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Diabetic foot ulcers - predictors of healing time and aspects of telemedicine • Hilde Smith-Strøm

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Thesis for the Degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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UNIVERSITY OF BERGEN

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Scientific environment

This PhD study was carried out at the Department of Global Public Health and Primary Care, University of Bergen, during the period 2013-2017. My PhD studies took place in the scientific environment of the Western Norway University of Applied Sciences, at the Centre for Evidence-Based Practice. During that time, I was a member of the Diabetes research group for Best practice (DiaBEST) led by Professor Marit Graue of the Faculty of Health and Social Sciences, Western Norway University of Applied Sciences.

The PhD study is part of an ongoing larger project funded by the Norwegian Research Council (project number 221065) and the Western Norway University of Applied Sciences led by Professor Marit Graue. The study is also connected to the Diabetic Foot and Telemedical Images Project (DiaFOTo) led by Professor Marjolein M. Iversen. The Norwegian Directorate of Health, the Western Norway Regional Health Authority, the Norwegian Diabetes Association, and the Western Norway University of Applied Sciences funded the DiaFOTo project.

From August 2016 to December 2016, I had the opportunity to be a visiting researcher at Duke University, School of Nursing in Durham, North Carolina, USA, following an invitation from Professor Bei Wu from the School of Nursing and Professor Truls Østbye from the Department of Community and Family Medicine. Professor Truls Østbye has been one of my supervisors and a co-author of two of the articles, and Professor Bei Wu, a co-author of one of the articles.

During the PhD period, I have participated annually in the Nordic Diabetes PhD and Postdoctoral Research Conference at Solstrand in Bergen, Norway. Further, I attended the European Academy of Nursing Science Summer School (EANS) for European PhD candidates for 3 years.

Due to different methodologies being used and two of the three studies being conducted in clinical practice, it was considered advisable to involve supervisors with different research and clinical backgrounds.

My supervisors have been:

Main supervisor: Professor Marjolein M. Iversen, Faculty of Health and Social Sciences, Western Norway University of Applied Sciences Bergen, Norway; and Department of Medicine, Section of Endocrinology, Stavanger University Hospital, Stavanger, Norway. Professor Iversen is the project investigator of the DiaFOTo project and leader of Work Package 2 connected in the DiaHealth project (DiaBEST research group). She has considerable experience in epidemiology mainly related to the field of diabetes.

Co-supervisor: Professor Truls Østbye, Department of Community and Family Medicine, Duke Global Health Institute, Duke University, Durham, NC, USA. Professor Østbye is a very experienced chronic disease epidemiologist and health services researcher.

Co-supervisor: Professor Marit Kirkevold, Department of Nursing Science, Institute of Health and Society, University of Oslo, Norway. Professor Kirkevold is a very experienced researcher, especially in the field of patient experiences related to chronic conditions and in qualitative research.

Co-supervisor: Dr. Med Svein Skeie, Department of Research, Stavanger University Hospital, Stavanger, Norway; Faculty of Medicine, Department of clinical sciences, University of Bergen, Bergen, Norway. Dr. Med Skeie is a researcher with long clinical experience in diabetes and is a member of the steering group of the DiaFOTo project. The DiaFOTo project is anchored to Stavanger University Hospital.

Co-supervisor: Professor Grethe S. Tell, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway. Professor Tell is a very experienced epidemiologist. She became part of the supervisory team in 2017 after Professor Berit Rokne from the Department of Global Public Health and Primary Care,

University of Bergen, withdrew from the supervisory team when she took up the position of rector for the newly established Western Norway University of Applied Sciences.

Further, there was scientific collaboration during parts of the study with Professor Marit Graue, head of the DiaBEST research group at the Faculty of Health and Social Sciences, Western Norway University of Applied Sciences and with Associate Professor and biostatistician Jannicke Igland from the Department of Global Public Health and Primary Care, University of Bergen. These researchers are co-authors of different articles from the study.

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Finally, I am deeply grateful to my cohabitant, Terje, for all support and patience he has given me during these years, to my son Øistein, our daughter Kristin, daughter in law Anita and to my mother Audhild Smith-Strøm for always being there.

Abstract

Background: A diabetic foot ulcer (DFU) is a feared complication of diabetes. Both duration and severity of ulcer before start of treatment in specialist health care are factors that can effect healing time for patient with DFUs. More research about duration and severity of DFUs before seeking care as predictors of healing time might contribute to knowledge of importance for clinical interventions. Treatment of DFUs puts pressure on the health care system in terms of utilization of available resources. Moreover, the prevalence of diabetes is increasing dramatically and, as a result, long-term diabetes-related complications are also likely to increase. Telemedicine can be one way to address these issues, because telemedicine follow up may enable more integrated care pathways across health care levels. Telemedicine has been used in different settings, but knowledge of telemedicine's effect on clinical outcomes and patients' experiences among patients with DFUs is limited.

Aims: The overall aim of this study was to provide new knowledge about predictors of healing time in patients with a DFU and to assess the effect of and experience with a telemedicine intervention for patients with a DFU. To achieve the overall aim, three specific aims were established:

1) to investigate whether A) duration of ulcer before start of treatment in specialist health care, and B) severity of ulcer according to the University of Texas (UT) classification system at the start of treatment (baseline), are independent predictors of healing time;
2) to evaluate whether telemedicine follow up of patients with DFUs treated in primary health care, in collaboration with hospital outpatient specialist care, is non-inferior to standard outpatient care in terms of ulcer healing time. Further, to assess for superior whether amputations, death, consultations and patient satisfaction are different from telemedicine follow up compared to standard outpatient care; and,
3) to explore the experiences of patients with DFUs receiving telemedicine compared to patients receiving standard outpatient care health care delivered in the context of a cluster randomised controlled trial.

Methods: Three different study designs were used. ***Study I****:* A retrospective cohort study included data from electronic medical records system of 105 patients with new DFUs from two outpatient clinics in Western Norway during 2009-2011. Competing risk regression with adjustment for potential confounders was used to evaluate the associations of duration and severity of the ulcer with healing time. ***Study II****:* In this pragmatic cluster randomised controlled non-inferiority trial, 182 patients (94/88 in telemedicine/standard outpatient care; 42 clusters) with a new DFU were recruited from three hospital outpatient clinics in Western Norway (from September 2012 to June 2016). The primary endpoint was healing time and secondary endpoints included amputation, death, number of consultations per month, and patient satisfaction. ***Study III****:* In the qualitative study individual interviews were conducted with 24 adults recruited from the cluster randomised controlled non-inferiority trial (n=13/ n=11 from the telemedicine /standard outpatient care group) in the period March 2014-May 2015.

Results: ***Study 1****:* Of the 105 adults, 48 (45.7%) achieved ulcer healing, 38 (36.2%) underwent amputations, 10 (9.5%) died before ulcer healing and 9 (8.5%) were lost to follow up. For those who healed, mean healing time was 3.8 months (113 days), measured from start of treatment in the specialist health care to end of follow up. Time from patient-reported ulcer onset to referral by general practitioner (GP) to specialist health care was found to be a strong predictor of healing time. Patients who were referred to specialist health care by a GP ≥ 52 days after ulcer onset had a 58% (Sub hazard ratio (SHR) 0.42, CI 0.18, 0.98) decreased healing rate compared with patients who were referred earlier. Ulcers with the highest severity i.e. ulcer penetrating to tendon or bone (grade 2/3) and peripheral arterial disease with and without infection (stage C/D) according to the UT classification system had an 86% (SHR 0.14, CI 0.05, 0.43) decreased healing rate compared with low severity i.e. superficial ulcer (grade 1) with infection (stage A/B) or ulcer penetration to tendon/capsula (grad 2) and clean ulcer (stage A). ***Study II:*** Of 182 patients, 142 (78.9%) achieved complete ulcer healing, and 75 (79.8%) healed in the telemedicine group and 67 (76.1%) in the standards outpatient care group. Mean healing including only those who healed was 3.4 months and 3.8 months in the telemedicine group and standard outpatient group,

respectively. Telemedicine was non-inferior to standard outpatient care regarding healing time (mixed-effects regression analysis: (mean difference –0.43 months, 95% CI –1.50, 0.65). This finding persisted also after taking into account competing risk from death and amputation (SHR 1.16, 95% CI 0.85, 1.59). There were no significant differences between the telemedicine follow up and standard outpatient care related to the effect estimate of the secondary outcomes, except for significantly fewer amputations in the telemedicine group. ***Study III:*** Three themes emerged from the analysis: 1) competence of health care professionals, 2) continuity of care, and 3) easy access, i.e. to receive treatment and follow up near home or at their home. Group allocation seemed to have limited impact on the patients' follow-up experiences. Competence of health care professionals and continuity of care were important, because they could either enhance or impair wound care. When telemedicine functioned as intended, it was an advantage in the treatment. Easy access was important for the participants, but the importance of accessibility appeared only when competence among health care professionals and continuity of care were present.

Conclusions: Early referral to specialist health care if an ulcer occurs is crucial for optimal ulcer healing and has a clear implication for routine care. Grade and stage severity are also important predictors for healing time, and early screening to assess the severity and initiation of prompt treatment is important. Telemedicine can be an alternative but also a supplement to usual care for patients with DFUs, at least for patients with more superficial ulcers. As the number of outpatient clinic consultations in the telemedicine group did not differ from the standard care group, there is need to focus on organisational aspects to facilitate the use of telemedicine. Health care professionals' competence, continuity of care and easy access to health care services were essential for patients with DFUs, and telemedicine may compensate for lack of these factors.

List of publications

The dissertation is based on the following papers.

I. Smith-Strøm H, Iversen MM, Igland J, Østbye T, Graue M, Skeie S, Bei W, Rokne, B. Severity and duration of diabetic foot ulcer (DFU) before seeking care as predictors of healing time: A retrospective cohort study. PLoS ONE. 2017; 12 (5):1-15. doi.org/10.1371/journal. PMID:28498862.

II. Smith-Strøm H, Igland J, Østbye T, Tell, GS, Hausken MF, Graue M, Skeie S, Cooper JG, Iversen MM. The Effect of Telemedicine Follow-Up Care on Diabetes-Related Foot Ulcers: A Cluster Randomized Controlled Non-Inferiority Trial. Diabetes Care 2018;41:1–8 | https://doi.org/10.2337/dc17-1025.

III. Smith-Strøm H, Iversen MM, Graue M, Skeie S, Kirkevold M. An integrated wound-care pathway, supported by telemedicine, and competent wound management-Essential in follow-up care of adults with diabetic foot ulcers. Int J Med Inform. 2016; 94:59-66. doi: 10.1016/j.ijmedinf.2016.06.020. PMID:27573312.

ABBREVIATIONS

BEON	Best Effective Care Level
DFU	Diabetic foot ulcer
DRG	Diagnosis-related groups
GP	General practitioner
HbA_{1c}	Glycated haemoglobin (identifies average plasma glucose concentration)
NOKLUS	The Norwegian Diabetes Register for Adults
OECD	The Organisation for Economic Cooperation and Development
RCT	Randomised controlled trial
SD	Standard deviation
SHC	Specialist health care
SHR	Sub hazard ratio
SIGN	Scottish Intercollegiate Guidelines Network
UT classification system	University of Texas classification system

Content

1. INTRODUCTION

A diabetic foot ulcer (DFU) is a severe and disabling complication of diabetes and is usually caused by a combination of neuropathy and peripheral vascular disease (1) . These ulcers will often need intensive treatment, frequent ambulatory care visits and hospitalisation (2). The ulcers can take months to heal and about 20% of infected ulcers will require some form of amputation (3). Approximatly 40% of patients will have a recurrence within one year after ulcer healing (4). A history of foot ulcer is also significantly associated with increased mortality (5, 6) and reduced quality of life (7).

The effect of factors promoting ulcer healing such as offloading, infection therapy, vacuum-assisted closure therapy and hyperbaric oxygen therapy are well documented (8). Less attention has been given to whether a delayed referral to specialist health care could be a factor associated with healing time, despite delayed referral being considered as a risk factor for lower extremity complications (9, 10). Use of screening tools to identify patients at risk of developing foot ulcers at an early stage is also important. The University of Texas (UT) classification system for diabetic foot ulcers is one of the few systems that has been validated in different countries (11-13), highlighting the need for more research to assess to what degree this system reflects different populations and predicts healing time accordingly (14) .

Treatment of DFUs is complex and costly and puts pressure on the health care system (4, 15-19). It is likely that the number of patients with DFUs will continue to increase due to an increasing incidence of diabetes, especially type 2 diabetes (18, 20). As a consequence, comorbidities of diabetes such as foot ulceration, peripheral vascular disease, osteomyelitis and lower extremity amputation are also expected to increase (18, 20-22). This will result in high demand for alternative care pathways for treatment of DFU (20).

Telemedicine follow up may be an effective approach to wound care management to meet these challenges. Telemedicine has the potential to enable more patients to be treated in or near their homes and to reduce the number of consultations in specialist

health care by transferring a larger proportion of treatment and follow up to primary health care while maintaining high-quality wound care (23-25). However, we lack knowledge about the effect of telemedicine follow up on clinical outcomes such as healing time, amputation and death as well as patients' experience with receiving telemedicine follow up (25-27).

Thus, the overall aim of this study was to provide new knowledge about predictors of healing time in patients with a DFU and to assess the effect of and experience with a telemedicine intervention for patients with a DFU.

1.1 Diabetes and diabetic foot ulcer

Diabetes mellitus is expected to increase dramatically both in Norway and globally (18, 20, 28). Globally, the prevalence of diabetes has been estimated to be 415 million, and it is projected to reach 642 million by 2040 due to an ageing population, physical inactivity and obesity (28). Diabetes is characterised by an increased risk of macrovascular (stroke, coronary artery disease and peripheral arterial disease) as well as microvascular (neuropathy, nephropathy and retinopathy) complications (29).

Foot ulceration is among the most severe complications of diabetes (30). The International Working Group on the Diabetic Foot has defined a diabetic foot ulcer in the following way: "*full thickness skin breakdown below the ankle in a person with diabetes, irrespective of duration*" (31), and this definition has been used in the studies in this dissertation.

Diabetic foot lesions rarely occur spontaneously, but rather in interaction with two or more risk factors, where diabetic peripheral neuropathy and peripheral arterial disease play central roles (1). Diabetic peripheral neuropathy and peripheral arterial disease may act in combination with other factors such as foot deformity, previous diabetic foot ulceration or lower extremity amputation (1, 11, 32). All these potential risk factors are consistently associated with increased risk of ulceration. Risk factors that have inconsistently been associated with risk of ulceration are older age, male gender,

diabetes of longer duration and high $HbA1_c$ (11). A systematic review reported that in patients with no previous history of foot ulceration or amputation, the predictive factors for increased risk of foot ulceration were inability to feel a 10-g monofilament test, absence of at least one pedal pulse and longer duration of a diabetic diagnosis (33).

DFUs are usually classified into two groups: neuropathic ulcers and ischemic ulcers (1). The majority of foot ulcers are neuro-ischaemic, caused by a combination of neuropathy and peripheral arterial disease. Neuropathy often leads to loss of sensation, foot deformities and abnormal walking patterns that can cause abnormal biomechanical loading on the foot (30). This results in high pressure in some areas leading to callus (thickened skin) often causing subcutaneous haemorrhage and ulceration. A minor trauma can result in ulceration of the foot (30). Peripheral arterial disease is generally caused by arteriosclerosis and is present in up to 50% of patients with DFUs (34-38). Peripheral arterial disease is an important risk factor for reduced ulcer healing, increased risk of infection and lower extremity amputation (30, 35, 39, 40).

Incidence of diabetic foot ulcer

The incidence rate of diabetic foot ulceration reported in some large population-based studies varies (41-45). In Norway, two previous studies from the population-based HUNT study (1995-1997; 2006-2008) showed a possible decrease in the cumulative incidence of people reporting a history of DFU (46, 47). The cumulative incidence of foot ulcers reported in HUNT3 (7.4% (95% CI 6.2%, 8.6%) appears to be lower than in HUNT2 (10.4% (95% CI 8.8%, 11.9%). In a recent study from Denmark, among 5,640 patients with diabetes type I, the incidence of DFUs decreased from 8.1 in 2002 to 2.6 per 1000 patient years in 2014 (48). Among 6,953 patients with diabetes type II in the same study, the incidence of DFUs decreased from 17.0 to 8.7 per 1000 patients years in the same period. In a study of 81,793 Dutch people with diabetes during 2010-2013, the annual incidence rate estimated was 0.34% (range 0.22 – 1.08%) for all DFUs (42). This is lower than reported from some previous studies (43-45, 49). A community-based study from North-West England reported a 2.2% annual incidence rate of diabetic foot ulceration during a 2-year follow up in the period 1994-1996 among 6,613 patients with diabetes (43). In a study from USA collecting retrospective

data from 8,905 people with diabetes in the period 1993-1995, Ramsey et al. (44) reported a cumulative 3-year incidence of 5.8%. More recently from Ireland, Hurley et al. in 2008-2009 reported an annual incidence rate of 2.6% from general practice among 563 patients with diabetes (45).

Healing of diabetic foot ulcer

Results from the Eurodiale study showed that 77% of DFUs healed (with or without a minor amputation) within 1 year (32). The prevalence of peripheral arterial disease was approximately 48% and was associated with poorer ulcer healing. Uccioli et al. (35) included patients with critical limb ischaemia and found the healing rate among patients treated with percutaneous angioplasty to be 62.3%, and without to be 48.1%. The majority of healed ulcers healed in less than 6 months. Ulcers with an ulcer area > $5cm^2$, infection, a combination of infection/ischemia and the presence of ischemic heart disease had significantly reduced healing. A United Kingdom cohort study included 449 patients with ulcers that were at different stages and grades based on the UT classification system (50). In total, 65.7% of the ulcers healed within 6 months, but only 59.2% remained healed after 12 months. Median healing time was 78 (range 7-364) days. Oyibo et al. (13) included patients with neuropathy and neuroischaemic ulcers. Of these, 67.0% were neuropathic and 26.3% were neuroischaemic. Of the 194 patients, 65% achieved ulcer healing. The median healing time for those who healed was 5 weeks. A higher stage in the UT classification system was associated with increased healing time. In summary, results from these studies showed that about 25-40% of ulcers do not heal (13, 32, 35, 50). The most important predictors for non-healing ulcers in the Eurodiale study were peripheral arterial disease either alone or in combination with infection (32).

Amputations

There is global variation in the incidence of amputation (10, 51, 52). In 1989, the aim of the St. Vincent Declaration was to reduce the rate of amputation among people with diabetes by half within 5 years (53). This 5-year goal was almost achieved after 20 years, as indicated by the reduction in incidence of lower extremity amputation reported in several studies (52, 54-56).

A report from the Organization for Economic Cooperation and Development (OECD) found a 40% decline in amputations among patients with diabetes over a 12-year period, with rates ranging from a mean of 13.2 to 7.8 amputations (minor and major) per 100,000 from 2000 to 2011 respectively (55). However, despite a reduction in amputation rate across these 12 years, it still remains high in most OECD countries (55).

The incidence rates of amputations are reported from some countries. In Norway, the incidence of amputations among patients with diabetes decreased from 2.4 amputations per 1000 in 2015 to 2.3 amputations per 1000 in 2016 (56). In the Eurodiale study, minor amputations among patients with diabetes differed markedly between countries ranging from 2.4% to 34%, suggesting that different management strategies and referral patterns between and within these countries might explain these variations (57). In a study in the Netherlands, the incidence rate of amputations as a consequence of diabetes was relatively low and stable over the years 2007-2011 (58). The annual rate of amputations between 2009 and 2011 ranged from 4.32 to 5.28 per 1000 patients in the secondary care sector. Kennon et al. (54) found a significant reduction in the incidence of amputations caused by diabetes in Scotland over a 5-year period. The incidence was reduced from 3.04 per 1000 in 2004 to 2.13 per 1000 in 2008 ($p > 0.001$), mainly due to a reduction in major amputations.

The incidence of amputation can be difficult to compare due to variation in the definition of amputation and the population selected (10, 51). Different factors can influence the decision as to whether or not to perform an amputation. A high incidence of amputations can indicate high disease prevalence, limited resources, late referral or a surgical intervention approach (10). In contrast, a low incidence of amputations can reflect a lower disease prevalence, a conservative approach or good foot care in primary and specialist health care. A high incidence of minor amputations could be regarded as a strategy leading to healing whereas major amputation cannot be regarded in this way.

