<td>15.1 ±10.1 months</td>
<td>Ischemia, patient less likely to have been prescribed custom shoes/insoles, and low albumin level at admission were factors related to higher risk for re-amputation to major amputation.</td>
<td>54.7 ± 8.3</td>
<td>63% revision and re-amputation</td>
<td>28% required major amputation</td>
</tr>
<tr>
<td>Yeager et al 1999</td>
<td>162</td>
<td>Diabetes + non diabetes</td>
<td>14% did not heal foot amputation.</td>
<td>Minor</td>
<td>25 months</td>
<td>Unsuccessful revascularization predicted non-healing and major amputation</td>
<td>Mean age 65 (range 29-90)</td>
<td>Major amputation rate 18.5% (23 pat non healing + 7 pat during follow-up)</td>
<td>Patients not expected to heal were excluded from the study. Mortality at 4 years 51%.</td>
</tr>
<tr>
<td>Nebler et al 1999</td>
<td>92</td>
<td>Diabetes</td>
<td>39% healed primary amputation. 25% did not heal.</td>
<td>Minor (digit amputations only)</td>
<td>21 months</td>
<td>Osteomyelitis and infection limited to the digit were factors associated with higher probability for healing after amputation.</td>
<td>53±14</td>
<td>Not reported</td>
<td>Retrospective review of patient records. Mortality 35% during follow-up.</td>
</tr>
<tr>
<td>Thomas et al 2001</td>
<td>41</td>
<td>Diabetes + non diabetes</td>
<td>11/29 diabetic patients healed</td>
<td>Minor only (transmetatarsal only)</td>
<td>1991-1998</td>
<td>Not reported</td>
<td>Mean age 71 (range 40-91)</td>
<td>15/41 required re-amputation to BKA (14) or Syme (1)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Study Period</td>
<td>Diabetes Type</td>
<td>Amputation Type</td>
<td>Amputation Rate</td>
<td>Healing Rate</td>
<td>Follow-up</td>
<td>Ulcer Recurrence</td>
<td>Amputation Rate</td>
<td>Follow-up Details</td>
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<tr>
<td>Van Damme et al 2001</td>
<td>1993-1998</td>
<td>Diabetes</td>
<td>Minor and major</td>
<td>Not reported</td>
<td>66 (mean age)</td>
<td>16% re-amputation</td>
<td>Neuro-ischaemic midfoot amputation: 28% re-amputation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalla Paola et al 2003</td>
<td>1993-1998</td>
<td>Diabetes</td>
<td>Neuropathic toe amputation: 14% re-amputation</td>
<td>66±9</td>
<td>17% ulcer recurrence during follow-up</td>
<td>8% re-amputation (no major amputation).</td>
<td></td>
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</tr>
<tr>
<td>Sheahan et al 2005</td>
<td>1993-1998</td>
<td>Diabetes</td>
<td>Limb salvage</td>
<td>Minor only</td>
<td>47.3 months</td>
<td>ESRD, transmetatarsal amputation (initial amputation), and subsequent revascularization were factors related to limb loss.</td>
<td>Not reported</td>
<td>Mortality 16% at 1 year</td>
<td></td>
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<tr>
<td>Berceli et al 2006</td>
<td>1993-1998</td>
<td>Diabetes</td>
<td>Minor only</td>
<td>2 years</td>
<td>Renal insufficiency</td>
<td>Not reported</td>
<td>25%</td>
<td></td>
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<tr>
<td>Uzzaman et al 2011</td>
<td>2000-2001</td>
<td>Diabetes</td>
<td>Not reported</td>
<td>Minor only</td>
<td>Not reported</td>
<td>75±12.9 (DM) 80.5±14.8 (non DM)</td>
<td>Retrospective 5 year mortality 27%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Battum et al 2011</td>
<td>2000-2001</td>
<td>Diabetes</td>
<td>18% of EURODIALE cohort underwent minor amputation. 75% healing rate in minor amputations.</td>
<td>Minor</td>
<td>1 year</td>
<td>Depth of ulcer, PVD, infection, and male sex predicted minor amputation.</td>
<td>65.2±11.6</td>
<td>Analysis of subgroup in the EURODIALE cohort. The rate of minor amputations differed between centres (2.4-34%). One explanation is the difference in disease severity at presentation.</td>
<td></td>
</tr>
<tr>
<td>Author/year</td>
<td>Number of patients</td>
<td>Patient selection</td>
<td>Outcome</td>
<td>Amputation level</td>
<td>Follow-up</td>
<td>Factors related to outcome</td>
<td>Age</td>
<td>Re-amputation rate</td>
<td>Comments</td>
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<tr>
<td>Kono et al 2012&lt;sup&gt;260&lt;/sup&gt;</td>
<td>116</td>
<td>Diabetes + non diabetes</td>
<td>Not reported</td>
<td>Minor only</td>
<td>3 years</td>
<td>Insulin dependent diabetes and gangrene were risk factors for re-amputation</td>
<td>66.8±11</td>
<td>57/116</td>
<td>Retrospective (single hospital, veterans) 5 year mortality 46%</td>
</tr>
<tr>
<td>Borkosky et al 2013&lt;sup&gt;256&lt;/sup&gt;</td>
<td>59</td>
<td>Diabetes</td>
<td>100%</td>
<td>Minor only</td>
<td>33.8 months</td>
<td>Not reported</td>
<td>63 (39-97)</td>
<td>42.4% new amputations on same site during study period</td>
<td>Retrospective chart evaluation. Mortality 47.5% at final chart review.</td>
</tr>
<tr>
<td>Caruana et al 2015&lt;sup&gt;277&lt;/sup&gt;</td>
<td>50</td>
<td>Diabetes</td>
<td>28/50 healed/IS healing (at 6 weeks follow-up)</td>
<td>Minor only</td>
<td>6 weeks</td>
<td>Toe pressure was higher in patients healed/healing</td>
<td>67.4 (mean age)</td>
<td>Not reported</td>
<td>Focus of study is on whether ankle brachial pressure index or toe pressure or ankle waveforms are better to predict healing after minor amputation.</td>
</tr>
<tr>
<td>Matsuzaki et al 2015&lt;sup&gt;394&lt;/sup&gt;</td>
<td>66</td>
<td>Diabetes (all patients have nephropathy, PTA and amputation)</td>
<td>Main outcome mortality, healing rate not reported</td>
<td>56 minor 10 major</td>
<td>Not reported</td>
<td>Not reported</td>
<td>68±11</td>
<td>Not reported</td>
<td>2 year mortality 41% (minor amp) 60% (major amp)</td>
</tr>
<tr>
<td>Wicssman et al 2015&lt;sup&gt;396&lt;/sup&gt;</td>
<td>565</td>
<td>Diabetes</td>
<td>Not reported</td>
<td>All amputation levels (minor and major, both above and below knee)</td>
<td>35 months</td>
<td>Not reported</td>
<td>68±12</td>
<td>Not reported</td>
<td>Primary study focus was one-year mortality, 1-year mortality 35.8% (all patients regardless of amputation level)</td>
</tr>
<tr>
<td>Beamey et al 2016&lt;sup&gt;406&lt;/sup&gt;</td>
<td>165</td>
<td>Diabetes</td>
<td>33/165 (20%) underwent 34 amputations (17 major, 17 minor)</td>
<td>Minor and major</td>
<td>Minimum 1 year</td>
<td>Factors related to amputation: less than 100% attendance, poor glycemic control, hypertension. Previous vascular surgery and low comorbidity associated with lower amputation risk</td>
<td>&lt;50 y: 28 50-54 y: 14 55-64 y: 29 65-74 y: 46 ≥75 y: 49</td>
<td>Not reported</td>
<td>Retrospective Case analysis of patients referred to diabetic foot clinic</td>
</tr>
<tr>
<td>Cha et al 2016&lt;sup&gt;416&lt;/sup&gt;</td>
<td>245</td>
<td>Diabetes</td>
<td>82.4% healed</td>
<td>Minor</td>
<td>5 years</td>
<td>Not reported</td>
<td>69±9</td>
<td>17.5% (1 year) 22.3% (3 year) 47.1% (5 year)</td>
<td>Study aim was to evaluate re-ulceration, re-amputation and mortality. Mortality: 5.8% (1 year) 15.1% (3 year) 32.7% (5 year)</td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>Treatment</td>
<td>Follow-up</td>
<td>Healing Rate</td>
<td>Amputation Rate</td>
<td>Major Re-amputation</td>
<td>Minor Re-amputation</td>
<td>Mortality</td>
<td></td>
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<tr>
<td>Malysar et al 2016&lt;sup&gt;193&lt;/sup&gt;</td>
<td>40335</td>
<td>DFS 17.3% PAD + DM 21.5% PAD 61.2%</td>
<td>Not reported</td>
<td>Minor and major</td>
<td>Maximum 4 years</td>
<td>70±12 DFS 72±10 PAD + DM 71±12 PAD</td>
<td>Major re-amputation: 7% (DFS), 12% (PAD + DM), 9.5% (PAD); Minor re-amputation: 19% (DFS), 12% (PAD + DM), 12% (PAD).</td>
<td>Study based on German register of health insurance. 4 year mortality: 30% (DFS) 39% (PAD + DM) 52% (PAD)</td>
<td></td>
</tr>
<tr>
<td>Mandleffino et al 2016&lt;sup&gt;165&lt;/sup&gt;</td>
<td>218</td>
<td>Diabetes + non diabetes 64% healed</td>
<td>Transmetatarsal</td>
<td>2008-2013</td>
<td>Not reported</td>
<td>Mean 67 years</td>
<td>33% re-amputation</td>
<td>1 year mortality 8% Aim of study was to define role and timing of vascular surgery</td>
<td></td>
</tr>
<tr>
<td>Wilbek et al 2016&lt;sup&gt;197&lt;/sup&gt;</td>
<td>777</td>
<td>Diabetes</td>
<td>Not reported</td>
<td>1231 minor amputations</td>
<td>1996-2013</td>
<td>Not reported</td>
<td>56 (27-83) DM type 1 men 52 (23-93) DM type 1 women 66 (35-91) DM type 2 men 71 (35-97) DM type 2 women</td>
<td>Not reported</td>
<td>Retrospective 5 year mortality: Type 1 DM 43%, Type 2 DM 52%</td>
</tr>
</tbody>
</table>
Aims of the studies