Mortality

There is strong evidence for excess mortality associated with DFU. A 10-year follow-up community-based study in Norway reported a mortality rate of 49% among 155 patients with a history of DFU compared with 35.2% among 1,339 patients with diabetes without DFUs and 10% of the 63,632 individuals without diabetes (5). In another study, an 11-year retrospective hospital study from the UK, including 268 patients with DFUs. Patients with a DFU had an increased mortality risk compared with non-ulcerated patients with diabetes. Ischaemic heart disease was the major cause of premature death and higher among patients who had neuropathic ulcerations compared to non-ulcerated patients with diabetes (6). Similar results were seen in Norway, but the proportion of patients who died due to cardiovascular disease did not differ between patients with diabetes with and without a DFU: 48.7% versus 50.1%, respectively (5).

1.2 Predictors of diabetic foot ulcer healing

Despite clinical guidelines recommending early referral of patients with DFUs (59-62), relatively few studies have investigated duration of ulcer as a predictor of ulcer healing (9, 63, 64).

An ulcer classification system to detect DFUs at an early stage to predict outcomes is of clinical importance, but no classification system is currently in widespread use (65), neither in Norway nor globally. The Norwegian diabetes national professional guideline from 2016 recommend using the Scottish Intercollegiate Guidelines Network (SIGN) classification system (59). How this should be used in clinical practice is not specified, but the SIGN system is soon to be incorporated into the Norwegian Diabetes Register for Adults (NOKLUS).

1.2.1 Duration of ulcer before treatment start in specialist health care

Norwegian and international guidelines recommend early referral of patients with DFUs to specialist health care to avoid severe complications (59-62). Although some

researchers have reported a relationship between duration of ulcer and ulcer healing among patients with DFUs (63, 66), many patients with DFUs still experience delayed referral to specialist health care (9, 63), possible due to lack of awareness of potential consequences of the delay, lack of knowledge among health care professionals and patients, as well as poor management strategies (9, 67, 68).

A sub-study within the Eurodiale study found that late referral defined as 3 months or longer before treatment started in specialist health care was found in 27% of all patients, ranging from 6% in the UK to 55% in Germany. Nearly half of these patients (44%) had been treated in primary health care experienced a late referral (9). The Eurodiale study data also showed marked differences in minor amputation rates between the different European countries. The authors suggested that one reason behind these variations might be the referral patterns in the various countries (57). However, referral patterns were not investigated in the Eurodiale study.

Only a few studies have found an association between duration of ulcer before treatment start in specialist health care and healing time. In a recent British audit including 5,105 patients from 129 specialist foot care teams (63), patients with DFUs who were referred to specialist health care more than 2 months after ulcer onset had significantly increased healing time compared with those who were referred earlier. Margolis and colleagues (66) found after evaluating more than 31,000 individuals with diabetic neuropathic forefoot ulcers that the ulcers were more likely to heal if the duration of the ulcer had been less than 6 months before treatment start in specialist health care. It was therefore of interest to examine the association between this factor and healing time among patients with DFUs in a Norwegian cohort study.

1.2.2 Severity of ulcer before treatment start in specialist health care

The severity of ulcers at presentation in specialist health care may affect the outcome. Studies have shown that the presence of infection and/or ischaemia increases the risk of amputation (13, 57), and that early detection of peripheral arterial disease, treatment of infection and surgical intervention can improve the outcome for the patients (35). Peripheral arterial disease is strongly linked to poor ulcer healing and it is present in

up to 50% of patients with DFU (36, 69, 70). Early screening of people with a DFU is important to assess the severity of the ulcer and to initiate adequate treatment to reduce the risk of severe complications. The UT classification system was validated in 1998 in the USA (12) and in 2001 in the UK (13) and demonstrated prediction of amputation and healing time (12, 13). However, it is emphasised that more research is needed to assess to what degree this system reflects the population for which it is intended (14).

1.3 Telemedicine as a health services delivery tool

There is considerable interest in the capacity of information and communication technologies (ICTs) to improve the outcomes of the health care service and ICTs may have the potential to meet with some of the challenges the health care service faces by enhancing access to, as well as efficiency, quality and cost-effectiveness of the health care services (23, 71-73). Telemedicine is presented as one solution that can deliver health care at a distance, especially for those with complex conditions, allowing more patients to be treated according to the BEON (Best Effective Care Level) principle (24). Telemedicine may provide continuous patient care pathways across health care levels and reduce the number of outpatient consultations (23, 24, 73-75). Use of telemedicine leads to new ways of organising health care services. However, the adoption of this technology is challenging (72, 73, 76, 77).

Different definitions have been used for the concept of telemedicine (78-81). 'Telemedicine' and 'telehealth' are the most frequently used terms (82). The World Health Organization has defined telemedicine broadly as follow:

"*The delivery of healthcare services, where distance is a critical factor, by all healthcare professionals using information and communications technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for continuing education of healthcare providers, all in the interest of advancing the health of individuals and their communities"* (23).

Telemedicine encompasses different technologies and is often classified into two types: store-and-forward teleconsultation (asynchronous, low-tech solution) and videoconferencing (synchronous, high-tech solution) (83, 84). The asynchronous application includes communication between patient and health care professional via email, cell phone, automated messaging or other equipment without face-to-face contact. The patients and the health care professionals do not need to be present at the same time. Synchronous solutions involve a lot of organisation and require face-to-face contact via videoconferencing, equipment and timing of involved stakeholders. In DFU care, asynchronous solutions are often used to provide close integrated care of patients between health care levels (85).

1.3.1 Telemedicine follow-up care of patients with DFUs

The Norwegian Coordination Reform (2008-2009) highlights the lack of a holistic approach to patients' needs in the current organisation of the health care system and emphasises the requirement for more coordinated and integrated health care for patients, especially for patients with complex conditions (24). The growing pressure on the health care system to deliver care to patients requires new approaches to organising the health care system. The use of ICT has been highlighted as an important aid in achieving a more coordinated and integrated health service (24), a process that emphasises seamless collaboration and continuity of care tailored to the needs of the patient (86).

In the current health care system in Norway, the general practitioner (GP) serves as a 'gatekeeper' by coordinating medical follow up to specialist health care (87). If a person needs an assessment from specialist health care, the GP is responsible for sending the referral to the actual specialist (88). The majority of specialist assessments and treatments are initiated with a referral from a GP. In Norway, the right to necessary health care from the specialist health care service is regulated by law (89). Priority depends on severity, the need for specialist health care, the likely benefit, the availability and the cost-effectiveness (90). The decisions are based mainly on the information from the GP's referral letter (89). However, some confusion exists as to

whether the patient with a DFU should be referred to the orthopaedic, surgical, dermatology or endocrinology department. In the Norwegian context, this often leads to different follow-up procedures for patients with DFUs (91). There are indications that patients with DFUs are treated for a substantial length of time in primary health care with limited continuity of care, few specialist nurses and lack of integrated care between health care levels (92, 93). A delayed referral to specialist health care is reported in some studies (9, 63, 66), despite international and national guidelines stressing the importance of early referral to specialist health care when ulcers occur to prevent severe complications (59, 61, 62).

Telemedicine interventions may enable a more coordinated and integrated health care between health care levels (83, 84). Telemedicine allows a direct communication between health care levels and between patients and health care professionals. Follow-up care of foot ulcers requires careful monitoring of treatment and follow up. By using interactive platforms combined with photographic devices and electronic transfer of high-quality digital images, remote assessment of wound status is possible while still maintaining high-quality care (75). This may reduce patient transportation and workload in specialist health care by decreasing the number of consultations in specialist health care. Telemedicine seems especially useful in wound management where a strong visual component is present in the assessment and follow up of ulcers (25, 75). In the systematic review published by Singh et al. (25), the authors concluded that telemedicine technology provides high diagnostic accuracy in diabetic foot management, and patients as well as health care professionals are positive about its use. However, it is not clear if telemedicine use in patients with DFUs has favourable clinical outcomes, and therefore more randomised controlled trials are needed (25) .

1.3.2 Telemedicine follow up compared to standard care related to clinical outcomes of DFUs

The literature in the context of telemedicine follow up of wound care includes to a large extent feasibility studies and small-scale studies (25, 94). One systematic review from Norway evaluated clinical, behavioural and organisational effects of telemedicine

regarding leg ulcers and diabetic foot ulcers (27). The authors concluded that there was insufficient evidence to determine whether telemedicine was as effective as standard outpatient care. Some studies have focused on telemedicine follow up compared with standard outpatient care on the effect on foot ulcer healing (95-99). Less focus has been on outcomes such as amputation and death, as well as patients' experiences (95).

Ulcer healing and healing time

A randomised controlled trial (RCT) involving 374 home care patients with DFUs in Denmark in 2015 found no significant differences in incidence of healing between telemedicine follow up compared with standard outpatient care (95). No difference was reported in complete healing between the two groups. Similar results were found in a non-randomised study from USA which included 140 consecutive patients with DFUs from two medical centres (96). There were no statistically significant differences in healing time between patients receiving telemedicine and traditional follow up after 12 weeks. Moreover, no statistically significant differences between groups were observed in the number of ulcers that had healed at 12 weeks. The authors suggested caution with respect to the results due to the low sample size and the risk of type 2 error, but emphasised that telemedicine was a feasible method for delivery of foot care to rural populations; however, more trials were needed. In an American study, Terry et al. (97) reported results of a prospective RCT on 103 home care adults with pressure ulcers or non-healing surgical wounds, claiming no benefit from the use of telemedicine in wound care. They found no statistically significant differences between the groups, and the results did not favour the telemedicine intervention. In contrast, Zarchi et al. (98) reported results of a non-randomised cluster-controlled trial with 95 home care patients with ulcers of mixed etiology (DFUs were included). This Danish study reported benefit from using telemedicine in wound healing. Telemedicine follow up was associated with significantly increased healing compared with standard outpatient care after adjusting for covariates. More patients healed in the telemedicine group compared with the control group. In the telemedicine group, 70% healed (35 of 50) compared with 45% (18 of 40) in the control group. A study from Australia concluded that telemedicine can support both patients and clinicians (99). A total of 93 patients

(telemedicine group n=50, control group n=43) were included in a 12-month prospective randomised cluster-controlled study including patients with ulcers of mixed etiology (DFUs were not included). Patients receiving telemedicine follow up had a positive healing rate of 6.8% per week, while the control group had a negative healing rate per week of -4.9% per week (p=0.012).

Amputations

In the previous mentioned Danish study by Rasmussen et al. (95), the authors found no significant differences in the incidence of amputations or in healing time between the groups and suggested that telemedicine was a relevant alternative to standard outpatient care. In the Australian study, Santamaria et al. (99) reported that 1 (2%) patient in the telemedicine group had amputation compared with the 6 (14.0%) in the control group.

Mortality

The results from the Danish study by Rasmussen et al (95) reported higher mortality in the telemedicine group compared with standard outpatient care. The authors presented no reasons that could explain these results. Despite the promising results of no difference in healing and amputation rate between the groups, the authors concluded that a more cautious approach to telemedicine follow up in patients with DFUs should be considered. Furthermore, more RCTs are recommended involving different subgroups to identify patients who can benefit most from a telemedicine intervention. Findings from the Australian study showed that 2 (4.7%) died in controlled group compared with none in the telemedicine group (99).

Overall, evidence on telemedicine follow up in wound care is limited and characterised mostly by low powered studies, heterogeneity in populations, methods and interventions applied, making study results difficult to compare (95-99). Only one RCT and one non-randomised controlled study focused specifically on DFUs and use of telemedicine follow up (95, 96). Few studies have reported on clinical outcomes such as ulcer healing, amputation and mortality. The results from these studies related to healing time are inconclusive as to whether telemedicine follow-up care is superior or no worse when compared with standard outpatient care. In conclusion, more evidence

is needed regarding the effect of telemedicine follow up compared standard outpatient care on clinical outcomes among patients with DFUs. No such study had, before ours, been performed in Norway.

1.3.3 Telemedicine follow up from a patient perspective

There are some reviews focusing on telemedicine and patient satisfaction, but not specifically for patients with DFUs. Overall, these reviews reported that the majority of patients found telemedicine satisfactory, but they also report methodological deficiencies and the need for further studies (100-102). However, some small studies about telemedicine and patient satisfaction in wound care have been published (103-107), but those related to telemedicine in diabetic foot care from the perspective of patients is limited (108, 109). Below is a summary of the studies that have explored the experiences with telemedicine follow up among patients with DFUs.

In a Danish pilot study, Clemensen et al. (109) conducted a qualitative study involving patients with DFUs, expert nurses, visiting nurses and a doctor in Denmark. The telemedicine intervention consisted of three video consultations that substituted three consultations at the outpatient clinic. All stakeholders reported satisfaction with the use of telemedicine. Patients emphasised the benefits of staying home during treatment, avoiding long transportation time and waiting time at the outpatient clinic, as well as increased contact between the patient and health care professionals. The authors concluded that telemedicine was useful and an appropriate alternative to standard outpatient care in these cases. Another study evaluated the experiences of five patients with DFUs who received telemedicine follow up by the community health podiatrist in an Australian rural community (108). The podiatrist sent image and text via mobile phone to the specialist clinic. The patients reported satisfaction with the use of telemedicine follow up with respect to immediacy of service, benefit of time saving, reduced travel time and cost saving. The author concluded that telemedicine follow up could be a useful supplement to standard outpatient care.

In summary, few studies have evaluated experience with telemedicine follow up among patients with a DFU, and evidence from RCTs that include the patients' perspective is

scarce. There is a need to incorporate qualitative approaches that might provide a more in-depth insight into the experiences of patients when new technology is used and provide additional insight into whether the setup is working as intended. Therefore, there is a need for more knowledge on the patient perspective on telemedicine intervention among patients with a DFU in large controlled trials.

2. OBJECTIVES

The overall aim of this study was to provide new knowledge about predictors of healing time in patients with a DFU and to assess the effect of and experience with a telemedicine intervention for patients with a DFU.

The specific aims of the thesis were as follows:

Study I:
To investigate the association between duration of ulcer and healing time. Duration of ulcer was defined as the time from patient-reported ulcer onset to start of treatment in specialist health care and was divided into two different fractions of duration of ulcer (Figure 2, p.20):

1) time from patient-reported ulcer onset to referral by GP to specialist health care, and
2) time from referral by GP to start of treatment in specialist health care

In addition, we explored whether severity of the ulcer in terms of grade and stage (as defined in the UT classification system) at start of treatment in specialist health care was associated with healing time. We also investigated whether duration of ulcer and ulcer severity showed independent associations after mutual adjustment and adjustment for other potential confounders (Table 2, p.21).

Study II:
The primary aim was to evaluate whether telemedicine follow up of patients with diabetes-related foot ulcers in primary health care, in collaboration with hospital outpatient specialist care, is non-inferior to standard outpatient care in terms of ulcer healing time. Our secondary aims were assessed for **s**uperiority**:** to evaluate whether amputations, death and outpatient consultations were less frequent in the telemedicine group compared to standard outpatient care; and to evaluate whether patients receiving telemedicine follow-up care were more satisfied with the treatment and follow-up care than patients receiving standard outpatient care.

Study III:

To explore the experiences of patients with diabetic foot ulcers receiving telemedicine compared to patients receiving standard outpatient health care delivered in the context of a cluster randomised controlled trial.

3. MATERIAL AND METHODS

Three different research designs were used in this dissertation: a retrospective cohort study (Study I), a pragmatic cluster RCT (non-inferiority) (Study II) and interpretive description (qualitative strategy) (Study III). Study III was designed in the context of the cluster non-inferiority RCT.

Table 1. Study overview

Study	Methods/Design	Sample	Data collection	Analysis
I	Retrospective cohort study	n=105 patients with diabetic foot ulcers Two clinical sites: Stavanger University Hospital, Stord Hospital	Electronic medical records system	Descriptive statistics (mean, median, SD, percentages,) Chi-square tests t-tests Cumulative incidence curves Competing risk analysis
II	Cluster randomised controlled non-inferiority trial	n=182 patients with diabetic foot ulcers Telemedicine, n=94 Standard outpatient care, n=88 Three clinical sites: Stavanger University Hospital, Stord Hospital, Haukeland University Hospital	Web-based ulcer record (®PleieNet) Electronic medical records system The Generic Short Patient Experiences Questionnaire (GS-PEQ)	Descriptive statistics (mean, SD, percentages,) Chi-square tests t-tests Linear mixed effects regression Generalised linear model Cumulative incidence curves Competing risk analysis
III	Interpretive description	n= 24 recruited from the RCT (n=13 from the telemedicine group, n=11 from the standard outpatient care group)	Individual interviews	Constant comparative analysis

3.1 Study I

3.1.1 Design

A retrospective cohort design was used to assess the associations between duration of ulcer, severity of ulcer with healing time.

3.1.2 Study sample

Patients with DFUs registered at two outpatient clinics in Western Norway: the Endocrinology units at Stavanger University Hospital and the surgical unit at Stord County Hospital between January 2009 and December 2011 were included.

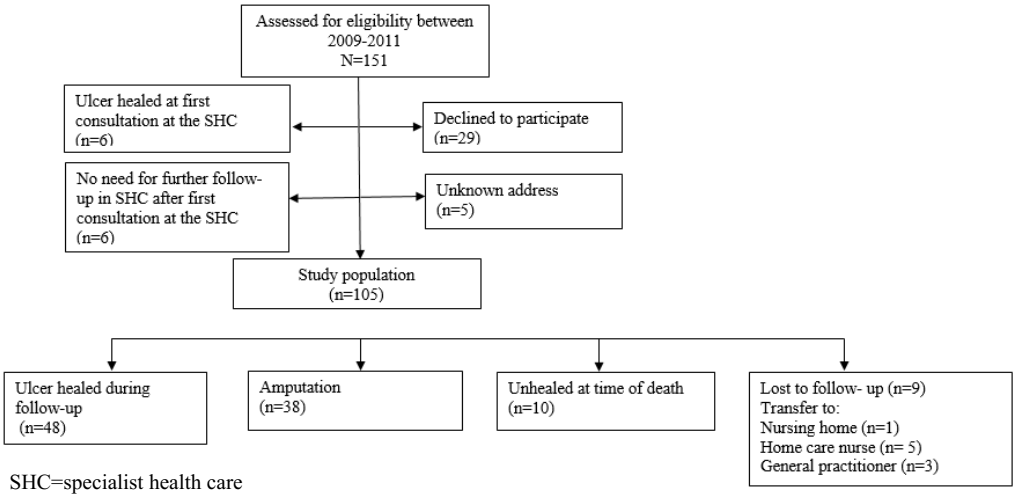
The inclusion criterion was: Patients with a new DFU presenting for the first time at one of the participating clinics. Exclusion criterion was: Patients treated for a foot ulcer on the same foot in the past 12 months before treatment start in specialist health care.

To identify patients with DFUs, different approaches were used: At Stavanger University Hospital, the appointment system in the electronic medical records and the appointment book for consultations were used to identify patients with a DFU. At Stord Hospital, the following ICD codes were used: L97: Unspecified wound of lower limb, L89.9: Unspecified bedsore or decubitus ulcer, , E10.5: Type 1 Diabetes mellitus with peripheral circulatory complications, E10.6 Diabetes 1 with special complications, E10.7: Diabetes 1 with multiple complications, E11.5: Type 2 Diabetes mellitus with peripheral circulatory complications, E11.6: Diabetes 2 with special complications, E 11.7: Diabetes 2 with multiple complications and M86.6: Osteomyelitis. In additional, the following NCMP/NCSP procedure codes were used: Qxb99: Unspecified dressing, Qdb05: Debridement on lower extremity, Qdb10: Larger dressing procedure on lower extremity, Qdgx10: Care of diabetic foot, Wlgx20: Vacuum treatment and Qxgx41: Thrombocyte concentrate.

3.1.3 Data collection

Data were collected from medical electronic record system at baseline and prospectively on ulcer healing, amputation and death using a standardised data collection form (Appendix 1). The data collection form was piloted on five patients (three patients at Stavanger University Hospital, two at Stord Hospital) to see if it was feasible to collate information on the variables via the data collection form. Not all variables included in the data collection form were used in this study. Data on weight, height and body mass index could not be collected from the electronic medical records system and the questions were removed from the data collection form. A specialist nurse at each outpatient clinic collected data from the medical electronic record system These data were filled into the data collection form by the first author (HSS).

A total of 151 patients were assessed for eligibility, and 105 were included. Written informed consent from participants was obtained (REK 2013/2327). Figure 1 gives an overview of the sample derivation.



SHC=specialist health care

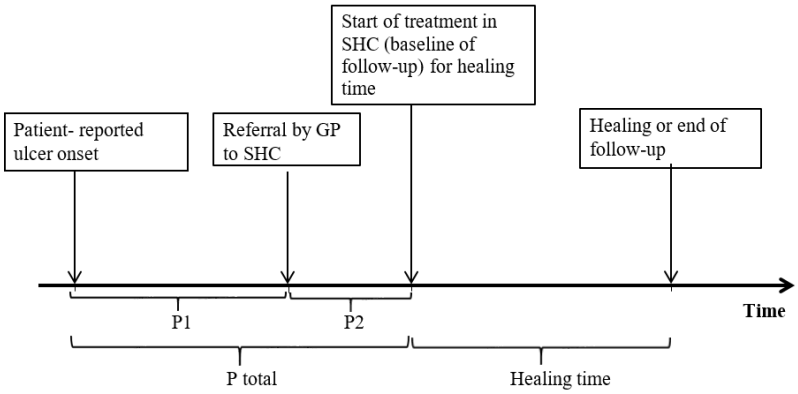
Figure 1. Flowchart. Study population

3.1.4 Main exposures and possible confounders

The main exposures in this study were duration of ulcer and ulcer severity. *Duration of ulcer* was defined as the time from patient-reported ulcer onset to start of treatment in specialist health care (P total) and divided into two fractions (Figure 2).

P1: Time from patient-reported ulcer onset to referral by GP to specialist health care divided into 3 groups using the following tertiles: 0-13 days, 14-51 days and ≥52 days and,

P2: Time from referral by GP to start of treatment in specialist health care divided into 3 groups using the following tertiles: 0 days, 1-13 days and ≥ 14 days.



P1= Patient reported ulcer onset to referral by general practitioner (GP) to specialist health care (SHC)
P2= referral from GP to start of treatment in SHC
P total = P1 and P2
Healing time = from start of treatment at SHC to healing or end of follow- up

Figure 2. Model illustrating the relation between duration of ulcer and healing time

Ulcer severity was classified according to the UT classification system (12, 13). This system assesses ulcer depth, the presence of wound infection and clinical signs of lower extremity ischaemia (12, 110).The system uses a matrix of grades on the horizontal axis and stages on the vertical axis, consisting of four grades and four stages, shown in Table 2. The matrix in Table 2 is shaded to differentiate between ulcer severities. A higher grade /stage indicates a more severe ulcer. Based on clinical judgement, grade

and stage were combined into three categories before analysis due to small numbers in some categories (Table 2).

Table 2. Matrix of University of Texas classification system

Stage		Grade 0	Grade 1	Grade 2	Grade 3
A	Clean wound				
B	PAD -, infection +				
C	PAD +, infection -				
D	PAD +, infection +				

PAD: Peripheral arterial disease
Grade 0: Pre-or post-ulcerative lesion, Grade 1: Superficial wound, not involving tendon, capsule or bone, Grade 2: Wound penetrating to tendon or capsule, Grade 3: Wound penetrating to bone or joint
Low severity: light grey shadow, medium severity: grey shadow and high severity: dark grey shadow

If the patient had more than one ulcer, the most severe ulcer was selected as the index ulcer based on the UT classification system by clinical judgement of health care professionals in the clinic. This selection was made before data were collected.

Potensial confounders

Potential confounders were selected based on the literature and expert advice from clinicians and epidemiologists. These were sex, age, HbA1c, coronary disease, vascular surgical treatment and neuropathy. Justification for the choices of the confounders are described at page 44.

3.1.5 Outcome (endpoint), competing events and follow-up time

The outcome was healing time. *Healing time* was defined as the time from the start of treatment in specialist health care to complete ulcer healing. *Healing* was defined as healing (intact skin) of the whole foot without minor or major amputations. *Competing events* were amputation and death. *Follow-up time* was defined as the time from the start of treatment in the outpatient clinic until ulcer healing, amputation or death, whichever came first. *Minor amputation* was defined as amputation below the ankle, while *major amputation* was above the ankle.

3.1.6 Statistical methods

Mean, median and standard deviations (SD) were used for continuous variables, and counts and percentages for categorical variables. To test for associations between categories of duration of ulcer and severity of ulcer, Chi-square tests were used and t-tests were used for continuous variables.

To calculate healing time of a DFU from start of treatment in specialist health care to healing, amputation or death, survival analysis was used. First, the cumulative incidence function was used to calculate healing time using the stcompet command in Stata with amputation and death treated as competing risk and calculated separately for: 1) duration of ulcer divided into two fractions, and 2) for the three combinations of grade and stage. Second, competing risk regression analysis by Fine & Gray (111, 112) was used to calculate the association of duration of ulcer, ulcer severity classified according to the UT classification system with healing time, and also for the association between amputation and ulcer severity. Competing events were amputation and death, while loss to follow up was treated as censored observations (111, 112). Results were reported as sub hazard ratio (SHR) with 95% confidence intervals (CI). First, the associations between predictors, potential confounders and the outcome using univariate competing risk regression models, were investigated. Second, a model was constructed where the main exposures, the two fractions of duration of ulcer and ulcer severity were mutually adjusted. Finally, a multivariate competing risk regression model including potential confounders, such as sex, age, HbA1c, coronary disease, vascular surgical treatment and neuropathy was constructed, in addition to the two fractions of ulcer duration and ulcer severity.

3.2 Study II

3.2.1 Design

To assess the effect of telemedicine follow-up care versus standard outpatient care for DFUs, we used a pragmatic cluster non-inferiority RCT (Clinicaltrials.gov:

NCT01710774) (Explanation of the terms pragmatic and non-inferiority is described on page 41-42). The trial protocol has been published previously (26). The patients were recruited from September 2012 to June 2016.

3.2.2 Study sample

Patients with diabetes-related foot ulcers referred to three hospitals in Western Norway: the Endocrinology Unit at Stavanger University Hospital, the Surgical Unit at Stord County Hospital and the Orthopaedic or Endocrinology Units at Haukeland University Hospital were included.

Inclusion criteria were: Patients with type 1 or type 2 diabetes, aged 20 years or older with a new DFU. Excluded were patients who 1) had an ulcer on the same foot as the new ulcer during the previous 6 months before inclusion; 2) were unable to complete questionnaires in Norwegian; 3) had received a diagnosis of mental disorders or cognitive impairment (including schizophrenia, other psychotic disorders, and dementia); or 4) had a life expectancy of less than 1 year (26).

3.2.3 Randomisation and Blinding

Municipalities or districts in the municipalities in Hordaland and Rogaland County were divided into 42 clusters and matched in 21 pairs based on the population size and rural and urban characteristics of the municipalities or districts. A person not participating in the conduct of the study performed the randomisation using SPSS. After patient consent and baseline data collection, the patients were randomised to treatment with telemedicine follow up or to standard outpatient care based on the cluster they belonged to. All patients in each cluster were in the same treatment group and stayed in the study until ulcer healing, amputation or death, but maximum 12 months (See Paper II consort flow diagram).

3.2.4 Telemedicine intervention

The follow up procedure for the intervention is shown in Figure 3. At baseline, all patients were diagnosed, an image of the foot ulcer was taken and the foot ulcer was

classified according to the UT classification system (12, 110). The community nurses received training in the telemedicine equipment during the 2 weeks after the patients were included in the study. The training consisted of written information about the study, a standard study procedure and practical training in how to use the telemedicine equipment.

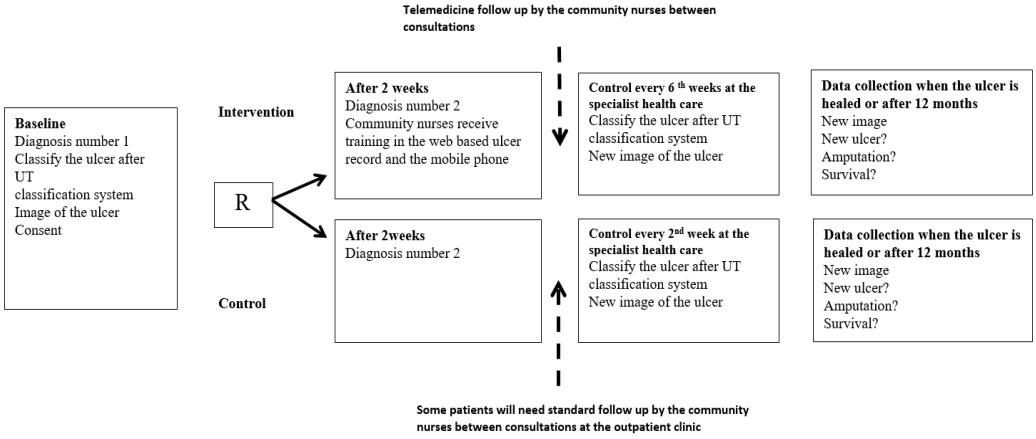


Figure 3.The follow up procedure for the intervention

Intervention group

The telemedicine intervention was asynchronous and consisted of an interactive web-based ulcer record '®PleieNet' and a mobile phone that facilitated the sending of image and text to the web-based ulcer record (26, 113) (Figure 4). Image and text were stored in the web-based ulcer record and transferred in an encrypted form to a server (113).

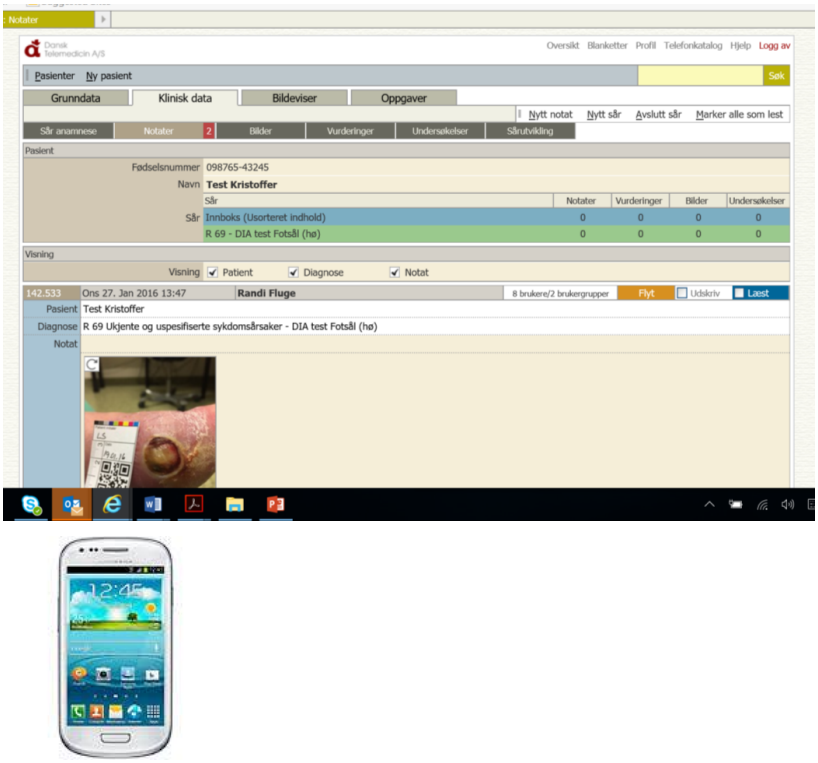


Figure 4. The telemedicine equipment; web-based ulcer record and mobile phone

The patients received telemedicine follow up by the nurses in the community with consultations at the outpatient clinic every 6th week until an endpoint occurred, up to a maximum of 12 months. During follow-up time in the community, the community nurses communicated weekly with the expert team at the outpatient clinic by sending an image and written assessment of the foot ulcer via the mobile phone or e-mail to the web-based ulcer record. They received assessment, feedback and further follow-up procedure instructions from the expert team. If image and text were not recorded weekly by the community nurse, a reminder was sent by the expert team.

Control group

Patients in the standard outpatient care group received standard outpatient care provided by the outpatient clinic, usually scheduled to take place every second week

(26). The treatment procedures were evidence-based and based on the quality system at the hospital.

3.2.5 Outcomes (endpoints) and competing events

Primary outcome measure

The primary outcome was *healing time,* defined as the time from the start of treatment in the outpatient clinic until the foot ulcer healed, but the maximum follow-up time for each patient was 12 months. *Healing of the ulcer* was defined as healing (intact skin) of the whole foot without any surgery (minor or major amputation) in the study period (26).

Secondary outcomes

Amputation was defined as minor or major amputations before ulcer healing.

Death was defined as death before ulcer healing.

Number of consultations per month of follow-up: For the telemedicine group each consultation at the outpatient clinic was registered in the web-based ulcer record. In the community care, the total number of consultations each patient received during follow up were documented in the web-based ulcer record by the community nurses.
For the standard outpatient care group: Each consultation at the outpatient clinic was registered in the web-based ulcer record. If the patients needed follow up from the community nurses, health care providers at the outpatient clinic documented the total number of consultations during follow up.

Patients' experience: The Generic Short Patient Experiences Questionnaire (GS-PEQ) (114) was used to measure patients' experience with either telemedicine follow up or standard outpatient care at the end of follow up. It consists of ten questions with a response score on a five point Likert scale ranging from 1-5 (1= not at all, 5=very strong degree). The Cronbach alpha for the 10 questions combined was 0.80. Question ten showed low item-to-total correlation and was therefore excluded before calculation of a mean satisfaction (experience) score for each patient. The patients completed the questionnaire at the end of the follow-up period.

3.2.6 Data collection

Data were collected from medical records and the web-based ulcer record (®PleieNet) using a standard data collection form. The data collection started in September 2012 and lasted until February 2017. The data collection on the last patient was completed on February 22nd 2017. The first author (HSS) participated in the data collection at Haukeland University Hospital.

At baseline (before randomisation), self-reported demographic data on age, sex, ethnicity, education, marital status, cohabitation and smoking status were collected. Clinical data on HbA_{1c}, type of diabetes, localization of ulcer, classification of ulcers on the basis of the UT classification system, and micro vascular complications (as neuropathy and nefropati) macro vascular complications (angina pectoris, myocardial infarction, and stroke) were collected (26).

Number of consultations per month of follow-up: See point 3.2.5 sub title secondary outcomes.

3.2.7 Statistical methods

The analyses were performed according to the protocol using the intention-to-treat analysis (26). We used mean and standard deviations (SD) for continuous variables, and counts and percentages for categorical variables. To test for the difference between groups on categorical variables, Chi-square test was used and t-test for continuous variables. A linear mixed effect regression to account for clustering in both groups was used to investigate differences in mean healing time among those patients whose ulcer healed, mean number of consultations per month and mean sum of a patient's experiences. To test for differences in proportion of amputation and death we used a generalised linear model with log-link and binomial distribution. Cumulative incidence curves for healing were calculated for the telemedicine group and standard outpatient care group separately using the stcompet-command in Stata with amputation and death treated as competing events. Competing risk regression analysis by Fine & Gray, with robust standard errors to account for clustering, was used to calculate the differences

in healing time between the telemedicine and standard outpatient care, treating amputation and death as competing events (111). Results were reported as sub hazard ratio (SHR) with 95% confidence interval (CI) comparing the telemedicine and standard outpatient groups.

In additional analysis, we used linear mixed model to test whether distance to the outpatient clinics affected the differences in consultations per months between the two groups. The model was also used to test whether there was an association between severity of ulcer and number of consultations per month. Further, to test whether there was a difference in number of consultations between the 3 hospitals within the telemedicine group.

To determine the number of patients necessary, a power calculation was done. To detect a difference in mean healing time of 1.5 months (115) with 80% power, a significance level of 0.025, a standard deviation of 3.6 months (116) and an intra-class correlation coefficient of 0.02 and an average cluster size of 10 participants, the number of participants needed to be included was 217. Since we expected an attrition rate of 5%, the number was set to 228, i.e. 114 patients in each group (26).

The non-inferiority margin of 1.5 months was chosen based on the telemedicine consultations at the outpatient clinic being planned to take place every 6th week. If an ulcer healed between two consultations, health care personnel verified that the ulcer had healed at the subsequent consultation at the outpatient clinic.

Thirteen patient did not receive telemedicine follow up due to 1) the patients did not want to receive follow up from the community nurses, 2) next of kin performed the treatment and 3) the ulcer was healed before the community nurses started follow up. All analyses were repeated (per protocol analysis) excluding the 13 patients in the telemedicine group who did not receive telemedicine follow up.

3.4 Study III

3.4.1 Design

Interpretive description as descried by Sally Thorne (117, 118), was used to explore experiences with telemedicine follow up and standard outpatient care in patients with DFUs delivered in a clustered RCT. The main objective of interpretive description is to provide knowledge that can have implications for nursing practice by giving methodological advice for developing such knowledge (117, 118).

The method was first described by Thorne and colleagues in 1997 (119). Interpretive description builds on elements from grounded theory, ethnography and phenomenology. The goal for a study using interpretive description is that the research question should have implications for practice as well as originate from a deep understanding of what is known/unknown about the research area. The data collection and analysis should be performed concurrently, using constant comparative analysis. In this process, Thorne recommended avoiding premature coding. According to Thorne, clinical interpretability is not adequate with a 'pure' description of the results, and therefore the analytical process should seek to discover associations, relationships and patterns within the phenomenon that have been described (117, p. 50). Interpretive description does not require the study to be positioned with a formal theory (117, 118).

3.4.2 Study sample

Among patients participating in the cluster randomized non-inferiority trial, a purposive sample was chosen. We decided to use a heterogeneous sample, because we assumed that informants with different characteristics and experiences with telemedicine follow up and standard outpatient care might have different views about their treatment experience and in addition, would best be able to answer the research question (117, 118, 120). The inclusion criteria were patients who had completed the telemedicine intervention or standard outpatient care or were close to the endpoint (healed ulcer), who differed on their distance from the hospital, age, gender, education,

employment, material status and comorbid diseases and were able to participate in a one-on-one interview (able to consent, speak Norwegian).

The study nurses at Stavanger and Stord Hospitals, responsible for the trial, organised patient recruitment based on the inclusion criteria previously described. The study nurse gave information about the interview and consent procedure. Patients who agreed to participate were contacted by the first author (HSS) to arrange the time and place for the interview.

3.4.3 Data collection

Individual interviews were used as the data collection strategy for this patient group, because we were interested in the individual experience with either telemedicine or standard outpatient care follow up. The first author (HSS) conducted all 24 interviews. The participant decided the time and place for the interview. Five interviews were conducted at the participants' workplaces. The other interviews were conducted in the participants' homes. Each interview lasted between 35 and 55 minutes. They were digitally recorded and each had a transcript prepared verbatim by the first author. The interviews were conducted over a period of 15 months between March 2014 and May 2015. Twenty-four interviews were conducted (13 in the telemedicine group and 11 in the standard outpatient care group). There is no consensus on the number of participants needed to be included to ensure rich data. Saturation (119) or information power (121) are terms used to describe when sufficient participants are recruited. After including 24 participants, adequate saturation was researched. This was based on a continuous review of the interview findings, and saturation became clear when no new categories, themes or explanation emerge from the data.

In order to compare and contrast the two groups, we kept the questions in the interview guide consistent and kept the core set of the questions as similar as possible for both groups. Exceptions were made for questions related to the patients' experiences with health care professionals' use of the telemedicine equipment and users' own views of health care professionals' use of digital images and remote assessment in wound care (Appendix 2). The interview guide was piloted with one patient from each group of the

trial to assess its usefulness and relevance of the questions. It was perceived as a functional tool with the need for only minor changes and the pilot interviews could therefore be included in the data material.

3.4.4 Analyses

According to the interpretive description strategy, the data collection and analysis of data should occur concurrently. The strategy does not provide the researcher with a 'cookbook' of how the data material should be analysed because use of a 'cookbook' approach might limit the researcher's creativity in the analysis process (117). Interpretive description allows for different analysis techniques, as long as the choice of the analysis technique is based on the research questions and the analytic process is logical and transparent. Important in the analysis process is creativity and intuition, and Thorne therefore recommend avoiding detailed coding at the beginning of the analysis process, because stricter coding might cause loss of valuable insight . A wider focus can prevent premature coding (117).

The analysis process comprised four phases: (1) researchers' immersion in the transcripts, (2) coding and developing of themes, (3) comparing and contrasting themes within the groups, and (4) comparing and contrasting themes between the groups (telemedicine/ standard outpatient care). Phase one started right after each interview field notes were taken. These field notes helped in the further analyses of the data, because they illuminated reflections on issues that arose during the interviews. In an ongoing process during the data collection period, the interviews were transcribed by the first author and read repeatedly in order to become familiar with the data. All transcripts ended up with tentative topics and preliminary interpretations of the text that were used in the further analysis process. In this process, the data material was read and discussed with the co-authors. During the analyses, it was important to be aware of one's own pre-understanding, personality and experiences that could influence the analysis process (117, 120). In the next step, the initial coding started with an inductive approach and the coding was broad-based to avoid premature closure. We chose codes that matched closely to the language inherent in the data. The codes

that seemed thematically related were then placed together. Different tentative themes were identified and used in the further analysis. In the next step, we used a constant comparison approach to compare data and patterns within every interview and between interviews. This approach was used for within-group comparisons and between-group comparisons to identify similarities and differences. During this process, questions were asked as to what we saw in the data material, but also attention was given to what we might not have seen which could be important. Finally, comparing and contrasting these patterns within and between the groups enabled us to identify themes that were common.