The overall aim of this thesis was to study certain aspects of the diabetic foot in a large cohort of consecutively presenting patients, and to identify factors related to outcome and risk of amputation.

Specific aims

Paper I  To analyse the characteristics and outcome of minor amputations in patients with diabetes and severe foot ulcers threatening the survival of the foot

Paper II To analyse the characteristics and outcome of patients with diabetes and a plantar forefoot ulcer

Paper III To analyse the characteristics and outcome of patients with diabetes and a heel ulcer

Paper IV To evaluate the outcome in a two-year follow-up study of patients with diabetes and a healed plantar forefoot ulcer with regard to development, characteristics, and outcome of recurrent and other new foot ulcers
Patients

Paper I

Paper I is a cohort study of consecutively presenting patients with diabetes, residing in the Lund/Orup area, who had a minor amputation between January 1, 1982 and December 31, 2006. During this time 309 patients underwent 410 primary minor amputations on 361 extremities (Figure 2). The median age was 73 (32–93) years and 64% of the patients were male. For a detailed description of clinical characteristics, see Paper I.

Paper II

Paper II is a cohort study of 3,684 consecutively presenting patients with diabetes and a plantar forefoot ulcer. Patients were included from January 1, 1983 to December 31, 2012. Inclusion criteria were diabetes and a plantar forefoot ulcer located in the distal metatarsal area or under the great toe. Patients with multiple ulcers were not included. During this time period 701 patients (median age 67 [range 22–95]) with a plantar forefoot ulcer were included (Figure 2). For a detailed description of clinical characteristics, see Paper II.

Paper III

Paper III is a cohort study of 4,273 consecutively presenting patients with diabetes and a heel ulcer. Patients were included from January 1, 1983 to December 31, 2013. Inclusion criteria were diabetes and a heel ulcer. Patients with multiple ulcers were not included. During this time period 768 patients (median age 73 [range 17–98]) with a heel ulcer were included (Figure 2). For a detailed description of clinical characteristics, see Paper III.
Paper IV

Of the 701 patients with a plantar forefoot ulcer in Paper II, 385 healed primarily, 173 healed after major debridement, 42 healed after minor amputation, and 18 healed after major amputation. One patient who healed after a major amputation had had a previous contralateral major amputation and was excluded from the study. Thus a total of 617 patients were available for analysis (Figure 2). Each patient is represented by the first recurrent ulcer or, if no recurrent ulcer occurred, by the first other new ulcer.

The outcome within two years following a healed plantar forefoot ulcer was investigated with regard to the presence or absence of a new ulcer as well as mortality and outcome of new ulcers. For a detailed description of clinical characteristics, see Paper IV.

The consort diagram for the studies is shown in Figure 2.
Figure 2. Consort diagram

1 Database of diabetic foot ulcers
2 Time period 1983-2012
3 Time period 1983-2013
4 Time period 1982-2006
5 Database of amputations
Method

Setting

The multidisciplinary diabetic foot care centre where these studies are performed is located at a university hospital with a primary care catchment area of approximately 700,000 people at the end of the studies. The centre is the single provider of specialized diabetic foot care in this area, from the year 2000 operating in two geographic locations, and is also a tertiary referral centre for surrounding regions. The management protocol at the diabetic foot clinic is based on a multidisciplinary approach and has been previously described. Briefly, it consists of inpatient and outpatient visits, regular podiatric care, individually adjusted footwear, regular ulcer dressings and access to specialists in vascular surgery, orthopaedics, and infectious diseases when needed.