4. Ethical and legal issues

The studies were performed in accordance with the ethical principles stated in the Declaration of Helsinki and were approved by the Western Norway Regional Committee for Medical and Health Research Ethics (REK2013/2327; REK 2001/1609).

Study I

Project number, Western Norway Regional Committee for Medical and Health Research Ethics: 2013/2327.

Written informed consent was required from all participants alive at inclusion. The participants were invited by letter to participate in the study. They were informed that active participation was not required, only consent to obtain information from medical records. All participants were informed about the meaning of voluntary participation, that is, their right to withdraw from the study at any time without any consequence for or influence on further treatment and care at the hospital. Further, they were informed about anonymisation and confidentiality of the data collected. If participants had any question related to the study, questions could be addressed to the project manager by phone or email.

We followed the STROBE Statement: guidelines for reporting observational studies (122).

Study II

Project number, Western Norway Regional Committee for Medical and Health Research Ethics: (2011/1609).

Participation was voluntary and written informed consent was required. All participants were informed about the meaning of voluntary participation, that is, their right to withdraw from the study at any time without any consequence for or influence on further treatment and care at the hospital. Further, they were informed about

anonymisation and confidentiality of the data collected. Participating in the study did not raise problematic or specific ethical issues.

The Norwegian Centre for Integrated Care and Telemedicine was the Counselor according data security and legal aspects of the project. Data controller agreements were established between all involved parties according to Norwegian legislation and security services. Risk assessment analysis after the pilot project and during the study period was conducted.

To improve the clarity, accuracy and transparency of our trial report we followed the CONSORT flow diagram extension to cluster randomised trials (123) together with the CONSORT checklist for non-inferiority and equivalence randomized trials (124).

Study III

Study 3 involved collection of new data from a subsample of patients involved in the RCT. Permission was given by the Western Norway Regional Committee for Medical and Health Research Ethics (2011/1609). Relevant participants were contacted by the study nurse who asked if they would be willing to participate. If they agreed, a formal appointment for an interview was obtained. Written consent was required by the participants before the start of the interview. Participants were informed about the ethical principles.

5. SUMMARY OF THE RESULTS

5.1 Study I

Severity and duration of diabetic foot ulcer (DFU) before seeking care as predictors of healing time: A retrospective cohort study.

Of the 105 patients included in this cohort, 45.7% achieved complete ulcer healing, 36.2% underwent amputation, 9.5% died before healing and 8.5% were lost to follow up (Figure 1, p. 19). The median follow-up time measured from start of treatment in specialist health care to end of follow up for the total sample (including those who healed, amputated, died and lost to follow up) was 67 days (2.2 months). Mean follow-up time was 130 days (4.3 months). The median time measured from start of treatment in specialist health care to ulcer healing for those who healed was 75.5 days (2.5 months). Mean healing time was 113 days (3.8 months). Baseline characteristics of the patients and baseline characteristics of severity of ulcers are shown in Tables 3 and 4.

Table 3. Baseline characteristics of patients with a diabetic foot ulcer

Characteristics	**Total** *(n = 105)*
Demographic variables	
Male sex, n (%)	74 (70.5)
Age (years) mean, (SD)	68.7 (±14.8)
Diabetes type	
Type II, n (%)	83 (79.0)
Disease-related variables	
Insulin treatment, n (%)	68 (64.8)
HbA1c (mmol/L), (SD)	63 (±17.5)
HbA1c (% units), (SD)	7.9 (±1.6)
Localization of ulcer, n (%)	
Toe	64 (61.0)
Metatarsal/plantar	19 (18.1)
Heel	22 (21.0)
Comorbidities	
Coronary diseases, n (%)	48 (45.7)
Neuropathy, n (%)	69 (65.7)

Table 4. Ulcer characteristics at baseline according to University of Texas classification of patient with diabetic foot ulcers

Stage		Grade 0	Grade 1	Grade 2	Grade 3	Total
A	Clean wound	-	16 (15.2)	1(1.0)	1 (1.0)	18 (17.1)
B	PAD -, infection +	-	8 (7.6)	10 (9.5)	11 (10.5)	29 (27.6)
C	PAD +, infection -	-	8 (7.6)	5 (4.8)	6 (5.7)	19 (18.1)
D	PAD +, infection +	-	5 (4.8)	10 (9.5)	24 (22.9)	39 (37.1)
Total, n, (%)		-	37 (35.2)	26 (24.8)	42 (40.0)	105 (100)

PAD: Peripheral arterial disease
Grade 0: Pre-or post-ulcerative lesion, Grade 1: Superficial wound, not involving tendon, capsule or bone, Grade 2: Wound penetrating to tendon or capsule, Grade 3: Wound penetrating to bone or joint

Thirty-eight point one percent of the patients had had an ulcer ≥ 60 days before the start of treatment in specialist health care, where 31.4% of the patients had had an ulcer 52 days or more from patient-reported ulcer onset to referral by GP to specialist health care. Thirty-four point three percent of the patients waited more than 14 days before start of treatment at the specialist health care after referral from the GP. Of patients classified in grade 3/stage D, 10 patients underwent minor amputation and 10 major amputation.

In the unadjusted univariate competing risk analyses, we found that there was a significant association between time from patient-reported ulcer onset to referral by a GP to specialist health care and healing time (SHR 0.33, CI 0.15, 0.72), but no association between referral from a GP to specialist health care and healing rate was found (SHR 1.30, CI 0.61, 2.76). In the adjusted multivariate competing risk analysis, these associations were maintained. We found that patients who had a duration of ulcer ≥ 52 days from patient-reported onset of ulcer until referral by a GP to specialist health care had 58% decreased healing rate compared with patients who were referred earlier (SHR 0.42, 95% CI 0.18, 0.98) in the adjusted model. There was no association between time from referral from GP to start of treatment in specialist health care and healing rate (SHR 1.84, 95% CI 0.70, 4.84).

For ulcer severity, we found that patients with ulcers of the highest stage and grade had 86% decreased healing rate compared with ulcers of low severity, after adjusted for referral time and other potential confounders (SHR 0.14, 95% CI 0.05, 0.43).

5.2 Study II

The Effect of Telemedicine Follow-Up Care on Diabetes-Related Foot Ulcers: A Cluster Randomized Controlled Non-Inferiority Trial

In total, 142 of 182 patients in the trial obtained complete healing: 75 (79.8%) in the telemedicine group and 67 (76.1%) in standard outpatient care group, respectively. Mean healing time for those who healed was 3.4 months in the telemedicine group and 3.8 months in the standard outpatient group. Baseline characteristics of the patients and baseline characteristics of severity of ulcers are shown in Tables 5 and 6.

Table 5. Baseline characteristics for the total sample of patients with a diabetic foot ulcer

Characteristics	**Study II** *(n* = 182)
Demographic variables	
Male sex, n (%)	135 (74.2)
Age (years), n (±SD)	66.4 (±16.6)
Subgroups of diabetes	
Type 2 diabetes, n (%)	144 (79.1)
Diabetes-related variables	
Insulin treatment, n (%)	116 (64.4)
HbA1c (% mmol/L), n (±SD)	62 (± 18.6)
HbA1c (% units), n (±SD)	7.8 (±1.7)
Ulcer characteristics	
Localization of ulcer, n (%)	
Toe	91 (50.0)
Metatarsal/plantar (study 1), Metatarsal (study II)	27 (14.8)
Heal	16 (8.8)
Other	48 (26.4)
Cardiovascular disease n (%)	56 (31.6)
Neuropathy, n (%)	120 (71.4)

Table 6. Ulcer characteristics at baseline according to University of Texas classification system by treatment groups

Stage		Telemedicine (n = 94)			Standard outpatient care (n = 88)		
		Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
A	Clean wound	29 (30.0)	2 (2.1)	0 (0.0)	34 (38.6)	2 (2.3)	0 (0.0)
B	PAD -, infection +	27 (28.7)	3 (3.2)	4 (4.3)	19 (21.6)	2 (2.3)	7 (8.0)
C	PAD +, infection -	14 (14.9)	1 (1.1)	1 (1.1)	14 (15.9)	3 (3.4)	2 (2.3)
D	PAD +, infection +	7 (7.4)	4 (4.3)	2 (2.1)	1 (1.1)	0 (0.0)	4 (4.6)

PAD: Peripheral arterial disease

Grade 0: Pre-or post-ulcerative lesion, Grade 1: Superficial wound, not involving tendon, capsule or bone, Grade 2: Wound penetrating to tendon or capsule, Grade 3: Wound penetrating to bone or joint

For the primary outcome, we found that telemedicine was non-inferior to standard outpatient care regarding healing time (mean difference -0.43 months, 95% CI -1.50, 0.65). Competing risk regression analysis showed no statistical differences between the groups in healing time (SHR 1.16, 95% CI 0.85, 1.59).

The analysis for the secondary outcomes showed significantly fewer amputations in the telemedicine group compared with standard outpatient care, 6 (6.4%) and 13 (14.8), respectively, (mean difference –8.3% with 95% CI –16.3%, –0.5%).

There were no significant differences in the proportion who died between the two groups, 5 (5.3%) in the telemedicine group and 5 (5.7%) in the standard outpatient group, respectively, (mean difference -0.4%, 95% CI -6.5%, 5.7%).

The number of consultations per month for the telemedicine group and standard outpatient group at the outpatient clinic was not significantly different, 2.0 and 2.5 consultations per months, respectively. The consultations were in favour of telemedicine group (mean difference -0.48 consultations per month, 95% CI –1.46, 0.49).The additional analyses showed that the hospital that was included first in the intervention showed significantly lower number of consultations per months within the telemedicine group compared with the hospital that was included last (mean difference -1.1, 95% CI -2.2,-0.1).

Within the telemedicine group, patients who lived more than 25 km from the outpatient clinic had significantly lower number of consultations per months compared to those who lived ≤ 25 km from the outpatient clinic (mean difference -1.0, 95% CI -1.9,-0.1).

There were also significantly fewer consultations per month in the telemedicine group compared to the standard outpatient care group when the analyses was restricted to patients living >25 km from the outpatient clinic (mean difference -1.2, 95% CI -2.4, -0.03).

Patients in both groups reported high satisfaction with the treatment and follow up and there were no significant differences between the two groups (mean difference 0.07, 95% CI -0.10, 0.24).

5.3 Study III

An integrated wound-care pathway, supported by telemedicine, and competent wound management-Essential in follow-up care of adults with diabetic foot ulcers.

An important requirement expressed by the patients was to feel secure about or have confidence in the treatment and follow up. From the interpretive description analysis, three themes emerged: *competence of health care professionals*, *continuity of care,* and *easy access* to health care. Type of follow up (telemedicine versus standard outpatient care) appeared to be less important in terms of the patients' follow-up experiences. The competence of health care professionals and continuity of care were essential because these two factors had the capacity to either strengthen or threaten high-quality foot ulcer care. If these two factors were absent among the home care nurses, the patients felt that they lost confidence in the wound care process. If this happened, patients pointed out that the expert knowledge from health care professionals in the outpatient clinic turn out to be an essential confidence factor for them, and was necessary to receive good foot care. When telemedicine functioned as intended, the analysis revealed positive process with use of telemedicine follow-up. This was related to that use of an image with the mobile phone could rapidly capture changes in the healing process. By forward the images to the expert team at the outpatient clinic this allowed both the home care nurse and the expert team to evaluate the ulcer and discuss necessary treatment cause. Easy access and proximity to the service were important for the patients. Follow up of the home care nurse was a relevant care pathway if the home

care service was available and of sufficient quality i.e. competence among home care nurses and continuity of care. If these two factors were presented, the patients preferred to receive follow-up from the home care nurses because treatment close to home provided flexibility in choosing time and place for treatment and thus limited travel time and waiting time at the outpatient clinic.

6. DISCUSSION

The overall aim of this study was to provide new knowledge about predictors of healing time in patients with a DFU and to assess the effect of and experience with a telemedicine intervention in patients with a DFU. More evidence is needed on alternative care pathways to follow-up DFUs and this RCT (paper II) is the second in the world investigating the effect of a telemedicine intervention on people with DFUs. The first part of this section considers strengths and limitations of the methodologies used in the three studies. In the second part, the main findings will be discussed.

6.1 Methodological considerations

6.1.1 Study design

A retrospective cohort study design, as used in Study I, is appropriate for describing associations between variables and was used to describe the association between duration of ulcer with healing time and ulcer severity with healing time. The design is characterised by the exposure and outcome having occurred in the past (exposure occurring before the outcome) and data having been collected from existing records, in this case electronic medical records (125). The strength is that the patients were followed over time, from start of treatment to the endpoint. We extracted data from the electronic medical records from 2009 to 2011and then followed the cohort forward in time to investigate the influence of the exposures (i.e. duration of ulcer and severity of ulcer) on the outcome (i.e. healing time). This research design allowed the description of observed associations but a limitation is that caution should be exercised in inferring this to be evidence of cause and effect.

To evaluate the effect of the telemedicine intervention, we used a pragmatic cluster randomised controlled non-inferiority trial in Study II. The design is a parallel cluster design that compares the results of a specific intervention (telemedicine follow up) with standard outpatient care used for the control group. This prospective and experimental study is characterised by the independent variable being manipulated and controlled by

the researcher and the dependent variables being collected under controlled conditions (126). However, this pragmatic trial investigating the telemedicine intervention in daily clinical practice at three clinical sites may lead to less control of the intervention and outcomes variables due to lack of blinding of the health care professionals and the patients (127).

The main advantage of an RCT compared to a cohort study is that causal relationships may inferred, albeit with some limitation regarding external validity of the findings from the RCT. A pragmatic trial approach may increase the external validity and generalisability of the results, because pragmatic trials measure the effect of the intervention in a real-life setting (127).

A non-inferiority approach was decided based on the expectation that telemedicine follow-up care would be no worse than standard outpatient care in terms of ulcer healing time. A non-inferiority approach is of interest from the premise that the new treatment has some other advantages than the standard or reference treatment (124). Telemedicine follow up may have the advantage that it might be preferable to standard outpatient care given that it may lead to more integrated care, allow more patients to be treated in or near their home, and thus contribute to more flexible health care services.

A cluster RCT is characterised by randomisation at group or cluster level and is used when it is difficult to apply an experimental intervention to individual subjects (128). The rationale for choosing a cluster RCT was that a classic RCT could threaten the internal validity of the findings. We therefore randomised municipalities and districts within municipalities (organisational units) to avoid that the community nurses treated patients in both the telemedicine and standard outpatient care groups, which could threaten the internal validity (26).

The rationale for choosing a qualitative approach in study III was to get in-depth knowledge of patients' experiences with receiving either follow up or standard outpatient care beyond the actual effect goals in the cluster non-inferiority RCT. The strength of a qualitative design is that data are collected in a real world setting, but a

weakness with the use of qualitative data is reduced generalizability of the findings (120). An additional limitation was that the data were collected only from two of the three clinics that were involved, making the conclusion not fully reflective of the whole picture. However, qualitative information can be an important supplement information in helping to evaluate whether use of telemedicine may be an alternative care pathway for patients with DFUs.

6.1.2 Internal validity (Paper I and II)

Internal validity in quantitative designs refers to the extent to which the results of the study demonstrate a cause-effect relationship between the independent and dependent variables (125). In a non-experimental study, like Study I, internal validity measures the extent to which the independent variable is a possible explanation for the relationship with the dependent variable (129). In experimental research, as in Study II, this means that the intervention causes the change in the dependent variable (130). The reporting of the studies are in line with the CONSORT statement: STROBE Statement for Study I (122), and CONSORT 2010 for the cluster randomised trial (123); CONSORT Statement 2006 for Non-inferiority and Equivalence Trials for Study II (124), which are intended to improve the reporting of trials and minimising the risk of bias.

Retrospective cohort study – Study 1

The internal validity in the retrospective cohort study is dependent mostly on issues such as confounding, selection bias, information bias and sample size. In cohort studies, randomisation is not applicable and controlling for confounders is therefore important (129).

A confounding variable, can affect the association between the independent variable (exposure) and dependent variable (outcome) that can affect the results (129). Support for confounding occur if we find that: 1) the potential confounder is associated with the exposure factor, 2) independently associated with the outcome, and that 3) the variable cannot be an intermediate between exposure and the disease (129). To adjust

for possible confounding different multivariable statistical techniques can be used such as multivariate regression analysis. Potential confounders should be identified *a priori* based on the knowledge of the field. Six potential confounders were identified *a priori* based on previous knowledge and before the statistical analysis. Age, sex, HbA1c, neuropathy and comorbidity such as coronary diseases are often well known confounders in the association between the exposure and outcome (11) and are often adjusted for in multivariate analyses. An additional argument for including neuropathy was that neuropathy is not included in the UT classification system, which has been emphasised as a limitation of the system (14, 65). Vascular surgery treatment as a proxy for peripheral arterial disease is less frequently assessed as a potential confounder (11), but it can be an important predictor in ulcer healing if the treatment leading to increased blood flow in the lower extremities is improved. The univariate analysis revealed that age and vascular surgery treatment were potential confounders in the association between duration of ulcer and healing time. These variables were associated with reduced healing time. We therefore adjusted for age and vascular surgery treatment in the multivariate competing risk analysis but also included the other potential confounders. In the adjustment analysis these association did not remain significant.

Selection bias is a result from the procedure used to select participants and from factors that influence study participation leading to a systematic error (129). Due to our sampling method, risk of selection bias may have occurred. In total, 30.5% of the eligible patients did not consent to participate. Non-participants might have been in worse health compared with participants, which could potentially have led to selection bias. Therefore, the increased healing time associated with duration of ulcer before start of treatment in specialist health care and severity of ulcer might have been under-estimated. On the other hand, patients might have had worse health when they were asked to participate, which in this retrospective study means at the end of the study. This does not mean that the overall health of the patients at the starting point was worse. We also excluded patients treated for foot ulcers during the previous 12 months. An under-representation of patients with chronic ulcers may have resulted in an under-estimation of the association between severity of ulcer and healing time. Altogether, this might have led to a selection bias, with our sample representing less severe ulcers.

Information bias can result from systematic errors concerning information documented in the electronic medical records that can lead to incorrect measurement in the exposure or outcome variable (129). Electronic medical records were used to collect data on the patients. We can assume that objective data such as disease-related variables, ulcer-related variables and the demographic variables of age and gender are reported reasonably accurately in electronic medical records. In Study I, we used patient-reported data on duration of the ulcer, which might be more inaccurate, as patients with neuropathy can have an ulcer without being aware of it. This might have under-estimated the association between duration of ulcer and healing time.

The sample size in Study I is relatively small, increasing the risk of type II error, i.e. failing to find statistically significant results even though there is an association between the variables in the population from which the sample was drawn (125). Of a total cohort of 151 patients registered between 2009 and 2011 at the two hospitals, 105 patients were included in our study. However, despite a small sample size, our findings showed that duration of ulcer and severity of ulcer were significantly associated with healing time after controlling for confounders.

Experimental design – Study 2

An experimental design, due to its manipulation of the independent variable, control of the experimental situation and randomisation, is considered to be the design that has most robust internal validity (130). However, different threats to internal validity and statistical conclusion validity need to be considered.

Selection bias may be a treat to internal validity. Selection bias in an experimental design refers to systematic differences in baseline characteristics between the two groups (126). Selection bias is usually ruled out in an RCT if successful randomisation occurs, but consideration of selection bias should nevertheless be given (130, 131). Randomisation at the cluster level can cause differences in the groups. We found that the baseline characteristics between the two groups were overall well matched except for a significant difference in localization of the ulcer and type of diabetes between the two groups. More patients in the telemedicine group had an ulcer in the toe region

compared with the standard outpatient group. Since the clusters in our study were relatively small, this might explain the difference in ulcer location between the two groups. However, when we adjusted for ulcer localization with healing time in the linear mixed effect regression model, the difference between the groups was still non-inferior (unadjusted: mean diff -0.43 (CI -1.50, 0.65) and adjusted: (mean diff -0.19 (CI -1.28, 0.90). In addition, in competing risk analysis with ulcer healing as the endpoint adjusted for ulcer localization, SHR did not change much (SHR 1.13, 95% CI 0.83, 1.57). A higher proportion of patients in the telemedicine group had type 2 diabetes, but the proportion of patients using insulin in both groups was not statistically different, indicating similarities in severity of diabetes between the groups. Due to these explanations, we consider the risk of selection bias caused by randomisation to be low.

In the analyses of mean healing time we included only those who healed in the two groups, excluding those who died or amputated and those who had not achieved ulcer healing after 12 months. This was necessary since it does not make sense to measure healing time for an ulcer which did not heal, but it may have led to some degree of selection bias since the amputation rate was higher in the standard outpatient care group. To account for this we also did competing risk regression where all patients were included. But since we had not decided upon an a priori non-inferiority margin for the confidence interval of the SHR we could not investigate non-inferiority in the competing risk analysis. We could thus only test for significant differences. Ideally, a non-inferiority margin should have been set a priori also for the SHRs, but it is difficult to select clinical relevant margins for a relative measure.

Another treat to internal validity is attrition bias which refers to a situations where patients in the experiment fail to complete some or all of the outcome measures (131). Thirteen patients in the intervention group did not receive the telemedicine intervention as intended in primary health care. Such occurrences can underestimate the effect of the intervention, since some patients did not get the assigned treatment (125). To test for this, we therefore repeated the analysis as a per-protocol analysis, excluding the 13 patients in the telemedicine group, and found that the results were approximately the

same. Therefore, we considered the risk of attrition bias to be low. There was also no attrition of clusters in the study.

Further, performance bias is a systematic difference in the care provided to patients between groups or in exposure to factors other than the intervention of interest (131). In the RCT, we could not blind the health care professionals at the outpatient clinics who delivered the intervention. This may have affected the number of consultations at the outpatient clinics or caused fewer amputations to be performed in the telemedicine group compared with the standard outpatient care group. We consider the risk of performance bias to be high.

Detection bias, is also a treat to internal validity, refers to a systematic difference between groups in how outcomes are determined (131). As we did not blind the patients, researcher and outcome assessors, the risk of detection bias increased.

In addition, time is an important factor to consider, as the real world setting will change during a 5-year trial that can be referred as *history bias* (126). During this period, the pressure on the health care system might have increased and consultations might have been delayed or re-scheduled more often. Another aspect is that even though we used the same technology throughout our trial, technology is continually developing and as more sophisticated technology is now available, this needs to be considered when generalising the findings.

Statistical conclusion validity concerns whether the presumed cause and effect covary and how strongly they covary and two types of error: type I and II, that can occur (130). Type 1 error can occur if we conclude that cause and effect covary when they do not or conclude that they do not covary when they do (type II error) (130). To prevent type 1 errors occurring, the type I error rate is usually set to $\alpha = 0.05$ (130), but in a non-inferiority trial, it is set to $\alpha = 0.025$. This implies that 5% or 2.5% of the co-variation will occur by chance.

There are many potential threats to statistical conclusion validity and some of these are relevant to this study:

Low statistical power is one important factor that can threaten statistical conclusion validity (130). With low statistical power, the risk of type II errors increases. One way of ensuring adequate statistical power is to estimate the sample size needed by using power analysis. Estimated sample size based on power analysis in Study II was 217 (26). We managed to include a total of 182 patients. The lower sample size in this study compared with estimated sample size may have prevented us from detecting significant differences between the groups. However, all effect estimates for the secondary clinical outcomes favored the telemedicine group, indicating that a larger sample size would not have resulted in any differences in favour of the standard outpatient group.

Unreliability of treatment implementation is another factor related to statistical conclusion validity. It refers to whether the intervention is implemented inconsistently (125). In this pragmatic trial, different outpatient clinics, different municipalities or districts within the municipalities provided the intervention, and it is unlikely that all the health care professionals conducted the intervention in a similar manner in and across all the communities. However, to ensure that the health care professionals involved in the intervention received similar training, the training received from the specialist clinic was standardised and all involved in the intervention used the same guidelines. We considered the risk of unreliability of treatment implementation bias to be moderate.

Statistical conclusion validity can also be influenced by *restriction of range* (130). We used one instrument for evaluating patients' experience with receiving telemedicine follow up versus standard outpatient care. The positive experience with the treatment and follow up found in both groups in this study measured by GS-PEQ might be caused by a ceiling effect. This may indicate that the instrument chosen was not sensitive enough since most patients were clustered near the highest score.

6.1.3 External validity (Paper I and II)

External validity in quantitative research is the ability to generalise study results to the target population (129, 130), while generalisation in qualitative design refers more to the degree to which the findings can be transferred to other contexts (117, 118, 120).

The target population for all three studies was patients with a DFU referred to specialist health care in Norway. Approximately 19% of the Norwegian population lives in Rogaland and Hordaland counties were the patients were recruited from. Both counties serve patients from urban and rural areas. The composition of the inhabitants with respect to age and sex in Rogaland and Hordaland counties are very similar to that of the overall population in Norway. It is therefore reasonable to believe that the people with a new diabetic foot ulcer in Rogaland and Hordaland do not differ from patients referred to specialist health care in other counties in Norway. The study sample in Studies I and II are ethnically homogeneous, indicating that our results may not be representative of other ethnic groups.

Our cohorts in Studies 1 and 2 seem to correspond well to other cohorts both nationally and internationally (9, 35, 46, 47, 95, 132) with respect to baseline characteristics such as age, sex, types of diabetes, which can indicate that our sample can be representative of the target population being studied. However, in Study II, we excluded patients if they had mental disorders or cognitive impairment (including schizophrenia, other psychotic disorders), an inability to complete questionnaires in Norwegian and a life expectancy of less than 1 year,- limitations that might have reduced its representativeness.

6.1.4 Credibility in the qualitative study (Paper III)

To judge the credibility of the qualitative research, Thorne (117, 118) suggests several criteria: epistemological integrity, representative credibility, analytic logic, interpretive authority, moral defensibility and pragmatic obligation.

Epistemological integrity refers to demonstrating a logical coherence throughout the entire research process, from the research question, to the interpretation of data and use

of analytical strategies (117). Our research question in Study III focused on exploring patients' experiences with telemedicine follow up and standard outpatient care to promote knowledge gained from patients' perceptions about whether use of telemedicine could be an alternative way to improve wound care management for patients with DFUs and thus have implications for clinical practice. This is consistent with interpretive description where the results should have implications for clinical practice, without demanding that the findings be true for all patients receiving telemedicine follow up or standard outpatient care. The results of the current study showed that the patients' experiences varied, which needs to be taken into consideration when determining whether telemedicine is a possible care pathway for patients with DFUs. The analytical strategy chosen for interpreting the data must also be logical from the research question and be in agreement with the principle of interpretive description (117). To explore our research questions, patients with different characteristics were invited to participate. To fully meet the constant comparative method, data collection and analysis of data occurred simultaneously. Using a constant comparative analysis approach enabled us to explore similarities and differences within the groups and between the groups. This interpretive description approach made it possible to generate patterns and themes that gave us insights into issues important in wound care for patients with DFUs.

To achieve *representative credibility,* the results reported must be consistent with the sampling strategy chosen (117). We chose a sampling strategy that selected patients who could most benefit from the study. We chose to include patients with diverse backgrounds and who lived at different distances from the outpatient clinic to ensure maximum variation and comparability, which we assumed was relevant for their experiences. What is considered an appropriate sample size in qualitative design is debated (117, 120). However, rather, to claim saturation, a good rule is to follow a strategy that ensures information strength in the sample through gradual recruitment and analysis (117, 120).We stopped including patients when new categories, themes or explanation stop emerging from the data. Nevertheless, it is difficult to be sure, whether the sample size is large enough, but it is important to have in mind that the findings may have been different if a larger sample had been interviewed. However, only two

out of three clinics were involved in the supplementary studies, and therefore, this conclusion may not apply to the clinic that attended the trial in 2015.

Thorne recommended the use of an audit trail to facilitate transparency, referred to as *analytic logic* (117, 118). An audit trail is an adequate description of the different steps and decision-making taken throughout the entire research process that should make it possible for other researchers to assess the process. The data collection method and the analysis phases are described in more detail in section 3.4.3 and 3.4.4 page 30-31 and in paper III.

Interpretive authority is related to credibility of the interpretation (117, 118). The analysis process is influenced by the researchers' backgrounds and prior understanding and the researchers need to be aware of this in the analysis process. To achieve credibility of the interpretation each author analysed the data individually, after which they came together to discuss the data. By doing so, it was possible to obtain a consensus of the interpretation of the patterns and themes that emerged during the analysis process. Important in this process was the collaboration with experienced researchers with extensive experience in qualitative analysis. A challenge in the process was the term broad-based coding that in the beginning of the coding process was not clear, but an understanding of the term broad-based coding arose during some rounds of coding. In addition, the level of interpretation and to what level the data should be abstracted during the analysis process presented challenges, but the aim of the study and the relevance for clinical practice underpinned the process.

Moral defensibility refers to that the researcher must know why the knowledge is necessary and the purpose with such knowledge (118, 119). The care pathway for patients with DFUs has not be optimal. There are indications that patients with DFUs are treated for a substantial length of time in primary health care with limited continuity of care, few specialist nurses and lack of integrated care between health care levels (92, 93). In additional, the increased pressure at the health care system to deliver care to patients has required new approaches to organising the health care system. Therefore, we decided to investigate whether use of telemedicine could achieve a more

coordinated and integrated health care and thus be an alternative care pathway for this patient group. As a result of the findings, this study has provided new knowledge and insight beneficial to further discussions as to whether use of telemedicine could be an alternative care pathway for patients with DFUs and thus facilitate flexibility in wound care.

P*ragmatic obligation* is also mentioned by Thorne as a credibility indicator, described as a duty or obligation to the researcher to consider the findings "as if" it might be used in practice (118). It was therefore of importance to construct a study that should have implication for the clinical field and thus be enable to maintain the moral mandate to produce knowledge that could be useful in the clinical field.

6.2 Discussion of the results

6.2.1 Predictors of ulcer healing

Duration of ulcer

Although the importance of early referral of DFUs to specialist health care to prevent severe complications is emphasised in national and international guidelines (59, 61, 62), this recommendation needs more attention in clinical practice. This is underlined by our study as many patients with DFUs seemed to have been delayed in being referred to specialist health care (9, 63). Findings from Study 1 showed that 38.1% of the patients had a 60 days or longer duration of ulcer prior to the start of treatment in specialist health care. Our study showed a strong association between delayed referral to specialist health care and healing time after adjustment for potential confounders. In contrast to previous studies, we assessed different fractions of the referral pathway in addition to the total period (Figure 2, Page 20). We found that the interval from patient-reported ulcer to referral by a GP to start of treatment in specialist health care was the main contributor to the association. Patients who were referred by a GP to specialist health care 52 days or more after ulcer onset had 58% decreased healing rate compared with those who were referred earlier. Our results reinforce previous evidence that early referral to specialist health care when an ulcer has occurred is important (9, 63).

Although we found that the interval from patient-reported ulcer to referral by a GP to start of treatment in specialist health care showed an association with healing time, we do not know how long patients waited before contacting the GP. Nor do we know how long the GP treated the ulcer before referral to the specialist health care. Such information could provide valuable information about what causes the delayed referral to specialist health care, so more in-depth research is needed.

The GP plays an important role in the follow up of patients with DFUs and in systematic risk assessments of ulcers and feet. The GP serves as a 'gate keeper' to specialist health care (87), and is responsible for an adequate referral practice in order to ensure appropriate treatment at the right place at the right time (133). National and international guidelines recommend that patients with diabetes who have infected ulcers, ulcers combined with ischaemia or neuropathy, previous foot ulcers, as well as recurrence of wounds, should be referred to the specialist health care service quickly with follow up by a multidisciplinary team (59, 61, 62). Early referral to specialised multidisciplinary foot teams offers good opportunities to treat foot ulcers that contribute to a more systematic treatment, shorter healing time and fewer amputations (134, 135). However, as of today, none of the multidisciplinary teams in Norway carry out consultations or supervision in the municipal health service (91). Thus, a closer collaboration between these two health care levels is important. A low threshold among GPs to confer with multidisciplinary teams regarding foot problems in high risk patients should therefore be highlighted (25, 59). The National Guideline for Diabetes encourages the use of telemedicine solutions to improve the service (59). Recent research showed that the use of telemedicine in treatment and follow up of patients with DFUs can contribute to a streamlined communication and collaboration between the two levels that lowers the threshold for contact (94, 136).

In Norway, access to care due to distance might be a problem as DFU multidisciplinary teams are not available at all hospitals. To further develop cooperation between specialist health care and the GPs, the use of a virtual outpatient clinic might facilitate supervision or guidance from specialist health care to promote early assessments and more integrated care. To this end, health care services in the UK have reported good

results (137-139). However, to facilitate such a service, there is a need for both technically safe equipment and organisational facilitation. Nevertheless, Norway has the technical potential and geographical needs to warrant the fostering of such national services.

Patient awareness of foot ulcer behaviour is also important and must be strengthened. Specific patient education programs seem to be important and can improve patient knowledge and behaviour with respect to foot care, even though there is a lack of robust evidence that education alone can prevent reductions in ulcer and amputation incidence (140). Research has shown a positive relationship between regular foot inspections by health care professionals and regular self-inspections suggesting that health care professional behaviour during the clinical encounter with patients with diabetes may play an important role in increasing patient awareness of foot care (141, 142). To strengthen patient awareness, patient education on a public health level might help. For example, patient education through the social media, public and commercial TV channels and not only via health professionals might promote awareness about the importance of examining feet and making early contact with health care services even with minor problems.

Severity of ulcers

We found that ulcers classified at the highest and medium stage and grade were associated with increased healing time and that ulcers with the highest severity had an 86% decreased rate of healing compared with low ulcer severity. In addition, patients with a combination of peripheral arterial disease, infection and ulcer-affected bones or joints were more likely to undergo amputations than ulcers with less severity. An association between severity of ulcer and amputation has been found in previous studies (13, 35, 57). These results indicate that early classification of patients with an ulcer is important. Grade and stage according to the UT classification system seem to be relevant predictors of healing time and amputation and thus act as a useful classification tool for clinicians in assessing the severity of the ulcers and initiating adequate treatment. Such a system may facilitate collaboration between the patient and the health care professional in improving outcomes and increasing patient awareness

of self-foot care. The classification system can be an important tool for the GP to describe the ulcer and assess the outcomes and can be used to increase the referral process between the two health care levels (143). In addition, the UT classification system could be supplemented with the use of 10-g monofilament to identify patients at risk of ulceration, since neuropathy is not part of the classification (33).

6.2.2 Sample characteristics in study I and II

Study I recruited patients from two out of the three hospitals included in Study II, but at different time periods. It may therefore have been of interest to see if there was a change in the quality of care with regard to characteristics and severity of ulcer. Baseline characteristics from Studies I and II showed that characteristics such as age, gender, type of diabetes, use of insulin, HbA_{1c}, localization of ulcer and neuropathy in the two cohorts were markedly similar, except for cardiovascular disease. However, there was a higher prevalence of superficial ulcers in the RCT (Study II, 2012-2016) than in the retrospective cohort study (Study I, 2009-2011). In Study I, 22.9% of the ulcers were Grade 3 and 15.2% Grade 1, compared with 6.7% Grade 3 and 68.6% Grade 1 in Study II, respectively. Table 3 and 4, point 5.1 and table 5 and 6 point 5.2.

A larger proportion of cardiovascular diseases was reported in Study I compared with Study II. One study has shown that macrovascular complications of diabetes is significantly related to a history of foot ulcer (46) and that they may reflect disease severity which can be one factor that may explain the differences in severity of ulcers between these two cohorts (46).

Another explanation of the differences in severity of ulcers in the two samples can be that there has been substantial work in public health care in Norway to improve the quality of diabetes care (59, 144, 145). This has been related to targets being set for HbA_{1c} at ≤ 8, stricter prevention of cardiovascular diseases among people with diabetes (144, 146), as well as a focus on prevention and early referral to specialist health care for treatment and follow up (59, 145). This has led to substantial improvement in health outcomes such as HbA_{1c}, systolic blood pressure and cholesterol, indicating that the GPs are responding to these guidelines regarding risk factors (144). However, it is

unclear whether this has affected the difference in severity of diabetic foot ulcers in Norway since both cohorts have been influenced by these guidelines and the HbA_{1c} in both groups was < 8. A more likely explanation might be the different inclusion criteria. In Study II, patients were excluded if they had a diagnosis of mental disorders or cognitive impairment (including schizophrenia, other psychotic disorders, and dementia), if they were unable to complete questionnaires in Norwegian, or if they had a life expectancy of less than one year. Mental disorders such as depression among patients with diabetes is associated with DFU and mortality and cohort studies of patients with DFUs have shown that depression is associated with more severe and larger foot ulcers at presentation (116, 147). It is therefore likely that exclusion of these patients has contributed to the high prevalence of superficial ulcers in Study II.

6.2.3 Telemedicine follow-up

The DiaFOTo project has, in addition to the studies included in this PhD thesis, published other studies contributing to the evidence base of telemedicine follow up for patients with DFUs (26, 113, 136, 148). In addition, some international studies have been published (94, 95, 103, 108, 109, 149, 150). The overall question is whether telemedicine follow up can be an alternative care pathway for patients with DFUs. To answer this question, I will discuss some prerequisites for implementation of telemedicine follow-up care of DFU such as clinical outcomes (healing, amputation and mortality), consultations and patient perspectives.

Clinical outcomes (healing, amputation and mortality)

Results from our study demonstrated that telemedicine was non-inferior to standard outpatient care in terms of healing time. Competing risk analyses showed no statistical differences in healing time between the two groups. Of the 182 patients, 78.9% experienced complete healing and there were no differences between the groups. The Danish study, which was comparable to our study due to the use of an asynchronous intervention and an RCT, found that telemedicine was not superior to standard outpatient care with respect to healing time (95). No statistical differences in healing time were found between the telemedicine and standard outpatient care groups and a

similar percentage healed in both studies (95). With respect to amputation, significantly fewer amputations occurred in the telemedicine group compared with the standard outpatient group in our study. This was in contrast to the Danish study where there were no significant differences between the two groups. These findings seem promising for telemedicine follow up.

However, a higher mortality rate in the telemedicine group compared with the control group was reported in a Danish study (95). This is in contrast to our study where no significant differences in mortality between the two groups were found, but it is questioned whether telemedicine is relevant for all patients with DFUs. Our study excluded patients with mental disorders and life expectation less than 1 year. No such limitation was reported in the Danish study (95). In addition, the population recruited in our study had a very high prevalence of superficial ulcers (Grade 1) that may explain that we found no difference in mortality rate between the two groups in our study. Classification of the ulcers was not reported in the Danish study (95).

It may be advisable to have a person-centred approach that individualises the treatment and not apply TM follow up initially to patients with complex and serious complications, but allow decisions to take place on a continuous basis. Our results from study II seems promising but the conclusions are most relevant for patients with more superficial ulcers. For some of these patients, telemedicine follow up may be relevant in phases where the wound healing is in progress. For many patients, such an approach may be appropriate, because the health condition or long travel time make it difficult to meet at the outpatient clinic (109, 151, 152). Such a decision should, however, be taken in close connection with the patient or the patient's relatives if necessary. Still, several patients with severe and complex conditions preferred consultations to occur at the hospital rather than via telemedicine follow up. However, further studies are needed to investigate which other groups can benefit most from a telemedicine follow up.

Outpatient consultations

An important assumption for telemedicine's success is that the number of consultations at the outpatient clinic would be reduced. Even though the study was not powered to

show differences in consultations between the two groups, it was unexpected that we did not find larger differences in the number of consultations between the telemedicine and standard outpatient groups. It may then be a possibility that the overall frequency of follow up in the outpatient clinic for the telemedicine group has affected the primary outcome. Similar findings have been reported in a qualitative study from Denmark where the staff did not find a decrease in the number of consultations in the outpatient clinic (94). On average, in our study, the telemedicine group had consultations every second week compared with the scheduled consultation every 6th week. The higher number of consultations in the telemedicine group was not explained by severity of ulcers in our study; that more severe ulcers need more frequent consultations at the outpatient clinic. Lack of strong leadership is also a factor that can hinder uptake of technology (148, 153, 154), but results from a supplementary article related to this RCT indicated that this was not a plausible explanation at the outpatient clinic (148). It is more likely that the experts at the outpatient clinic might not have had enough clinical experience with the telemedicine equipment, or that the community nurses requested frequent outpatient consultations due to lack of confidence in wound care or that the expert team at the outpatient clinic did not trust the competence of the community nurses. This is supported by patients' experiences in Study III, where several patients expressed lack of competence and continuity of care among nurses in community health care as well as their failure to take any images of the ulcer. Similar findings related to lack of competence and continuity of care among nurses in community health care have been reported in previous studies (92, 155). However, only two out of three clinics were involved in the supplementary studies, and therefore, this conclusion may not apply to the clinic that attended the trial in 2015. Nevertheless, there is a potential for reducing the number of consultations using telemedicine.