When presenting with a foot ulcer the patients are seen by the multidisciplinary foot care team, consisting of a diabetologist, an orthopaedic surgeon, a diabetes specialist nurse, an orthotist and a chiropodist. The team works in close cooperation with vascular surgeons, and also has access to specialists in infectious diseases. Patients were included consecutively. At inclusion all patients were questioned for medical history and examined, and the findings recorded according to a pre-set protocol. The lesions were classified according to Wagner. The patients are followed by the team until final outcome (healing with or without amputation or deceased unhealed). General, extremity and ulcer related characteristics were recorded. Systolic toe and ankle blood pressure measurements were obtained using strain gauge and Doppler techniques as previously described.

Treatment

The basic management at the diabetic foot clinic is in accordance with a multidisciplinary approach, as described above and in Table 1. Treatment was performed in close cooperation with primary care and home care.
Non-surgical treatment
Individually adjusted off-loading equipment (total contact cast, individually fitted shoes and/or insoles, orthosis, and/or half shoes) was offered to all patients. Type, duration, and utilization of off-loading were not recorded.

Infection, metabolic control, peripheral vascular disease, oedema, and co-morbidity were managed in close cooperation with the specialists concerned. When clinical signs of infection were present, oral antibiotics were given. Patients with deep abscess or osteomyelitis were hospitalized and intravenous antibiotics were administered. Analgesia was used related to cause and intensity of pain. Hospitalization was used in case of need for acute surgical treatment, parenteral antibiotics, or when there was a deterioration of infection despite non-operative treatment. The treatment chosen in each case was based on written guidelines at our institution (in cooperation with the department of infectious diseases) including antibiotic treatment, and changed when decided necessary by the responsible physician.

Topical treatment was prescribed by the multidisciplinary foot care team according to the individual wound bed condition. Dressing changes were supervised by a registered nurse in primary health care and/or home nursing services. Telephone support during daytime was provided by the team.

Surgical treatment
Minor debridement was performed as required at the outpatient clinic by a chiropodist without anaesthesia. Major debridement and amputation were performed at the discretion of, and by, an orthopaedic surgeon. No Achilles tendon tenotomy or any kind of osteotomy was performed. A non-healing ulcer was not per se considered an indication for amputation. Vascular surgery (including endovascular and open methods) was performed at the discretion of, and by, a vascular surgeon. Resection of less than the distal phalanx was not considered as an amputation.

Statistical analysis
Values are given as numbers or median (range) unless otherwise stated. Statistical analysis (chi2) was performed for those who healed primarily versus those who healed after major debridement or amputation. A stepwise multiple logistic regression model with backward selection, including variables with p<0.1, was performed to determine factors related to outcome. Statistical analysis in Paper I was performed using NCSS 2004 (NCSS statistical software, Kaysville, Utah,
USA). All statistical analysis in Papers II–IV was performed using IBM SPSS Statistics 21 (SPSS, Chicago, Ill, USA).
Results

Paper I

In 309 patients undergoing 410 primary minor amputations, the median age at inclusion was 73 (range 32–93) years and 64% of the patients were male. With regard to patient-related data, results are given relating to the first amputation in each patient (n=309) after entering the study. With regard to amputation-related data, results are given relating to all primary amputations (n=410) in this study.

Sixty-four percent of the minor amputations (261/410) healed at a level below the ankle, and 80% (329/410) healed at the primary or at a more proximal level. In surviving patients the healing rate below the ankle was 79% (261/330). The total number of major amputations before healing or death was 84 (20%).

Patients younger than the median age of 73 years displayed a higher healing rate below the ankle (78%) compared to patients at or above the median age (50%), \( p < 0.001 \). Healing rate was related to the severity of tissue involvement at inclusion. A higher healing rate below the ankle (75%) was seen in amputations with an ulcer classified as Wagner grade 0–3 as compared to those with Wagner grades 4–5 (54%; \( p < 0.001 \)).

In 81% of minor amputations there was presence of SVPD and/or general vascular disease. If SPVD was present there was a lower healing rate below the ankle (56%) than if SPVD was not present (75%), \( p < 0.001 \). Minor amputations in patients who had vascular surgery had a lower healing rate below the ankle compared to amputations in those who had not (51% and 70%, respectively) \( p < 0.001 \).

Of primary minor amputations, 150/410 (37%) subsequently required one or more than one re-amputation, either at the same or at a more proximal level. One third of these (49/150) healed at a level below the ankle. Seventy-nine percent (118/150) healed after re-amputation irrespective of level.

Median healing time from primary amputation to wound healing was 26 (range 2–250) weeks for those amputations that healed below the ankle, and 15 (range 4–190) weeks for those amputations that healed above the ankle. The longest healing time (median 42 weeks) was seen for partial forefoot amputations not including
the first ray. Toe amputations had the shortest healing time in this study, 18 (range 2–200) weeks.

In a multivariate analysis including the first minor amputation in each patient (n=309) vascular intervention (before and after amputation) and the presence of intractable pain (as one indication for amputation) were found to be associated with a lower healing rate below the ankle. A low Wagner grade and a low age at amputation were found to be associated with a higher healing rate below the ankle.

In a multivariate analysis including all minor amputations in all patients (n=410), the presence of CLI or SPVD, and vascular intervention (before or after amputation) were found to be associated with a lower healing rate below the ankle. A low Wagner grade was found to be associated with a higher healing rate below the ankle.

In summary, despite long healing time, it is possible for minor amputations to heal in a large proportion of patients with diabetes, although patients are elderly, with extensive co-morbidity and with severe foot ulcers including infection and/or gangrene in many cases.

**Paper II**

In 701 patients with a plantar forefoot ulcer, the median age at inclusion was 67 (range 22–95) years, the median duration of diabetes at inclusion was 13 (range 0–62) years, and 66% of the patients were male. SPVD was present in 26% of patients.

Seventy-nine per cent (558/701) of patients achieved healing; of these 385 healed without and 173 healed after major debridement. Nine per cent healed after an amputation either below or above the ankle, and 12% died unhealed. Progress of Wagner grade was seen in 20% of patients.

Median healing time from inclusion was 17 (range 1–252) weeks.

In multivariate analysis Wagner grades 1 or 2 at inclusion (p<0.0001), no progress in Wagner grade (p<0.0001), independent living (p=0.02), and age at inclusion ≥67 years (p=0.02) were factors found to be related to healing without major debridement or amputation.