Diffusion of telemedicine solutions requires redesign of the health care service and new ways of cooperating between the two health care levels that need to be learned and accepted (156, 157). The subgroup analysis showed a reduced number of consultations in the outpatient clinic with the most experience. This seems logical, because experts at the outpatient clinic might be more confident collaborating with community nurses, more experienced with the telemedicine tool, and more convinced that treatment and

follow up works well between the two health care levels. The analysis also showed that within the telemedicine group, patients who lived more than 25 km from the outpatient clinics had significantly fewer consultations per month compared with patients who lived closer to the outpatient clinics. This was not the case for patients receiving standard outpatient care. Successful adoption of new technology is dependent on the technology being user-friendly and easy to learn (76, 148), on the health care professionals seeing advantages with its use (76, 148) and on the opportunity to discuss the expectations and usefulness of the telemedicine tool (77). To address these issues, risk analysis of the telemedicine intervention has been performed continuously during the process to improve the quality of the intervention (158). Further, the main strength with the telemedicine intervention used in our study was use of images supplemented with text, and the direct communication and collaboration between the two health care levels. This may have strengthened the clinical proximity and confidence between the expert nurses and community nurses, thus resulting in less need for frequent consultations at the outpatient clinic. Several studies have found that using digital images is helpful in clinical assessment to help nurses avoid over- and under-treating patients with wounds (159-161).

Patients' experience of follow up

A reduction in the number of consultations at the outpatient clinic should not be seen in isolation, but also, seen in the context of the patient's experiences and needs. This relationship was not directly measured, but the patients in both groups emphasised in the interviews (152) that factors such as competence and continuity of care among community nurses in primary health care was of great importance (Study III). As long as these two factors were present, follow up in primary health care seemed to be an excellent care pathway. An absence of these factors led to a lack of confidence in wound care management and treatment, with the result that follow up at the outpatient clinic was then preferred. However, telemedicine seemed to counteract some of these challenges if telemedicine was used as intended. The patients in Study III claimed that the use of images and text together with continuous feedback and communication between the two health care levels seemed to be the factors that improved the

knowledge and skills of the community nurses. Similar findings among health care professionals have been previously reported in research (94, 109, 162) and recently in a supplementary article conducted during this trial about health care professionals' experience with using telemedicine follow up (136). Telemedicine seems to be a unique arena that can promote professional discussions and reflections on clinical issues among health care professionals (136). This is opposite to standard outpatient care where the community nurses operate mostly alone and no formal cooperation between the two health care levels are usual. Another advantage with use of telemedicine is that telemedicine also appears to counteract some of the uncertainty the patients in study III experienced in the absence of continuity of care. Telemedicine can rapidly exchange information between the community nurses and expert nurses independent of which community nurse follows up the patient and thus promote continuity of care. From a management perspective this is valuable, because continuity of care can be difficult to establish due to shift schedules. However, the findings from study III indicated that use of telemedicine could be questionable in a number of circumstances. Some of the patients in Study III reported that the community nurses failed to take any images, and some nurses lacked the skills necessary to use the telemedicine devices. Similar issues have been reported in previous studies (94, 163). In addition, clear wound guidelines as well as clear guidelines for delegation of responsibility in the case of sickness and vacation among key staff are essential elements for success. All these issues need to be addressed before telemedicine can be successfully implemented in usual care (148, 152).

7. Conclusions and clinical implications

- Duration of diabetic foot ulcer before start of treatment in specialist health care was an important predictor for ulcer healing. It is therefore necessary that people with diabetes and health care professionals are aware of the benefit of early contact with the health care system if foot ulcers occur.

- The UT classification system seems to be an adequate tool to assess severity of ulcers and to predict outcomes such as healing time and amputation. The classification system can be an important tool for the GP to describe the ulcer and assess the outcomes used in the referral process and can be used to improve the referral process between the two health care levels.

- Telemedicine has proven to be non-inferior compared to standard outpatient care in terms of time to healing. Further, there were no differences regarding mortality and patient satisfaction as well as fewer amputations in the telemedicine group, the findings suggest that telemedicine follow up can be an alternative and/or supplement to usual care. However, the conclusion seems to be most relevant for patients with more superficial ulcers due to the low proportion of ulcers of severe grade and stage and for patients with long distance from specialist health care. Telemedicine can thus reduce the burden long travel time and distance entails and reduce the pressure in the specialist health care.

- An effective care pathway for patients with DFUs was dependent on a combination of competence and professional skills in wound care management and continuity of care. The combination of these two factors did not only promote a more integrated care pathway, but also increased patient's confidence. Telemedicine can promote both professional's competence and continuity of care, but depends on telemedicine being used as intended.

- We did not find fewer consultations in the telemedicine group compared with the standard outpatient care group, but found that number of consultations were lower when health care providers gained more experience using the telemedicine equipment. Adoption of new technology in diabetes foot care involves health care providers working across different levels with different organisational systems and cultures. Therefore, user-friendly technology, ongoing training in how to use the technology and clear distribution of responsibilities are needed for successful adoption of the technology (76, 148). Further, as of today, there is no financial incentive or diagnosis-related groups (DRG) reimbursement for asynchronous systems in relation to telemedicine consultations or systematic work conditions that are intended for use of such a service. This means in practice that health care professionals must perform telemedicine tasks in addition to their normal tasks (72). Further, the web-based ulcer record system used in Study II is not integrated into the internal hospital or community electronic medical records of collaborating partners due to legal aspects (113). Lack of a shared medical record system makes the documentation overly complicated and the collaboration challenging (113). This may indicate that if telemedicine is to be implemented more as a service, these issues need to be solved.

- Use of technological solutions open up new ways to communicate and collaborate between primary and specialist health care and support integrated care for patients with DFUs. To further develop cooperation between specialist health care and GPs, the use of a virtual outpatient clinic might facilitate supervision or guidance from specialist health care to promote early assessments and more integrated care (164). Another solution is to replace the mobile phone with a tablet computer that allows virtual access to the web-based ulcer record in order to facilitate an improved workflow for the health care professionals (148).

8. Further Research

This study has identified some further questions and need for further research.

Early contact with the health care system if an ulcer occur: We found a positive association between duration of ulcer and healing time, but we do not know how long patients waited before contacting the GP, nor do we know how long the GP treated the ulcer before referral to the specialist health care. Such information could be valuable regarding causes for the delayed referral to specialist health care and these issues can successfully be explored by a qualitative approach.

Telemedicine follow up: Results from the RCT in the present study generate research questions such as which groups of patients with DFUs that could benefit most from telemedicine follow up. In addition, different telemedicine solutions should be investigated in further collaboration between health care levels and between health care providers and patients.

Telemedicine follow up and cost-effectiveness: The impact of costs-effectiveness of telemedicine follow up is of importance to inform policy decisions. Focus on cost-effectiveness of telemedicine follow up compared with standard outpatient care of patients with DFUs should be encourage as there is limited research on these issues.

Patient experience: The findings from study III indicated that the patient's experiences are valuable in the decision of implementation of telemedicine follow up. Further research should focus on patients reported outcomes (quality of life) when new technology is applied.

Telemedicine across countries: Few studies have been performed regarding telemedicine follow up among patients with DFU worldwide. Therefore, it would be of interest at an international level to perform multicenter prospective across-countries research of telemedicine follow up among patients with DFUs.

Competence among health care professionals and continuity of care: Findings from study III indicate that these issues were of importance in follow up of patients with DFUs. Further research should be directed to explore whether health care personnel increase their competencies as a result of telemedicine use and if this contributes to a more coordinated care pathway between the two health care levels.

9. REFERENCE

1. Boulton AJ. The pathway to foot ulceration in diabetes. Med Clin North Am. 2013;97(5):775-90. doi:10.1016/j.mcna.2013.03.007
2. Skrepnek GH, Mills JL, Lavery LA, Armstrong DG. Health Care Service and Outcomes Among an Estimated 6.7 Million Ambulatory Care Diabetic Foot Cases in the US. Diabetes Care. 2017:dc162189. doi:10.2337/dc16-2189.
3. Lavery LA, Armstrong DG, Murdoch DP, Peters EJ, Lipsky BA. Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. Clin Infect Dis. 2007;44(4):562-5. doi:10.1086/511036
4. Armstrong DG, Boulton AJ, Bus SA. Diabetic Foot Ulcers and Their Recurrence. N Engl J Med. 2017;376(24):2367-75. doi:10.1056/NEJMra1615439
5. Iversen M, Tell GS, Riise T, Hanestad BR, Ostbye T, Graue M, et al. History of Foot Ulcer Increases Mortality Among Individuals With Diabetes: Ten-year follow-up of the Nord-Trondelag Health Study, Norway. Diabetes Care. 2009;32(12):2193-9. doi:10.2337/dc09-0651
6. Chammas N, Hill R, Edmonds M. Increased Mortality in Diabetic Foot Ulcer Patients: The Significance of Ulcer Type. Journal of Diabetes Research. 2016;2016:Article ID 2879809. doi:10.1155/2016/2879809
7. Ribu L, Hanestad BR, Moum T, Birkeland K, Rustoen T. A comparison of the health-related quality of life in patients with diabetic foot ulcers, with a diabetes group and a nondiabetes group from the general population. Qual Life Res. 2007;16(2):179-89. doi:10.1007/s11136-006-0031-y
8. Markakis K, Bowling FL, Boulton AJ. The diabetic foot in 2015: an overview. Diabetes Metab Res Rev. 2016;32(Suppl 1):169-78. doi:10.1002/dmrr.2740
9. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. Delivery of care to diabetic patients with foot ulcers in daily practice: results of the Eurodiale Study, a prospective cohort study. Diabet Med. 2008;25(6):700-7. doi:10.1111/j.1464-5491.2008.02445.x
10. Jeffcoate W, Van Houtum W. Amputation as a marker of the quality of foot care in diabetes. Diabetologia. 2004;47(12):2051-8.
11. Monteiro-Soares M, Boyko E, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Predictive factors for diabetic foot ulceration: a systematic review. Diabetes Metab Res Rev. 2012;28(7):574-600. doi:10.1002/dmrr.2319
12. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care. 1998;21(5):855-9.
13. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Harkless LB, Boulton AJ. A Comparison of Two Diabetic Foot Ulcer Classification Systems. The Wagner and the University of Texas wound classification systems. Diabetes Care. 2001;24(1):84-8. doi:10.2337/diacare.24.1.84
14. Game F. Classification of diabetic foot ulcers. Diabetes Metab Res Rev. 2016;32(Suppl 1):186-94. doi:10.1002/dmrr.2746
15. Solli O, Jenssen T, Kristiansen IS. Diabetes: cost of illness in Norway. BMC Endocr Disord. 2010;10(1):15. doi:10.1016/j.diabres.2016.10.012
16. Hjort A, Gottrup F. Cost of wound treatment to increase significantly in Denmark over the next decade. J Wound Care. 2010;19(5):173-84. doi:10.12968/jowc.2010.19.5.48046

17. Kerr M, Rayman G, Jeffcoate W. Cost of diabetic foot disease to the National Health Service in England. Diabet Med. 2014;31(12):1498-504. doi:10.1111/dme.12545
18. van Dieren S, Beulens JW, van der Schouw YT, Grobbee DE, Neal B. The global burden of diabetes and its complications: an emerging pandemic. Eur J Cardiovasc Prev Rehabil. 2010;17(1 suppl):S3-8. doi:10.1097/01.hjr.0000368191.86614.5a
19. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis dagger. Ann Med. 2017;49(2):106-16. doi:10.1080/07853890.2016.1231932
20. Tamayo T, Rosenbauer J, Wild S, Spijkerman A, Baan C, Forouhi N, et al. Diabetes in Europe: an update. Diabetes Res Clin Pract. 2014;103(2):206-17. doi:10.1016/j.diabres.2013.11.007
21. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. The Lancet. 2005;366(9498):1719-24. doi:10.1016/S0140-6736(05)67698-2
22. Gregg EW, Williams DE, Geiss L. Changes in diabetes-related complications in the United States. N Engl J Med. 2014;371(3):286-7. doi:10.1056/NEJMc1406009
23. World Health Organization. Telemedicine; opportunies and developmenst in Member States; report on the second global survey on ehealth. Geneva World Health Organization; 2010.
24. St.meld. nr. 47 (2008-2009). Samhandlingsreformen — Rett behandling – på rett sted – til rett tid [The Coordination Reform — Proper treatment – at the right place and right time]. Oslo: Ministry of Health and Care Services; 2009.
25. Singh TP, Vangaveti VN, Kennedy RL, Malabu UH. Role of telehealth in diabetic foot ulcer management - A systematic review. Aust J Rural Health.24(4):224-9. doi:10.1111/ajr.12284
26. Iversen MM, Espehaug B, Hausken MF, Graue M, Ostbye T, Skeie S, et al. Telemedicine Versus Standard Follow-Up Care for Diabetes-Related Foot Ulcers: Protocol for a Cluster Randomized Controlled Noninferiority Trial (DiaFOTo). JMIR Res Protoc. 2016;5(3):e148. doi:10.2196/resprot.5646
27. Nordheim LV, Haavind MT, Iversen MM. Effect of telemedicine follow-up care of leg and foot ulcers: a systematic review. BMC Health Serv Res. 2014;14(1):565. doi:10.1186/s12913-014-0565-6
28. IDF. IDF Diabetes Atlas – 7th Edition. 2016. Available from: http://www.vision2020uk.org.uk/idf-diabetes-atlas-7th-edition/.
29. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabetes. 2011;29(3):116-22. doi:10.2337/diaclin.26.2.77
30. Schaper N, Van Netten J, Apelqvist J, Lipsky B, Bakker K, Foot IWGotD. Prevention and management of foot problems in diabetes: a Summary Guidance for Daily Practice 2015, based on the IWGDF Guidance Documents. Diabetes Res Clin Pract. 2017;124:84-92. doi:10.1016/j.diabres.2016.12.007
31. Apelqvist J, Bakker K, van Houtum WH, Nabuurs-Franssen MH, Schaper NC. International consensus and practical guidelines on the management and the prevention of the diabetic foot. Diabetes Metab Res Rev. 2000;16 Suppl 1:S84-92. doi:10.1002/dmrr.848.
32. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: Focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia. 2008;51(5):747-55. doi:10.1007/s00125-008-0940-0
33. Crawford F, Cezard G, Chappell FM, Murray GD, Price JF, Sheikh A, et al. A systematic review and individual patient data meta-analysis of prognostic factors for

foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). Health Technol Assess. 2015;19(57):1-210. doi: 10.3310/hta19570
34. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia. 2007;50(1):18-25. doi:10.1007/s00125-006-0491-1
35. Uccioli L, Gandini R, Giurato L, Fabiano S, Pampana E, Spallone V, et al. Long-term outcomes of diabetic patients with critical limb ischemia followed in a tertiary referral diabetic foot clinic. Diabetes Care. 2010;33(5):977-82. doi:10.2337/dc09-0831
36. Forsythe R, Brownrigg J, Hinchliffe R. Peripheral arterial disease and revascularization of the diabetic foot. Diabetes, Obesity and Metabolism. 2015;17(5):435-44. doi:10.1111/dom.12422
37. Hinchliffe RJ, Andros G, Apelqvist J, Bakker K, Friederichs S, Lammer J, et al. A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. Diabetes Metab Res Rev. 2012;28(Suppl 1):179-217. doi:10.1002/dmrr.2249.
38. Brownrigg J, Apelqvist J, Bakker K, Schaper N, Hinchliffe R. Evidence-based management of PAD & the diabetic foot. Eur J Vasc Endovasc Surg. 2013;45(6):673-81. doi:10.1016/j.ejvs.2013.02.014
39. Mills JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The society for vascular surgery lower extremity threatened limb classification system: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg. 2014;59(1):220-34. e1-2. doi:10.1016/j.jvs.2013.08.003
40. Ward R, Dunn J, Clavijo L, Shavelle D, Rowe V, Woo K. Outcomes of critical limb ischemia in an urban, safety net hospital population with high WIfI amputation scores. Ann Vasc Surg. 2017;38:84-9. doi:10.1016/j.avsg.2016.08.005
41. Rasmussen BS, Yderstraede KB, Carstensen B, Skov O, Beck-Nielsen H. Substantial reduction in the number of amputations among patients with diabetes: a cohort study over 16 years. Diabetologia. 2016;59(1):121-9. doi:10.1007/s00125-015-3781-7
42. Stoekenbroek RM, Lokin JL, Nielen MM, Stroes ES, Koelemay MJ. How common are foot problems among individuals with diabetes? Diabetic foot ulcers in the Dutch population. Diabetologia. 2017;60(7):1-5. doi:10.1007/s00125-017-4274-7
43. Abbott C, Carrington A, Ashe H, Bath S, Every L, Griffiths J, et al. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabet Med. 2002;19(5):377-84. doi:10.1046/j.1464-5491.2002.00698.x
44. Ramsey SD, Newton K, Blough D, McCulloch DK, Sandhu N, Reiber GE, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes Care. 1999;22(3):382-7. doi:10.2337/diacare.22.3.382
45. Hurley L, Kelly L, Garrow AP, Glynn LG, McIntosh C, Alvarez-Iglesias A, et al. A prospective study of risk factors for foot ulceration: the West of Ireland Diabetes Foot Study. QJM. 2013;106(12):1103-10. doi:10.1093/qjmed/hct182
46. Iversen MM, Midthjell K, Ostbye T, Tell GS, Clipp E, Sloane R, et al. History of and factors associated with diabetic foot ulcers in Norway: the Nord-Trondelag Health Study. Scand J Public Health. 2008;36(1):62-8. doi:10.1177/1403494807085314
47. Molvaer AK, Graue M, Espehaug B, Ostbye T, Midthjell K, Iversen MM. Diabetes-related foot ulcers and associated factors: results from the Nord-Trondelag Health Survey (HUNT3) (2006-2008). J Diabetes Complications. 2014;28(2):156-61. doi:10.1016/j.jdiacomp.2013.10.010

48. Rasmussen A, Almdal T, Anker Nielsen A, Nielsen KE, Jorgensen ME, Hangaard S, et al. Decreasing incidence of foot ulcer among patients with type 1 and type 2 diabetes in the period 2001-2014. Diabetes Res Clin Pract.130:221-8. doi:10.1016/j.diabres.2017.05.025
49. Muller IS, De Grauw WJ, Van Gerwen WH, Bartelink ML, Van Den Hoogen HJ, Rutten GE. Foot Ulceration and Lower Limb Amputation in Type 2 Diabetic Patients in Dutch Primary Health Care. Diabetes Care. 2002;25(3):570-4. doi:10.2337/diacare.25.3.570
50. Jeffcoate WJ, Chipchase SY, Ince P, Game FL. Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. Diabetes Care. 2006;29(8):1784-7. doi:10.2337/dc06-0306
51. Margolis DJ, Jeffcoate W. Epidemiology of foot ulceration and amputation: can global variation be explained? Med Clin North Am. 2013;97(5):791-805. doi:10.1016/j.mcna.2013.03.008
52. Moxey P, Gogalniceanu P, Hinchliffe R, Loftus I, Jones K, Thompson M, et al. Lower extremity amputations—a review of global variability in incidence. Diabet Med. 2011;28(10):1144-53. doi:10.1111/j.1464-5491.2011.03279.x
53. Krans HM, World Health Organization. Diabetes care and research in Europe: the St Vincent Declaration action programme: Implementation document. 2nd ed. Copenhagen: World Health Organization; 1995.
54. Kennon B, Leese GP, Cochrane L, Colhoun H, Wild S, Stang D, et al. Reduced Incidence of Lower-Extremity Amputations in People With Diabetes in Scotland: A nationwide study. Diabetes Care. 2012;35(12):2588-90. doi:10.2337/dc12-0511
55. Carinci F, Benedetti MM, Klazinga N, Uccioli L. Lower extremity amputation rates in people with diabetes as an indicator of health systems performance. A critical appraisal of the data collection 2000–2011 by the Organization for Economic Cooperation and Development (OECD). Acta Diabetol. 2016;53(5):825-32. doi:10.1007/s00592-016-0879-4
56. helsenorge.no. Amputasjoner blant pasienter med diabetes : [Amputations among patients with diabetes]. Oslo: helsenorge.no; 2017. Available from: https://helsenorge.no/Kvalitetsindikatorer/diabetes/amputasjoner-blant-pasienter-med-diabetes.
57. van Battum P, Schaper N, Prompers L, Apelqvist J, Jude E, Piaggesi A, et al. Differences in minor amputation rate in diabetic foot disease throughout Europe are in part explained by differences in disease severity at presentation. Diabet Med. 2011;28(2):199-205. doi:10.1111/j.1464-5491.2010.03192.x
58. Nijenhuis-Rosien L, Hendriks SH, Kleefstra N, Bilo HJG, Landman GWD. Nationwide diabetes-related lower extremity amputation rates in secondary care treated patients with diabetes in the Netherlands (DUDE-7). J Diabetes Complications. 2017;31(4):675-8. doi:10.1016/j.jdiacomp.2017.01.015
59. The Norwegian Directorate of Health. Diabetes: Nasjonal faglig retningslinje for diabetes [Diabetes: National professional guidelines]. Oslo: The Norwegian Directorate of Health; 2017. Available from: https://helsedirektoratet.no/retningslinjer/diabetes.
60. American Diabetes Association. 9. Microvascular complications and foot care. Diabetes Care. 2016;39(Supplement 1):S72-S80.
61. Bus S, Netten J, Lavery L, Monteiro-Soares M, Rasmussen A, Jubiz Y, et al. IWGDF Guidance on the prevention of foot ulcers in at-risk patients with diabetes. Diabetes Metab Res Rev. 2015. doi:10.1002/dmrr.2696