In summary, most of surviving patients with a plantar forefoot ulcer heal without an amputation within an average 4 months but frequently after a major debridement. One out of four of these patients have signs of SVPD, although in the literature this is often described as purely neuropathic.
Paper III

In 768 patients with a heel ulcer, the median age at inclusion was 73 (range 17–98) years, the median duration of diabetes at inclusion was 17 (range 0–72) years and 56% of the patients were male. SPVD was present in 31% of patients.

Sixty-six per cent of patients (504/768) achieved healing without (n=447) or with (n=57) major debridement, nine per cent (72/768) healed after an amputation, and 25% (192/768) died unhealed. Primary healing in surviving patients was 78% (447/576). Median healing time from inclusion was 17 (range 1–416) weeks.

In a multivariate analysis vascular surgery (p<0.0001), nephropathy (p=0.007), and oedema (p=0.007) were factors related to a lower probability of healing without major debridement or amputation, and a creatinine level below 91 µmol/L (p=0.03) was found to be related to a higher probability of healing without major debridement or amputation.

In summary, despite long healing time, two-thirds of patients with diabetes and a heel ulcer healed without amputation treated in a multidisciplinary setting.

Paper IV

Out of 617 patients in paper II who had healed a plantar forefoot ulcer, 250 (41%) did not develop any new ulcer, 262 (42%) developed a new ulcer, 87 (14%) died and 18 (3%) were lost to follow-up. Fifty-one patients (8%) developed a recurrent ulcer. The remaining 211 patients developed ulcers only at other sites than the previously healed ulcer (112 on the same foot and 99 on the contralateral foot). Of the 87 patients who died within two years, 57 had not developed any new ulcer, no one had a recurrent ulcer, and 30 patients had developed other new ulcers.

In those 262 patients who developed a new ulcer within 24 months, primary healing was achieved in 137 (52%) and the ulcer healed after major debridement in 51 patients (19%). Healing was achieved after minor amputation in 10 patients (4%), and after major amputation in 12 patients (5%). Thirteen patients (5%) died with the ulcer still unhealed, 24 patients (9%) had ongoing treatment at last follow-up and 15 (6%) were lost to follow-up.

Ninety-two patients developed more than one new ulcer during the two-year follow-up. The total number of recurrent or other new ulcers was 384.

There were no differences between men and women, or between patients with or without SPVD, regarding development of new ulcers. Major debridement or
amputation prior to healing of index ulcer did not affect the risk of developing new ulcers, nor did the location of the index ulcer.

In summary, patients with diabetes who have healed a plantar forefoot ulcer have a high risk of developing new ulcers irrespective of site and side. Few patients developed a recurrent ulcer on the same side and site. A concise definition of new ulcers is suggested, since there seems to be general confusion regarding definitions in the literature.
Discussion

Diabetes mellitus is increasing worldwide and is one of the most challenging healthcare dilemmas of the 21st century. Diabetes is associated with both micro- and macrovascular complications. These complications all contribute to an increased risk of foot ulcer and amputation. The St Vincent Declaration (1989) set a goal of a 50% reduction in amputations in patients with diabetes. A multidisciplinary team approach has been shown to be important to lower the incidence of major amputation in diabetic patients. In 2005, The Lancet had on its front cover “Every 30 seconds a lower limb is lost somewhere in the world as a consequence of diabetes”. Dr Andrew Boulton concluded that through research we have the power to help thousands of people with diabetic complications. The reduced rates of major amputations nationwide in diabetics in England, despite a rising prevalence of diabetes, suggest improvements in the process of diabetes care delivery. The overall aim of this thesis was to study certain aspects of the diabetic foot in a large cohort of consecutively presenting patients, and to identify factors related to outcome and risk of amputation.

Minor amputation

In patients with diabetes, the immediate objective of a minor amputation is often to control infection and halt the progression of gangrene, thereby minimizing the risk of major amputation and thus optimizing ambulatory function. Paper I is, to my knowledge, the first large population-based study of consecutively presenting patients with diabetes undergoing minor amputation. All patients are consecutively included and almost all followed to healing or death. Although the vast majority of patients had severe lesions that threatened the survival of the foot, two thirds of patients healed at a level below the ankle and thus had a retained limb for ambulation, but at the price of long healing times. During part of the same study period the number of major amputations in the same defined area decreased. This strongly indicates that minor amputations in diabetic patients with infections and/or gangrene, treated in a multidisciplinary setting, are worthwhile. The fact that over 400 amputations were included, and all but four followed until healing or death, further strengthens the value of this study.
Most studies/reports regarding the incidence of lower limb amputations are focused on major amputations. These studies tend to underestimate the total number of diabetes-related amputations performed. There is still some controversy concerning the benefit of a primary minor amputation versus primary major amputation (below knee).\textsuperscript{42,75} The objective of a minor amputation is often to control infection and halt the progression of gangrene, thereby minimizing the risk of major amputation and thus optimizing ambulatory function. Minor amputations are associated with higher re-amputation rate and as a consequence longer wound healing time. The advantage of primary major amputation is a lower re-amputation rate and shorter healing time. However, the energy expenditure of walking with a prosthesis, necessary for ambulation after a major amputation, is greater than that of walking with an intact limb.\textsuperscript{150} Since many patients are older and have extensive co-morbidity, retaining a limb for support is therefore important.

There is limited information in the literature describing indications for minor amputation. No randomized controlled studies on amputation versus non-amputation exist. The indications for amputation in patients with diabetes suggest the indications are often multifactorial, of which progressive gangrene and infection are most common, frequently in combination.\textsuperscript{1,126} Most studies regarding particularly minor amputation either do not mention indication or use the term at the discretion of the surgeon. In Paper I, multiple indications (more than one) for amputation were present in 52%. In the presence of pain and/or progressive gangrene there was a significantly lower healing rate below the ankle than if pain and/or progressive gangrene were not present. In contrast, if deep infection was present as one indication for amputation, more amputations healed below the ankle than if no deep infection was present. However, even in the presence of pain or progressive gangrene as one indication, healing below the ankle was seen in almost half of amputations. Thus, no indication excludes the possibility of healing below the ankle.

Table 4 above shows an overview of studies on minor amputations, including factors related to outcome and re-amputation rate. Many studies have a mixture of diabetic and non-diabetic patients, or a selection of specific amputations. There are various difficulties in comparing the results of Paper I with those of the literature, due to variations in definitions regarding patient selection, ulcer classification, indications, minor amputation, re-amputation, and healing. Sometimes there is even a lack of definitions.\textsuperscript{132-134,141-143,182,183}

In paper I, the healing rate below the ankle was 79% in surviving patients. Reported healing rates at minor amputation levels, in studies with diabetes patients and mixed cohorts of diabetes and non-diabetes patients, range from 12% to 100%.\textsuperscript{52,86,136,141,144,145,151-158} These variations might be explained by differences in
patient selection, definitions, included patients/procedures, and length of follow-up.

In paper I, SVPD and/or general vascular disease was present in 81%. If SPVD was present there was a lower healing rate below the ankle than if SPVD was not present. Despite various limitations SVPD seems to be a risk factor that needs to be evaluated, and if possible, treated in patients with minor amputations pending or recently performed, although no consensus exists as to which measure of PVD best can predict outcomes.\(^{60}\)

In paper I, more than one in three patients subsequently required one or more than one re-amputation, either at the same or at a more proximal level and 21% of the amputations had a re-amputation to a level above the ankle. The latter patients constitute the group where the primary treatment strategy failed. The rate of re-amputation when reported for various minor amputations, in patients with and without diabetes, varies between 8% and 63%.\(^{86,132,136-138,141,142,145,151-154,162,164,184,185}\) Comparison of re-amputation rates suffers from the same biases mentioned above. The aim for the future is to achieve even better identification of patients who will most likely heal below the ankle and those where a primary major amputation should be performed instead.

The long healing times and costs attributed to minor amputations has been mentioned as a reason to perform a major amputation instead. In paper I, the median healing time in patients undergoing primary amputation to wound healing varied between 18 and 42 weeks depending on primary minor amputation level. With regard to the long healing time in patients who underwent amputation, two circumstances should be pointed out. First, these do not reflect the time from amputation to healing, but from the time of arrival at the foot clinic to healing. Second, in most minor amputations the operation wound had to be left open for secondary healing. Assessing healing time, and comparing results in this regard, presents great difficulties. There is often a delay from onset of ulcer until it is seen by a healthcare practitioner, and then there is a further delay until the patient arrives at a specialized clinic. We count the healing time from the day the patient is seen at our clinic until the day the ulcer is healed. The time from surgical treatment (major debridement or amputation) to healing is not presented.

In 2016 Pickwell and colleagues\(^{159}\) published a report on the EURODIALE cohort regarding minor amputation and quality of life. This report showed that minor amputation did not reduce the quality of life in patients with diabetic foot ulcer. This further underlines the importance of using minor amputation whenever possible to avoid a major amputation. Furthermore, the functional outcome of a major amputation is worse and the cost of a major amputee by far exceeds the cost of a minor amputation.\(^{2,72}\)
In summary, the findings of paper I support the use of minor amputation in patients with diabetes and severe foot ulcers. The price to pay may be long healing times and the risk of repeated surgical interventions.

**Plantar forefoot ulcer**

In Paper II, studying consecutively presenting patients with diabetes and a plantar forefoot ulcer during a 30-year period, 80% healed without an amputation, 6% healed after minor amputation, 3% healed after major amputation, and 12% died unhealed. In mixed cohort studies regarding short-term outcome, primary healing rates of 64–85%, amputation rates of 8–23% (irrespective of level) and mortality rates of 10–20% have been described from centres of excellence. In randomized controlled trials of neuropathic diabetic foot ulcers (mostly plantar) healing rates over 12–20 weeks of 36–60% have been reported. In all papers in this thesis, the definition of healing was set at the start of the inclusion in 1983. The time of healing of the index ulcer was defined as the date when the wound was considered healed with macroscopically complete epithelialization, and healing had to be confirmed at a 6-month check-up. If the ulcer was still present at that time, the original assessment of healing was revised. Many studies in the literature do not have a definition of healing, and in those which do report a definition of healing, it is often reported as a single observation which makes comparisons uncertain.

Median healing time from inclusion in Paper II was 17 (range 1–252) weeks. The shortest healing time was seen in patients with healing without major debridement or amputation (median 13 weeks) and the longest for patients who healed after amputation (median 36 weeks). There are not many studies on healing time and since healing is not always defined, comparing results is not easy. Reported healing times range from 6 to 12 weeks indicating other selection of patients than in Paper II. Most data in the literature are from trials with less than 20 weeks follow-up, which means that many ulcers are not given enough time to heal.

When assessing healing time it is important to know from when the time is counted. Is the starting point when the patient says the ulcer first appeared, is it from the first visit to the diabetic foot centre or is it the time from surgical intervention? Assessing healing time, and comparing results in this regard, presents great difficulties. There is often a delay from onset of ulcer until it is seen by a health care practitioner, and then there is a further delay until the patient arrives at a specialized clinic. In the studies of this thesis, healing time is counted...
from the day the patient is seen at the centre until the day the ulcer is healed. The time from surgical treatment (major debridement or amputation) to healing is not presented.

Wagner grade and age at inclusion, and independent living were factors found to be related to healing without amputation in Paper II. Comparing these results with those in the literature is not easy since there is a lack of studies focusing solely on plantar forefoot ulcers. In the EURODIALE study, which has a mixed cohort of ulcer location, older age, male sex, larger ulcer size, heart failure, inability to stand or walk without help, ESRD, neuropathy and PVD were factors predicting failure to heal a diabetic foot ulcer.\textsuperscript{24} Patients exhibiting PVD had a worse healing rate, more major amputations and higher mortality than patients without PVD.\textsuperscript{24,29} In addition, if a patient with PVD also presented with infection of the ulcer, a worse healing rate was seen.\textsuperscript{24,29} Margolis and colleagues found that initial ulcer area, duration of ulcer and patient ethnicity were factors related to healing of neuropathic foot ulcers.\textsuperscript{87} Renal impairment and smoking have also been reported as predictors of failure to heal a diabetic foot ulcer.\textsuperscript{51} A recently published retrospective review of patients with diabetic foot ulcer admitted through emergency department showed that elevated CRP (C-reactive protein) at arrival indicated a higher risk of major amputation.\textsuperscript{187}

As regards factors related to outcome of diabetic foot ulcers, and plantar forefoot ulcers specifically, there is a lack of uniformity in the literature. Some general factors, for example the presence of neuropathy and PVD, are generally agreed to influence outcome negatively. But when it comes to determining certain specific factors for outcome, it seems difficult to come to a consensus. One explanation for this could be the differences in patient selection between studies. It would seem as if diabetic foot ulcers are a heterogeneous group, and it might be that there is no single specific factor, or specific factors, responsible for determining outcome. This is an interesting area of research to pursue for the future.

In the literature PVD is reported to be around 50\% in patients with diabetic foot ulcer.\textsuperscript{37} These studies are mostly on mixed cohorts. In the literature plantar forefoot ulcers are frequently regarded as neuropathic and there are no studies detailing the frequency of PVD in patients with plantar forefoot ulcer. Paper II shows that a quarter of patients with plantar forefoot ulcer also have SPVD. Although not related to outcome in multivariate analysis, it is important that patients presenting with a plantar forefoot ulcer should be subject to evaluation of lower limb circulation as a substantial portion of these patients also have SPVD.
Heel ulcer

An ulcer located in the heel in patients with diabetes is a serious complication. In a larger cohort of foot ulcers, regardless of ulcer location, heel ulcers made up ten per cent of all foot ulcers. To my knowledge Paper III with its 768 patients is to date the largest study on heel ulcers in patients with diabetes, with a number of patients included that is equal to all the other presented studies together, Table 3. Most studies with regard to ulcers located in the heel in patients with diabetes thus have small numbers or a selected category of patients.