62. The national Institute for Health and care Exellence (NICE). Diabetic foot problems: prevention and management. NICE guideline (NG19). 2015. Available from: https://www.nice.org.uk/guidance/ng19.
63. Clinical Audit and Registries Management Service, Health and Social Care Information Centre. National diabetes foot care audit report 2014-2015. England and Wales. Health and Social Care Information Centre; 2016. p. 1-36.
64. Ince P, Kendrick D, Game F, Jeffcoate W. The association between baseline characteristics and the outcome of foot lesions in a UK population with diabetes. Diabet Med. 2007;24(9):977-81. doi:10.1111/j.1464-5491.2007.02189.x
65. Monteiro-Soares M, Boyko E, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Risk stratification systems for diabetic foot ulcers: a systematic review. Diabetologia. 2011;54(5):1190-9. doi:10.1007/s00125-010-2030-3
66. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: the association of wound size, wound duration, and wound grade on healing. Diabetes Care. 2002;25(10):1835-9.
67. Lamchahab F, El Kihal N, Khoudri I, Chraibi A, Hassam B, Ourhroui MA. Factors influencing the awareness of diabetic foot risks. Ann Phys Rehabil Med. 2011;54(6):359-65. doi:10.1016/j.rehab.2011.07.004
68. Sanders AP, Stoeldraaijers LG, Pero MW, Hermkes PJ, Carolina RC, Elders PJ. Patient and professional delay in the referral trajectory of patients with diabetic foot ulcers. Diabetes Res Clin Pract. 2013;102(2):105-11. doi:10.1016/j.diabres.2013.09.016
69. Schaper N, Andros G, Apelqvist J, Bakker K, Lammer J, Lepantalo M, et al. Diagnosis and treatment of peripheral arterial disease in diabetic patients with a foot ulcer. A progress report of the International Working Group on the Diabetic Foot. Diabetes Metab Res Rev. 2012;28(S1):218-24. doi:10.1002/dmrr.2255
70. Hinchliffe R, Brownrigg J, Andros G, Apelqvist J, Boyko E, Fitridge R, et al. Effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review. Diabetes Metab Res Rev. 2016;32(Suppl 1):136-44. doi:10.1002/dmrr.2705
71. Jones SS, Rudin RS, Perry T, Shekelle PG. Health information technology: an updated systematic review with a focus on meaningful use. Ann Intern Med. 2014;160(1):48-54. doi:10.7326/M13-1531
72. Larsen SB, Sørensen NS, Petersen MG, Kjeldsen GF. Towards a shared service centre for telemedicine: Telemedicine in Denmark, and a possible way forward. Health Informatics J. 2016;22(4):815-27. doi:10.1177/1460458215592042
73. Dorsey ER, Topol EJ. State of telehealth. N Engl J Med. 2016;375(2):154-61.
74. Meld. St. 29 (2012-2013). Morgendagens omsorg [Future Care]. Oslo: Ministry of Health and Care Services; 2013.
75. Chanussot-Deprez C, Contreras-Ruiz J. Telemedicine in wound care: a review. Adv Skin Wound Care. 2013;26(2):78-82. doi:10.1097/01.ASW.0000426717.59326.5f
76. Zanaboni P, Wootton R. Adoption of telemedicine: from pilot stage to routine delivery. BMC Med Inform Decis Mak. 2012;12(1):1. doi:10.1186/1472-6947-12-1
77. Sanders C, Rogers A, Bowen R, Bower P, Hirani S, Cartwright M, et al. Exploring barriers to participation and adoption of telehealth and telecare within the Whole System Demonstrator trial: a qualitative study. BMC Health Serv Res. 2012;12(1):220-32. doi:10.1186/1472-6963-12-220
78. Currell R, Urquhart C, Wainwright P, Lewis R. Telemedicine versus face to face patient care: effects on professional practice and health care outcomes. Cochrane Database Syst Rev. 2000;2(2):CD002098. doi:10.1002/14651858.CD002098

79. Fatehi F, Wootton R. Telemedicine, telehealth or e-health? A bibliometric analysis of the trends in the use of these terms. J Telemed Telecare. 2012;18(8):460-4. doi:10.1258/jtt.2012.gth108
80. Kvedar J, Coye MJ, Everett W. Connected health: a review of technologies and strategies to improve patient care with telemedicine and telehealth. Health Aff (Millwood). 2014;33(2):194-9. doi:10.1377/hlthaff.2013.0992
81. Bashshur R, Shannon G, Krupinski E, Grigsby J. The taxonomy of telemedicine. Telemed J E Health. 2011;17(6):484-94. doi:10.1089/tmj.2011.0103
82. Lindberg B, Nilsson C, Zotterman D, Söderberg S, Skär L. Using information and communication technology in home care for communication between patients, family members, and healthcare professionals: a systematic review. Int J Telemed Appl. 2013;2013. doi:10.1155/2013/461829
83. Verhoeven F, van Gemert-Pijnen L, Dijkstra K, Nijland N, Seydel E, Steehouder M. The contribution of teleconsultation and videoconferencing to diabetes care: a systematic literature review. J Med Internet Res. 2007;9(5):e37. doi:10.2196/jmir.9.5.e37
84. Verhoeven F, Tanja-Dijkstra K, Nijland N, Eysenbach G, van Gemert-Pijnen L. Asynchronous and synchronous teleconsultation for diabetes care: a systematic literature review. J Diabetes Sci Technol. 2010;4(3):666-84. doi:10.1177/193229681000400323
85. Foltynski P, Wojcicki JM, Ladyzynski P, Migalska-Musial K, Rosinski G, Krzymien J, et al. Monitoring of diabetic foot syndrome treatment: some new perspectives. Artif Organs. 2016;35(2):176-82. doi:10.1111/j.1525-1594.2010.01046.x
86. Wootton R. Twenty years of telemedicine in chronic disease management–an evidence synthesis. J Telemed Telecare. 2012;18(4):211-20. doi:10.1258/jtt.2012.120219
87. Forskrift om fastlegeordning i kommunene av 2012-08-29 nr. 842. 2012.
88. Pasient- og brukerrettighetsloven. Lov om pasient- og brukerrettigheter av 1999-07-02 nr. 63. 1999.
89. Prioriteringsforskriften. Forskrift om prioritering av helsetjenester, rett til nødvendig helsehjelp fra spesialisthelsetjenesten, rett til behandling i utlandet og om klagenemnd av 2000-12-01 nr. 1208 [Regulation to prioritize health services, the right to necessary care from specialist health care services, the right to have treatment abroad an to appeal]. 2000.
90. Helsedirektoratet. Endringer i pasient - og brukerrettighetsloven og prioriteringsforskriften. . Oslo: Helsedirektoratet; 2013. Available from: https://helsedirektoratet.no/retningslinjer/aktuell-informasjon-om-lov-og-forskrift-for-prioriteringsveilederne/seksjon?Tittel=2-endringer-i-pasient-2764.
91. Robbestad M, Bentzen S, Berg T, Iversen M. Diabetes fotsårteam i norske sykehus. Tidsskr Nor Laegeforen. Forthcoming.
92. Ribu L, Wahl A. How patients with diabetes who have foot and leg ulcers perceive the nursing care they receive. J Wound Care. 2004;13(2):65-8. doi:10.12968/jowc.2004.13.2.26578
93. Iversen M, Hausken, M., & Vetlesen, K. Forprosjekt. Diabetes fotsår. Utvikling av nye telemedisinske systemer/produkter. [Project. Diabetic foot ulcer. Development of new telemedical systems/products.]. Stavanger: Stavanger universitetssjukehus; 2012. Available from: http://www.innomed.no/media/media/prosjekter/rapporter/59_-_Telemedisinsk_oppfolging_av_diabetes_fotsar_1.pdf.
94. Rasmussen BS, Jensen LK, Froekjaer J, Kidholm K, Kensing F, Yderstraede KB. A qualitative study of the key factors in implementing telemedical monitoring of diabetic

foot ulcer patients. Int J Med Inform. 2015;84(10):799-807. doi:10.1016/j.ijmedinf.2015.05.012
95. Rasmussen BS, Froekjaer J, Bjerregaard MR, Lauritsen J, Hangaard J, Henriksen CW, et al. A randomized controlled trial comparing telemedical and standard outpatient monitoring of diabetic foot ulcers. Diabetes Care. 2015;38(9):1723-9. doi: 10.2337/dc15-0332
96. Wilbright WA, Birke JA, Patout CA, Varnado M, Horswell R. The use of telemedicine in the management of diabetes-related foot ulceration: a pilot study. Adv Skin Wound Care. 2004;17(5 Pt 1):232-8.
97. Terry M, Halstead LS, O'hare P, Gaskill C, Ho PS, Obecny J, et al. Feasibility study of home care wound management using telemedicine. Adv Skin Wound Care. 2009;22(8):358-64. doi:10.1097/01.ASW.0000358638.38161.6b
98. Zarchi K, Haugaard VB, Dufour DN, Jemec GB. Expert advice provided through telemedicine improves healing of chronic wounds: prospective cluster controlled study. J Invest Dermatol. 2015;135(3):895-900. doi:10.1038/jid.2014.441
99. Santamaria N, Carville K, Ellis I, Prentice J. The effectiveness of digital imaging and remote expert wound consultation on healing rates in chronic lower leg ulcers in the Kimberley region of Western Australia. Prim Intent. 2004;12(2):62-70.
100. Mair F, Whitten P. Systematic review of studies of patient satisfaction with telemedicine. BMJ. 2000;320(7248):1517-20. doi:10.1136/bmj.320.7248.1517
101. Kraai IH, Luttik MLA, de Jong RM, Jaarsma T, Hillege HL. Heart failure patients monitored with telemedicine: patient satisfaction, a review of the literature. J Card Fail. 2011;17(8):684-90.
102. Williams TL, May CR, Esmail A. Limitations of patient satisfaction studies in telehealthcare: a systematic review of the literature. Telemed J E Health. 2001;7(4):293-316. doi:10.1089/15305620152814700
103. Larsen SB, Clemensen J, Ejskjaer N. A feasibility study of UMTS mobile phones for supporting nurses doing home visits to patients with diabetic foot ulcers. J Telemed Telecare. 2006;12(7):358-62. doi:10.1258/135763306778682323
104. Litzinger G, Rossman T, Demuth B, Roberts J. In-home wound care management utilizing information technology. Home Healthc Nurse. 2007;25(2):119-30.
105. Kim HM, Lowery JC, Hamill JB, Wilkins EG. Patient attitudes toward a Web-based system for monitoring chronic wounds. Telemed J E Health. 2004;10(Suppl 2):S26-S34. doi:10.1089/tmj.2004.10.S-26
106. Finkelstein SM, Speedie SM, Demiris G, Veen M, Lundgren JM, Potthoff S. Telehomecare: quality, perception, satisfaction. Telemed J E Health. 2004;10(2):122-8. doi:10.1089/tmj.2004.10.122
107. Binder B, Hofmann-Wellenhof R, Salmhofer W, Okcu A, Kerl H, Soyer HP. Teledermatological monitoring of leg ulcers in cooperation with home care nurses. Arch Dermatol. 2007;143(12):1511-4. doi:10.1001/archderm.143.12.1511
108. Devine J. User satisfaction and experience with telemedicine service for diabetic foot disease in an Australian rural community. Sydney: Greater Southern Area Health Service; 2009. Available from: http://www.heti.nsw.gov.au/Global/Rural/RRCBP/Pre%202012%20RRCBP%20Intake/jenni_devine_report.pdf.
109. Clemensen J, Larsen SB, Kirkevold M, Ejskjaer N. Treatment of diabetic foot ulcers in the home: video consultations as an alternative to outpatient hospital care. Int J Telemed Appl. 2008:1. doi:10.1155/2008/132890
110. Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. J Foot Ankle Surg. 1996;35(6):528-31.

111. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144
112. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol. 2009;170(2):244-56. doi:10.1093/aje/kwp107
113. Christiansen EK, Skipenes E, Hausken MF, Skeie S, Østbye T, Iversen MM. Shared Electronic Health Record Systems: Key Legal and Security Challenges. J Diabetes Sci Technol. 2017:1932296817709797. doi:10.1177/1932296817709797
114. Sjetne IS, Bjertnaes OA, Olsen RV, Iversen HH, Bukholm G. The Generic Short Patient Experiences Questionnaire (GS-PEQ): identification of core items from a survey in Norway. BMC Health Serv Res. 2011;11(1):88-100. doi: 10.1186/1472-6963-11-88
115. Julious SA. Sample sizes for clinical trials with normal data. Stat Med. 2004;23(12):1921-86. doi:10.1002/sim.1783
116. Ismail K, Winkley K, Stahl D, Chalder T, Edmonds M. A cohort study of people with diabetes and their first foot ulcer: the role of depression on mortality. Diabetes Care. 2007;30(6):1473-9. doi:10.2337/dc06-2313
117. Thorne SE. Interpretive description. Walnut Creek: Left Coast Press; 2008.
118. Thorne SE. Interpretive description: qualitative research for applied pratice. 2nd ed. New York: Routledge; 2016.
119. Thorne S, Kirkham SR, MacDonald-Emes J. Focus on qualitative methods. Interpretive description: a noncategorical qualitative alternative for developing nursing knowledge. Res Nurs Health. 1997;20(2):169-77.
120. Malterud K. Kvalitative forskningsmetoder for medisin og helse fag. 4th ed. Oslo: Universitetsforlaget; 2017.
121. Malterud K, Siersma VD, Guassora AD. Sample size in qualitative interview studies: guided by information power. Qual Health Res. 2016;26(13):1753-60. doi:10.1177/1049732315617444
122. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12(12):1495-9. doi:10.1016/j.ijsu.2014.07.013
123. Campbell MK, Piaggio G, Elbourne DR, Altman DG. Consort 2010 statement: extension to cluster randomised trials. BMJ. 2012;345:e5661. doi:10.1136/bmj.e5661
124. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG, Group C. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA. 2012;308(24):2594-604. doi:10.1001/jama.2012.87802
125. Polit D, Beck, C. Nursing research. Generating and assessing evidence for nursing practice. 10th ed. Philadelphia: Wolters Kluwer; 2017.
126. Shadish WR. Experimental and Quasi-Experimental Designs for Generalized Causal Inference. 2008.
127. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ. 2008;337:a2390. doi:10.1136/bmj.a2390
128. Donner A, Klar N. Design and analysis of cluster randomization trials in health reseach: Oxford University Press; 2000.
129. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. Philadelphia: Wolters Kluwer; 2008.
130. Shadish WR. Experimental and quasi-experimental designs for generalized causal inference. Boston: Houghton Mifflin; 2001.

131. Higging J, Green S. Cochrane handbook for systematic reviews of interventions. Chichester: Wiley-Blackwell; 2008.
132. Ince P, Game FL, Jeffcoate WJ. Rate of healing of neuropathic ulcers of the foot in diabetes and its relationship to ulcer duration and ulcer area. Diabetes Care. 2007;30(3):660-3. doi:10.2337/dc06-2043
133. Sosial- og Helsedirektoratet. … Og bedre skal det bli! Nasjonal strategi for kvalitetsforbedring i Sosial- og helsetjenesten [And better it will be - National strategy for quality improvement in the social and health services]. Oslo: Sosial- og Helsedirektoratet; 2005. IS-1162.
134. Weck M, Slesaczeck T, Paetzold H, Muench D, Nanning T, Von Gagern G, et al. Structured health care for subjects with diabetic foot ulcers results in a reduction of major amputation rates. Cardiovasc Diabetol. 2013;12(1):45. doi:10.1186/1475-2840-12-45
135. Buggy A, Moore Z. The impact of the multidisciplinary team in the management of individuals with diabetic foot ulcers: a systematic review. J Wound Care. 2017;26(6):324-39. doi:10.12968/jowc.2017.26.6.324
136. Kolltveit B-CH, Gjengedal E, Graue M, Iversen MM, Thorne S, Kirkevold M. Telemedicine in diabetes foot care delivery: health care professionals' experience. BMC Health Serv Res. 2016;16(1):134-42. doi:10.1186/s12913-016-1377-7
137. Wallace P, Haines A, Harrison R, Barbour J, Thompson S, Jacklin P, et al. Joint teleconsultations (virtual outreach) versus standard outpatient appointments for patients referred by their general practitioner for a specialist opinion: a randomised trial. The lancet. 2002;359(9322):1961-8.
138. Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, et al. Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations. Health Technol Assess. 2004;8(50):1-106, iii-iv.
139. Basudev N, Crosby-Nwaobi R, Thomas S, Chamley M, Murrells T, Forbes A. A prospective randomized controlled study of a virtual clinic integrating primary and specialist care for patients with Type 2 diabetes mellitus. Diabet Med. 2016;33(6):768-76. doi:10.1111/dme.12985
140. Dorresteijn J, Kriegsman D, Assendelft W, Valk GD. Patient education for preventing diabetic foot ulceration. Cochrane Database Syst Rev. 2014(12):CD001488. doi:10.1002/14651858.CD001488.pub5
141. Iversen MM, Østbye T, Clipp E, Midthjell K, Uhlving S, Graue M, et al. Regularity of preventive foot care in persons with diabetes: Results from the Nord-Trøndelag Health Study. Res Nurs Health. 2008;31(3):226-37.
142. De Berardis G, Pellegrini F, Franciosi M, Belfiglio M, Di Nardo B, Greenfield S, et al. Are Type 2 diabetic patients offered adequate foot care? The role of physician and patient characteristics. J Diabetes Complications. 2005;19(6):319-27.
143. Thorsen O, Hartveit M, Baerheim A. The consultants' role in the referring process with general practitioners: partners or adjudicators? a qualitative study. BMC Fam Pract. 2013;14(1):153.
144. Cooper JG, Claudi T, Jenum AK, Thue G, Hausken MF, Ingskog W, et al. Quality of Care for Patients With Type 2 Diabetes in Primary Care in Norway Is Improving Results of cross-sectional surveys of 33 general practices in 1995 and 2005. Diabetes Care. 2009;32(1):81-3.
145. The Norwegian Directorate of Health. Diabetes: Forebygging, diagnostikk og behandling [National professional guidelines: Diabetes - Prevention, diagnosis and treatment]. Oslo: The Norwegian Directorate of Health; 2009. IS-1674.