Reported healing rates of heel ulcers in patients with diabetes vary between 51% and 95%, Table 3. In clinical practice heel ulcers are often referred to as difficult and hopeless cases, in many cases ending up with a major amputation. The results of Paper III, and of other reports in the literature, show a more favourable outcome. A team approach to this group of patients, early referral to a centre with expertise in caring for diabetic foot ulcers, and adequate pressure relief are key elements in the treatment strategy at the centre, and might have played a role in the favourable outcome. The price to pay is often a long healing time.

The patients in Paper III had a median age of 73 years. Many studies in the literature combine both diabetic and non-diabetic patients. In studies reporting only on diabetic patients the median age is often 10 years younger than in Paper III. In Paper III, despite being elderly and having co-morbidities, two thirds of patients with a heel ulcer still healed without an amputation. From both patient and society perspective this can be considered a good outcome. The subgroup of patients who had a pressure heel ulcer had a higher mortality than patients with other precipitating factors. This could be due to these patients having more co-morbidity. The findings in Paper III indicate that ulcers located in the heel in patients with diabetes overall do not have a poor outcome. However, pressure heel ulcers may be considered a separate entity with a potentially poorer prognosis. It is important to identify different subgroups of patients with a potentially poorer prognosis at an early stage, before there has been too much tissue damage to facilitate healing.

The median healing time among patients in Paper III was 17 weeks. A longer healing time was seen in patients who had an amputation or major debridement than for those who healed primarily. In studies where healing time is reported the healing time was 10–33 weeks. Comparing healing times between studies is not easy since there are no clear definitions and healing is not always defined. In Paper III all patients are followed to final outcome, and unlike in many other studies there is no set time limit to follow-up. Another important difference from most other studies is that time to heal is registered from date of arrival at the foot clinic, not from date of surgery.
In the literature there are some studies which look at factors related to outcome of heel ulcers. Treiman and colleagues \(^{112}\) found, in 91 patients (both diabetic and non-diabetic), that normal renal function, a palpable foot pulse, functioning posterior tibial artery, and the number of functioning tibial arteries predicted healing of heel ulcers. Bakheit and colleagues \(^{113}\) found, in 100 patients with diabetes, that short duration of diabetes, adequate circulation, and a superficial wound were factors associated with healing, while Chipchase and colleagues \(^{111}\), in 97 patients with diabetes, found that a larger ulcer and presence of peripheral vascular disease predicted a worse outcome. In a report from the EURODIALE study of diabetic foot ulcers co-morbidity, SVPD, infection and extent of tissue involvement were factors associated with outcome.\(^{1,24}\)

Multivariate analysis in Paper III showed that vascular surgery, nephropathy, and oedema were factors related to poor outcome, whereas a creatinine level below 91 µmol/L was the only factor related to a higher probability for healing without major debride ment or amputation. Further studies on factors related to outcome are needed. Reported factors in the literature vary widely, indicating different selection of patients in different studies. It is possible that no single factor has the power to influence outcome by itself. Rather, it is a combination of factors, both patient and environmental, which contribute to outcome.

**Risk of new foot ulcers and lack of definitions**

In Paper IV the results show that 47% of patients with a healed plantar forefoot ulcer develop one or more new foot ulcers within two years following healing. This stresses the importance of an active follow-up and intense preventive measures following healing of plantar forefoot ulcers in diabetic patients. However, in only 8% of the patients did a new ulcer develop on the same foot and at the same site as the previously healed ulcer, thus fulfilling the definition of recurrent ulcer. This marked difference between recurrent ulcers and other new ulcers highlights the importance of making a clear distinction between these two groups. Of all new ulcers, 17% were recurrent ulcers.

There are few large cohort studies regarding the risk of new foot ulcers, particularly in individuals with diabetes and plantar forefoot ulcers. In available reports, new ulceration rates following healing of a foot ulcer of various aetiologies in subjects with diabetes vary widely.\(^{50,51,80,81,91,94,95,98-100}\) The lowest rate (8% at a mean follow-up time of 24 months) is reported by Batista et al\(^ {98}\), in a study on percutaneous Achilles tendon lengthening in 52 patients, and the highest rate (34%, 61%, and 70% after 1, 3, and 5 years, respectively) is reported by Apelqvist et al\(^ {50}\) in a study of 558 patients with all types of diabetic foot ulcers.
These differences could be explained by differences in patient selection, types of ulcers included, definitions used, as well as length of follow-up. Whether the low rate of recurrent ulcer in Paper IV is a true low rate compared to other centres is difficult to say, since there is no uniformity regarding definitions. To be able to compare results there is a need for more uniform definitions and more specified methodological descriptions.

In Paper IV, 8% of patients developed a new ulcer on the same side and site as the previously healed ulcer. There are few studies which differentiate between new ulcer locations. Only two other studies reporting outcome with regard to new ulcer location\textsuperscript{100,188} have been found. Galea and colleagues\textsuperscript{100} report recurrence rates similar to the results in Paper IV, albeit in a small study population (32 patients). In a study by Piaggesi and colleagues\textsuperscript{188}, who evaluate the outcome after conservative surgery versus a non-surgical approach to plantar foot ulceration (in 41 patients), patients in the non-surgery group re-ulcerated at the same site, while patients receiving surgery developed a new ulcer at another site. In Paper IV there was no difference in development of new ulcers with regard to location of index ulcer or whether the index ulcer healed primarily or after major debridement or amputation. Identifying subgroups of ulcer sites is an important tool to improve preventive strategies.

There is no consensus regarding the terminology of ulcers appearing after an initial ulcer has healed. In the literature these ulcers are termed recurrent ulcer\textsuperscript{51,91,94,98,99}, reulceration\textsuperscript{94,99,100}, new ulcer\textsuperscript{95}, and transfer ulcer\textsuperscript{80,81}. Often there is no definition of ulcer recurrence at all.\textsuperscript{101-104} Since there is a lack of uniformity in defining new ulcers, comparing results from the literature is not possible. A concise definition is a prerequisite for meaningful comparisons of treatment strategies and for identifying risk factors and preventing new foot ulcers. The findings in Paper IV indicate the need for a more precise description and terminology. As a first step, a new terminology is suggested, differentiating recurrent foot ulcers (on the same foot and at the same site) from other new foot ulcers (at any other site on the same foot, or at any site on the contralateral foot).

In Paper IV, the time of healing of the index ulcer was defined as the date when the wound was considered healed with macroscopically complete epithelialization, and healing had to be confirmed at a 6-month check-up. If the ulcer was still present at that time, the original assessment of healing was revised. This strict definition of healing could be one explanation for the low rate of recurrent ulcers. Many studies in the literature do not have a definition of healing, and in those which do report a definition of healing, it is often reported as a single observation.\textsuperscript{51,53,64,91,93,186,188}

In 2010, the European Wound Management Association Patient Outcome Group published a report on recommendations for reporting on wound management. In
this report it is suggested that a healed wound be reconfirmed at two consecutive visits two weeks apart. The FDA states in a document from 2006 that a follow-up evaluation of at least 3 months following complete wound closure is recommended to help distinguish actual wound healing from transient wound coverage.

A wide variety of factors have been reported as related to ulcer recurrence following healing of a foot ulcer. Most studies have mixed ulcer locations and in some studies patients with PVD or previous foot ulcers have been excluded. Mantey and colleagues were the first to report on factors related to the risk of new ulcers, and in a study on 51 diabetic patients with foot ulcer they found poor glycaemic control, neuropathy, delay in reporting symptoms and increased alcohol intake to be related to the risk of new ulcers. Both Connor et al and Dubsky et al also found glycaemic control to be relevant in risk assessment for new ulcer development, with Connor et al also reporting on alcohol as a contributing factor. Neither of these studies specified the location of the index ulcer.

PVD, plantar location of index ulcer, insulin treatment, osteomyelitis, a low maximal Wagner grade, and vascular surgery have also been reported as factors related to development of new ulcers. Interestingly Faglia et al, in a study on 115 patients, could not find any factor significantly determining the risk of new ulcers. A study on plantar foot ulcers reported minor lesions, day-to-day variation in stride count, and cumulative duration of previous foot ulcers as factors related to ulcer recurrence. Another study on 35 patients with plantar foot ulcer, which evaluated ulcer recurrence after metatarsal head resection, reported that resection of less than 25% of the metatarsal led to a higher rate of ulcer recurrence.

So far, it is not possible to point out any one specific factor, or specific factors, which can predict the risk of future new foot ulcers. The rate of new ulcers is relatively high and many factors have been reported to be related to the risk of new ulcer development. Perhaps diabetic patients are such a heterogeneous group that it is not possible to define a specific factor. Rather, it is important to be aware of the risk of new ulcer development, to take preventative measures, and be vigilant regarding foot inspection.
General and methodological considerations

Some methodological considerations need to be borne in mind when evaluating the studies. Potential negative selection bias always has to be considered, since the patients were admitted to a university-based foot centre. It cannot be excluded that more superficial ulcers of neuropathic origin were treated in primary healthcare, nursing homes, or home care without the knowledge of the centre. There was general agreement at the hospital that irrespective of where patients were admitted, they would be passed on to the foot centre.

Definition of healing varies between studies, and 6 months was considered necessary to prove that patients remained healed. Definitions of outcome can be very complex, an issue that has been previously analysed. Comparisons between studies are difficult due to differences in design, setting, patient selection, definitions, follow-up time, and other confounding factors. Healing was defined as intact skin for 6 months or intact skin at time of death, whereas other studies provided no definition or failed to report follow-up. The patients were followed until healing or death, whereas most other studies report on healing within a specified time, usually 6 to 12 months.

In Paper IV 92 patients had more than one new ulcer and the total number of new ulcers was 384. A pitfall in reporting on new ulcers in patients with diabetes is that more than one new ulcer on either side might develop simultaneously or subsequently. In the literature there are no unanimous reports on how to handle this. When evaluating patient outcome it is important to differentiate between number of patients and number of ulcers. Reporting clearly on this will render the scientific discussion more complete and reduce the risk of misinterpretations. The finding in Paper IV also highlights that not only the number of patients suffering new ulcers needs be taken into account, but also the number of ulcer episodes.

Patients in these studies were divided into groups according to outcome: primary healing, minor amputation, major amputation, and patients deceased unhealed. In some studies minor amputations are included in primary healed and also the definition of amputation varies. Comparisons between centres are difficult, due to the heterogeneity of patients and complexity of the disease. In many health care systems there are limited possibilities for following up patients until healing is achieved. The Swedish health care system, due to its geographical responsibilities and reimbursement system, enables patients to be followed up until a specific endpoint, irrespective of who the caregiver is.

A large amount of missing data on retinopathy was mainly due to patients being unable to attend fundoscopy. Duration of diabetes is in most cases an uncertain variable, since the disease may have gone unrecognized for a shorter or longer
time, maybe for years. This is particularly true for type 2 diabetes. The duration of diabetes is based on the year the diagnosis was set until the year the patient was seen at the foot care centre. Duration of diabetes unknown refers to the fact that the diagnosis of diabetes was previously known but that time of diagnosis could not be established and verified through medical records. Duration of ulcer when presenting at the foot centre is the most uncertain variable, due to a combination of patients’ unawareness of the need to seek healthcare and healthcare providers’ choice of treatment and willingness to refer patients. It is uncertain how the ulcer was treated before referral to the foot centre, due to lack of proper documentation from the primary care or home nursing services. The clinical characteristics and variables included in the study such HbA1c and serum creatinine levels, were registered at baseline without further follow-up during the study period.

Ulcers in this study were classified according to Wagner. This classification has a weakness; it does not describe ulcer area or extent of infection. Unfortunately, it is not possible to reclassify the ulcers to more recent systems retrospectively as the older records lack information on, for example, ulcer size and classification of infection.

Strengths and limitations

The strength of the studies in this thesis is the size of the consecutively included and followed patient cohort, followed by a protocol and specific pre-set criteria and definitions, as well as the length of follow-up. There is no set time limit to follow-up and patients are followed to healing or death. Since the multidisciplinary foot care team is the single provider of specialized diabetic foot care in the region there is little risk of selection bias. All diabetic patients with foot ulcers needing specialist care are referred to the centre.

The studies have a long inclusion time, from 1983. During that time, new treatments in foot ulcer care were introduced, including local treatments, antibiotics, anticoagulants, radiological examinations, endovascular techniques, surgery, off-loading, and drug treatment. This database spans over three decades. There has undoubtedly been progress in both medical and surgical care during this time. However, the long-time follow-up which this database provides gives us important insights into the course of these ulcers. In the studies of this thesis, no attempt to analyse these changes over time has been made.

In Papers II–IV each patient is represented by one ulcer per patient. This ulcer is the first or worst ulcer appearing during the study period. If a patient presented with more than one ulcer at the same time, the worst ulcer was included. In Paper
III patients with an ulcer located in the heel were included. Patients classified as having multiple ulcers were not included. Among the patients admitted to the centre 671 were classified as having multiple ulcers. In this group of patients there could be a number of heel ulcers as well. Discerning which of these patients had a heel ulcer as well is not possible. Analysis of patients with multiple ulcers admitted to the centre showed that these patients had a higher mortality rate (33%) and a lower primary healing rate (21%) than patients with ulcers located in the heel. One possible reason for this is that patients with multiple ulcers can have more severe disease and co-morbidity.\textsuperscript{25}

In patients with multiple ulcers on the same foot it was not possible to verify which of the ulcers determined outcome. This issue illustrates the challenge to differentiate factors related to outcome whether they are related to the individual, the extremity, the foot or the ulcer(s).

A systematic review by Bus and colleagues\textsuperscript{79} showed that therapeutic footwear worn by the patient can prevent ulcer recurrence. Adherence to prescribed footwear is unfortunately not part of the protocol in the studies of this thesis. All patients at the multidisciplinary diabetic foot care centre are prescribed therapeutic footwear for indoor and outdoor use as well as a recommendation for regular chiropody.

Plantar forefoot ulcers are classified as located in the plantar surface of the foot. Classification of ulcers with a medial part on the first metatarsophalangeal joint or a lateral part on the fifth metatarsophalangeal joint is at the discretion of the physician.

The difficulty in reporting on patients and ulcers is that each patient may have one or more simultaneous ulcers, and/or one or more subsequent ulcers. Each patient also has two legs, thus further complicating the situation.

In Paper I amputations are presented both as one amputation per patient (the first amputation during the study period) and as all amputations. It is clearly stated what is presented to minimize the risk of misunderstanding. Failure to clearly report how the data has been analysed may contribute to misunderstanding and wrongful comparisons.

The findings from these studies indicate the heterogeneity and complexity with regard to aetiology, treatment, and outcome among individuals with diabetes.

Future studies with regard to treatment and/or preventive strategies and “high-risk feet” might need to be more focused on specific lesions considering aetiology and locations such as ulcers located in the heel, ulcers related to disturbed biomechanics, or neuro-ischaemic/ischaemic ulcers.
Future perspectives

Ideally a patient with a diabetic foot ulcer should never progress as far as to need to see an orthopaedic surgeon. In the perfect setting diabetic foot ulcers would be preventable, and if an ulcer appears, it can be healed without surgical intervention. But if an ulcer appears which cannot be healed primarily, then I want the orthopaedic surgeon to be aware of the fact that a major amputation is usually not necessary and that these ulcers can heal with a minimal amount of surgery and a large amount of time and patience.

My dream when I started this research project was to develop a clinical guideline for diabetic foot ulcer patients and when and where it is best to perform major debridement or minor amputation, and when it is best to perform major amputation. Along the way I have realized that this is probably not possible, these patients are complex and multifactorial, and every patient is unique.

An evaluation of the effects of vascular surgery over time, and the effect of the shift towards endovascular procedures, is something which would be interesting to study.

Studying the difference in quality of life in patients with diabetes only, diabetes and an ulcer, and diabetes and an amputation (both minor and major) is interesting and something to plan for future studies.

A study on amputation level selection would be interesting, albeit difficult to design.
Conclusions

Despite long healing time, it is possible for minor amputations to heal in a large proportion of patients with diabetes, although patients are elderly, with extensive co-morbidity and with severe foot ulcers including infection and/or gangrene in many cases. This indicates that healing is possible even in these difficult circumstances and warrants a liberal approach to minor amputation to avoid a major amputation. However, when applying this approach, it must be borne in mind that a protracted healing process, particularly if jeopardizing mobilization, might not always be in the patient’s best interest. For the orthopaedic surgeon, this clinical situation represents a delicate balance between recommending a major amputation too early or too late.

Four out of five patients with diabetes and a plantar forefoot ulcer heal without the need for an amputation. SPVD was present in one out of four patients with plantar forefoot ulcer, indicating the importance of vascular assessment in these patients.

Two-thirds of patients with diabetes and a heel ulcer healed without amputation.

In patients with diabetes and a plantar forefoot ulcer almost half of all patients develop a new foot ulcer within two years, although the risk of recurrent ulcers (on the same foot and at the same site as the index ulcer) is small. It is important that both patients and health care professionals recognize the high risk of future foot ulceration.

There is a lack of uniform terminology regarding new foot ulcer development. A concise definition of new foot ulcers is suggested, since there seems to be general confusion regarding definitions in the literature. This may facilitate comparison and enhance scientific discussions.
Svensk sammanfattning


Komplikationer till följd av diabetes är till exempel neuropati (försämrad nervfunktion i framför allt nedre extremiteter), kärlsjukdom (bland annat hjärtssjukdom och försämrad blodcirkulation till nedre extremiteter), retinopati (ögonsjukdom) och nefropati (njursjukdom). Till följd av nedsatt känslor och försämrad blodcirkulation till foterna finns det risk att patienter med diabetes utvecklar fotsår. Uppkomsten av fotsår hos diabetiker är en allvarlig komplikation som är förenad med risk för amputation och död.

Syftet med denna avhandling är att undersöka förutsättningarna för att rädda foten hos patienter med diabetes och fotsår med olika lokalisation.

I delarbete I studeras patienter med diabetes som genomgått amputation nedom fotleden. Totalt 309 patienter genomgick 410 amputationer. Medianåldern var 73 år och durationen av diabetes var i genomsnitt 16 år. Av alla amputationer läkte 64 % nedom fotleden, trots att patienterna var gamla, multisjuka och hade allvarliga fotsår. Reamputation innan läkning behövdes hos 37 %.

I delarbete II studeras 701 patienter med ett sår på framfotens trampdyna. Medianålder var 67 år och durationen av diabetes var i genomsnitt 13 år. Försämrad blodcirkulation till foten noterades hos 26 % av patienterna. Av alla patienter läkte 79 % sitt sår. Av dessa läkte 69 % utan operation och 31 % efter kirurgisk revision av såret.

I delarbete III studeras 768 patienter med ett sår på hälen. Medianålder var 73 år och durationen av diabetes i genomsnitt 17 år. Av alla patienter läkte 66 % sitt hälsår utan amputation.

Av de 701 patienterna i delarbete II med ett sår på framfotens trampdyna läkte 618. En patient hade tidigare genomgått underbensamputation på det andra benet. Således studerades 617 patienter i delarbete IV med avseende på risken för att utveckla nya sår. Av dessa utvecklade 47 % nya sår inom 2 år efter läkning av det ursprungliga såret. Endast 8 % utvecklade sår på samma ställe som det tidigare läkta såret. Både patient och sjukvårdspersonal bör vara uppmärksamma på denna risk för nya sår.
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References


42. Apelqvist J, Larsson J. What is the most effective way to reduce incidence of amputation in the diabetic foot? Diabetes Metab Res Rev 2000; 16: S75–83


a multidisciplinary team in patient with diabetes foot ulcer. BMC Endocr Disord. 2016 Jul 7;16(1):38