146. Claudi T. NSAMs handlingsprogram for diabetes i allmennpraksis [Action plan for diabetes in general practice]. Oslo: Norwegian Society of General Practitioners; 1995.
147. Williams LH, Rutter CM, Katon WJ, Reiber GE, Ciechanowski P, Heckbert SR, et al. Depression and incident diabetic foot ulcers: a prospective cohort study. Am J Med. 2010;123(8):748-54 e3. doi:10.1016/j.amjmed.2010.01.023
148. Kolltveit BH, Gjengedal E, Graue M, Iversen MM, Thorne S, Kirkevold M. Conditions for success in introducing telemedicine in diabetes foot care: a qualitative inquiry. BMC Nurs. 2017;16:2. doi:10.1186/s12912-017-0201-y
149. Fasterholdt I, Gerstrom M, Rasmussen BS, Yderstraede KB, Kidholm K, Pedersen KM. Cost-effectiveness of telemonitoring of diabetic foot ulcer patients. Health Informatics J. 2016;16. doi:10.1177/1460458216663026
150. Clemensen J, Larsen SB, Ejskjaer N. Telemedical treatment at home of diabetic foot ulcers. J Telemed Telecare. 2005;11(Suppl 2):S14-S6. doi:10.1258/135763305775124830
151. Yderstræde KB, Rasmussen BSB, Frøklære J, Beck-Nielsen H. Har telemedicine en rolle ved diabetiske fotsår? Behandlerbladet. 2016;3:19-24.
152. Smith-Strom H, Iversen MM, Graue M, Skeie S, Kirkevold M. An integrated wound-care pathway, supported by telemedicine, and competent wound management-Essential in follow-up care of adults with diabetic foot ulcers. Int J Med Inform. 2016;94:59-66. doi:10.1016/j.ijmedinf.2016.06.020
153. Fairbrother P, Ure J, Hanley J, McCloughan L, Denvir M, Sheikh A, et al. Telemonitoring for chronic heart failure: the views of patients and healthcare professionals–a qualitative study. J Clin Nurs. 2014;23(1-2):132-44. doi:10.1111/jocn.12137
154. Broderick A, Lindeman D. Scaling telehealth programs: Lessons from early adopters. 2013. Available from: http://www.mtelehealth.com/wp-content/uploads/2015/09/1654_Broderick_telehealth_adoption_synthesis1.pdf.
155. Gjevjon ER, Romøren TI, Kjøs BØ, Hellesø R. Continuity of care in home health-care practice: two management paradoxes. J Nurs Manag. 2013;21(1):182-90. doi:10.1111/j.1365-2834.2012.01366.x
156. McLean S, Protti D, Sheikh A. Telehealthcare for long term conditions. BMJ. 2011;342:d120. doi:10.1136/bmj.d120
157. Kidholm K, Ekeland AG, Jensen LK, Rasmussen J, Pedersen CD, Bowes A, et al. A model for assessment of telemedicine applications: mast. Int J Technol Assess Health Care. 2012;28(1):44-51. doi:10.1017/S0266462311000638
158. Nasjonalt senter for samhandling og telemedisin. Rapport fra risikovurdering. Diabetes Fotsår – elektronisk veiledning til kommunene. Stavanger: Stavanger universitetssykehus; 2015.
159. Buckley KM, Adelson LK, Agazio JG. Reducing the risks of wound consultation: adding digital images to verbal reports. J Wound Ostomy Continence Nurs. 2009;36(2):163-70. doi:10.1097/01.WON.0000347657.02594.36
160. Williamson DA, Allen HR, Martin PD, Alfonso AJ, Gerald B, Hunt A. Comparison of digital photography to weighed and visual estimation of portion sizes. J Am Diet Assoc. 2003;103(9):1139-45. doi:10.1016/S0002-8223(03)00974-X
161. Sarhan F, Weatherburn G, Graham A, Thiyagarajan C. Use of digital images in the assessment and treatment of pressure ulcers in patients with spinal injuries in community settings. J Telemed Telecare. 2010;16(4):207-10. doi:10.1258/jtt.2010.004013

162. MacNeill V, Sanders C, Fitzpatrick R, Hendy J, Barlow J, Knapp M, et al. Experiences of front-line health professionals in the delivery of telehealth: a qualitative study. Br J Gen Pract. 2014;64(624):e401-e7. doi:10.1258/jtt.2010.004013
163. Finch T, Mair F, May C. Teledermatology in the UK: lessons in service innovation. Br J Dermatol. 2007;156(3):521-7. doi:10.1111/j.1365-2133.2006.07608.x
164. Daniel H, Sulmasy LS. Policy recommendations to guide the use of telemedicine in primary care settings: An american college of physicians position paperrecommendations for the use of telemedicine in primary care settings. Ann Intern Med. 2015;163(10):787-9. doi:10.7326/M15-0498

Paper I-III

I

PLOS ONE

RESEARCH ARTICLE

Severity and duration of diabetic foot ulcer (DFU) before seeking care as predictors of healing time: A retrospective cohort study

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Abstract

Objectives

To investigate whether A) duration of ulcer before start of treatment in specialist health care, and B) severity of ulcer according to University of Texas classification system (UT) at start of treatment (baseline), are independent predictors of healing time.

Methods

This retrospective cohort study, based on electronic medical record data, included 105 patients from two outpatient clinics in Western Norway with a new diabetic foot ulcer during 2009–2011. The associations of duration of ulcer and ulcer severity with healing time were assessed using cumulative incidence curves and subdistribution hazard ratio estimated using competing risk regression with adjustment for potential confounders.

Results

Of the 105 participants, 45.7% achieved ulcer healing, 36.2% underwent amputations, 9.5% died before ulcer healing and 8.5% were lost to follow-up. Patients who were referred to specialist health care by a general practitioner $\geq$ 52 days after ulcer onset had a 58% (SHR 0.42, CI 0.18–0.98) decreased healing rate compared to patients who were referred earlier, in the adjusted model. High severity (grade 2/3, stage C/D) according to the UT classification system was associated with a decreased healing rate compared to low severity (grade1, stage A/B or grade 2, stage A) with SHR (95% CI) equal to 0.14 (0.05–0.43) after adjustment for referral time and other potential confounders.

Abbreviations: UT classification system, University of Texas classification system; PAD, peripheral arterial disease; SHR, subdistribution hazard ratio; GP, General practitioner; SHC, specialist health care.

Conclusion

Early detection and referral by both the patient and general practitioner are crucial for optimal foot ulcer healing. Ulcer grade and severity are also important predictors for healing time, and early screening to assess the severity and initiation of prompt treatment is important.

Introduction

Diabetic foot ulcer is a feared complication of diabetes with a yearly incidence around 2–4% [1]. A diabetic foot ulcer has a variety of causes, often including peripheral ischemia, neuropathy or both. Ulcer healing takes weeks or months, and one-third of ulcers never heal with amputation as the consequence [2].

Factors affecting healing time include duration of ulcer, but limited research on the influence of duration of ulcer before treatment starts in specialist health care is available. Although some have investigated the associations between duration of ulcer before specialist health care treatment and healing time among persons with a diabetic foot ulcer [3–7], referral pathways are still not optimal. Many patients have delayed specialist health care referral due to lack of awareness of the potential consequences of a diabetic foot ulcer among patients and health care professionals and poor management strategies or ischemia detection [8]. In Norway, general practitioners coordinate medical follow-up and serve as "gate keepers" to specialist care, but still there are unclear referral practices between primary and specialist health care [9]. The importance of optimal referral patterns is also emphasised in international guidelines [10, 11]. However, to our knowledge, no studies have assessed the different periods of the referral pathway among individuals with diabetic foot ulcers. More evidence is therefore needed to assess the delay in referral pathways and the impact of these delays.

Diabetic foot ulcer treatment is challenging and time-consuming. Thus, predicting outcomes among patients with diabetic foot ulcers help clinicians to provide effective management strategies [12]. Using screening tools to identify vulnerable subgroups to detect diabetic foot ulcers at an early stage is important. However, the use of classification systems as a screening tool in clinical practice is scarce [13]. The University of Texas (UT) classification system is one of few systems that have been validated [13–15]. Although widely used, it is emphasised that more research is needed to assess to what degree this system reflects the population for which it is intended [16]. In Norway, a diabetic foot risk classification system has not yet been implemented in national guidelines. Thus, the UT classification system might be relevant for investigating predictors for healing time.

By utilizing a Norwegian cohort of foot ulcer patients from specialist health care outpatient clinics our main aim was to investigate the association of the following time fractions with healing time: the total duration of ulcer before start of treatment in specialist health care, defined as the time from patient-reported ulcer onset to start of treatment in specialist health care and two different fractions of duration of ulcer: 1) time from patient-reported ulcer onset to referral by general practitioner to specialist health care and 2) time from referral by general practitioner to start of treatment in specialist health care. In addition, we wanted to explore whether severity of the ulcer in terms of grade and stage at start of treatment in specialist health care was associated with healing time and whether duration of ulcer and severity showed independent associations after mutual adjustment and adjustment for other potential confounders.

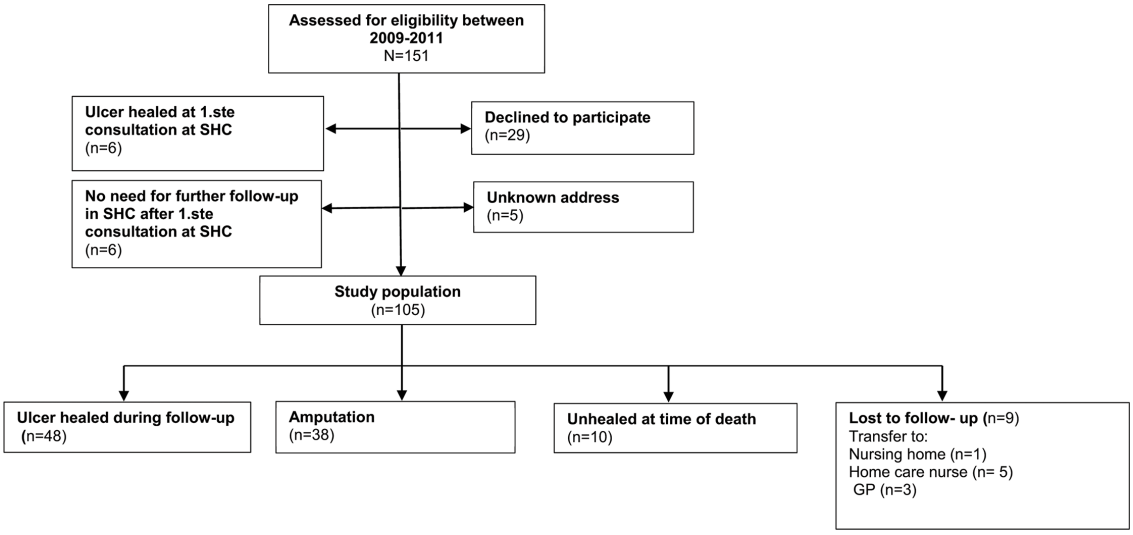

Fig 1. Flowchart: Study population.

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Material and methods

This retrospective cohort study included all patients with a new diabetic foot ulcer presenting for the first time at two specialist outpatient clinics in Western Norway between 1 January 2009 and 31 December 2011 (Fig 1). In this study period, guidelines for foot assessment and treatment were provided through the National Professional Guideline for Diabetes—prevention, diagnosis and treatment (IS-1674) [17].

Patients previously treated for foot ulcers in specialist health care in the last 12 months before baseline were excluded. Each patient was followed to healing, amputation or death. A foot ulcer was defined as a skin lesion below the ankle. Participant information relating to baseline and follow up was obtained from medical electronic records. We recorded data on a standardised record form designed for this study and based on the research literature, clinical guidelines and expert opinions. A nurse specialized in diabetes and wound treatment from each outpatient clinic collected data from medical records. Data were collected between February 8, 2015 and January 2, 2016.

Missing values for the different variables are reported in Table 1. In the competing risk analysis missing data were addressed by listwise deletion. Overall, most of the information required was available, except for information on ulcer area. 41.9% of the patients did not have this information on ulcer area, thus, we decided not to include ulcer area as a study variable.

Main exposures

The main exposure variables were duration of ulcer and ulcer severity. Duration of ulcer was defined as the time from patient-reported ulcer onset to start of treatment in specialist healthcare using the tertiles: 0–27 days, 28–59 days and $\geq$ 60 days and further divided into two periods: 1) time from patient-reported ulcer onset to referral by general practitioner to specialist health care (divided into three groups using the tertiles: 0–13 days, 14–51 days and $\geq$ 52 days)

and 2) time from referral by general practitioner to start of treatment in specialist health care (divided into three groups using the tertiles: 0 days, 1–13 days and $\geq$ 14 days). There are no established cut-off criteria for defining short, medium and long referral time; therefore, we chose to use tertiles to avoid biased cut-offs.

Ulcer severity was classified according to the UT classification system [15, 18] as grade 1 (superficial wound not involving tendon, capsule or bone), grade 2 (penetrating to the tendon or capsule) or grade 3 (penetrating to the bone or joint). Patients with ulcer grade 0 (completely healed ulcer) were excluded. Stages were: clean wounds (stage A); non-ischemia, infected (stage B); ischemia, non-infected (stage C); or ischemia, infected (stage D). Because of the small numbers in some categories, we combined grade and stage into three categories defined as low severity, medium severity and high severity determined from a clinical perspective. Low severity was defined as Grade 1 + stage A/B or grade 2 + stage A. Medium severity was defined as: Grade 1 + stage C/D or grade 2 + stage B or grade 3 + stage A/B and high severity was defined as grade 2/3 combined with stage C/D.

If the patient had multiple ulcers, the most severe ulcer (according to UT classification system), was selected as the index ulcer. This selection was made before collecting data on whether the ulcer healed.

Demographic and clinical variables

Demographic and clinical variables which were considered to be potential confounders were sex, age, HbA1c, coronary disease, vascular surgical treatment, and neuropathy. These variables were selected based on previous literature and clinical judgement. Age was defined as the age at first consultation at the outpatient clinic. HbA1c measurements were reported in the International Federation of Clinical Chemistry units (mmol/mol) in addition to derived NGSP units (%) upon attendance at the outpatient clinic. Coronary disease was defined as having angina pectoris, history of myocardial infarction, previous coronary angioplasty or artery coronary bypass operation. Vascular surgical treatment includes information on percutaneous transluminal angiography of the peripheral arteries or bypass. Neuropathy was defined as an abnormal pressure sensation evaluated with the 10-g monofilament [19].

Outcome, competing events and follow-up time

The outcome was healing time, defined as the time from the start of treatment in specialist health care until ulcer healing. Healing was defined as healing (intact skin) of the whole foot without any surgery in the period of study. Amputation and death were considered competing events. Follow-up time was calculated as time from the date of inclusion (= treatment start in specialist health care) until healing, amputation, death or loss to follow-up, whichever came first. Amputation performed below the ankle was defined as minor amputation, whereas amputation above the ankle was defined as major amputation [20].

Statistical analysis

Descriptive statistics for the study population at baseline were calculated as mean, standard deviations, counts and percentages. Tests for associations between categories of referral time and categories of ulcer severity were conducted using chi-square tests. Cumulative incidence functions for healing time were calculated using the *stcompet* command in Stata, with amputation and death treated as competing events. Cumulative incidence functions were calculated separately for duration of ulcer divided into two periods, and for the three combinations of grade and stage. Fine & Gray competing risk regression analysis [21] were used to calculate the association of duration of ulcer, ulcer severity classified according to the UT classification

system and healing time, and association between amputation and ulcer severity. Amputation and death were treated as competing events in the subdistribution hazard regression model while loss to follow up were treated as censored observations [22]. Results were reported as sub distribution hazard ratio (SHR) with 95% confidence intervals.

We investigated the associations of predictors, potential confounders and the outcome using univariate competing risk regression models (model 1). Then, we constructed a model where the main exposures, the two factions of duration of ulcer and ulcer severity, were mutually adjusted (model 2). Finally, we constructed a multivariate competing risk regression model including potential confounders, such as age, sex, HbA1c, coronary disease, vascular surgical treatment and neuropathy, in addition to the two fractions of ulcer duration and ulcer severity (model 3). Potential deviations from the proportional hazards assumption were investigated by including covariates as time-dependent covariates in the model. No significant time-dependent effects were found.

Statistical significance was defined as $P < 0.05$ in all analyses. SPSS version 22 was used for the description of baseline data, and Stata version 14 was used for competing risk regression and to construct cumulative incidence function curves in competing risk analyses.

Ethics

The study was approved by the Western Norway Regional Committee for Medical and Health Research Ethics (2011/1609). Study information was sent to all participants still alive at registration, and informed consent was obtained.

Results

Subjects characteristics

In total, 151 participants with a diabetic foot ulcer were identified from 2009–2011, and 46 patients were excluded because they did not meet the inclusion criteria; ulcer healed at first consultations at the specialist health care clinic, (n = 6), no need for further follow-up in specialist health care at first consultation in specialist health care (n = 6), declining to participate (n = 29) and unknown address (n = 5). Thus, the study sample comprised 105 patients (Fig 1). The clinical characteristics of the patients are reported in Table 1. The average age among the patients was 68.7 years (SD ±14.8), 70.5% were men, 79% had type 2 diabetes with a mean HbA1c 7.9% (SD ±1.6). Coronary disease and neuropathy were present in 45.7% and 65.7% of patients respectively, and 38.1% had an ulcer duration of 60 days or more before the start of the treatment at the specialist outpatient clinic (Table 1).

The association between the three-category ulcer severity variable and time from patient-reported ulcer onset to referral by general practitioner to specialist health care is shown in Table 2. The association was significant (P = 0.042) with a higher proportion with short duration time from ulcer onset until referral among those with less severe ulcers (50%), compared to those with more severe ulcers (34.9%). Fifty percent of patients with low ulcer severity had ulcer duration of 0–13 days before referral to specialist health care, while only 16% of patients with high severity had 0–13 days duration before referral. In the group with high severity, 34.9% of the patients had waited 52 days or more before referral. Corresponding tests for the other two referral time variables showed no significant associations with ulcer severity.

Main exposures

Thirty-eight point one percent of patients had had an ulcer 60 days or more before the start of treatment in specialist health care, 31.4% of patients had had an ulcer for $\geq$ 52 days from

patient-reported ulcer onset to referral by general practitioner to specialist health care, whereas 34.3% waited more than 14 days from referral by general practitioner to treatment start in specialist health care (Table 1).

Ulcer characteristics of patients with a diabetic foot ulcer according to UT classification system at baseline is presented in Table 3. Peripheral arterial disease, infection and ulcer penetrating to bone or joint were present in 24 (22.9%) patients (grade 3/stage D), of these, 20 underwent amputation (10 minor amputations, 10 major), 2 experienced complete ulcer healing and 2 died before the ulcer healed. No patients with grade 1, stage A underwent amputation (Table 3). The categorization of patients into low-medium and high severity is shown with shadings in the table.

Table 1. Baseline characteristics of patients with a diabetic foot ulcer.

Characteristics	Total n = 105
Demographic variables	
Sex, n (%)	
Male	74 (70.5)
Age, years, mean, (SD)	68.7 (14.8)
Disease-related variables	
Diabetes type n (%)	
Type II	83 (79.0)
Insulin treatment, n (%)	
Did use insulin	68 (64.8)
HbA1c (mmol/l), Mean (±SD)	63 (±17.5)
HbA1c (%), Mean (±SD)	7.9 (±1.6)
Coronary diseases, n (%)	48 (45.7)
Neuropathy, n (%)	69 (65.7)
Ulcer variables	
Time from patient-reported ulcer onset to start of treatment in specialist health care, n (%)	
0–27 days	33 (31.4)
28–59 days	28 (26.7)
≥ 60 days	40 (38.1)
Missing	4 (3.8)
Time from patient-reported ulcer onset to referral by general practitioner to specialist health care, n (%)	
0–13 days	26 (24.8)
14–51 days	40 (38.1)
≥ 52 days	33 (31.4)
Missing	6 (5.7)
Time from referral by general practitioner to start of treatment in specialist health care, n (%)	
0 days	26 (24.8)
1–13 days	41 (39.1)
≥ 14 days	36 (34.3)
Missing	2 (1.9)
Localization of ulcer, n (%)	
Toe	64 (61.0)
Metatarsal/plantar	19 (18.1)
Heel	22 (21.0)
Vascular surgical treatment	
Percutaneous transluminal angiography /Bypass	26 (24.8)

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Table 2. Association between severity of ulcer according to the UT classification system and time from patient-reported ulcer onset to referral by general practitioner to specialist health care.

Time from PRUO[1] to referral by GP[2] to SHC[3]	Low severity	Medium severity	High severity	Total	p
0–13 days	12 (50.0)	7(21.9)	7 (16.3)	26 (26.3)	0.042
14–51 days	6 (25.0)	13 (40.6)	21 (48.8)	40 (40.4)	
≥ 52 days	6 (25.0)	12 (37.5)	15 (34.9)	33 (33.3)	
Total	24 (100)	32 (100)	43 (100)	99(100)	

[1]PRUO = patient reported onset of ulcer

[2]GP = General practitioner

[3]SHC = Specialist health care

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Outcome

In total, 48 (45.7%) patients' ulcers healed completely without preceding amputation (either major or minor) and 38 (36.2%) underwent amputation (24 minor amputations and 14 major amputation). Ten (9.5%) patients died before the ulcer healed and nine (8.5%) patients were lost to follow-up. The median follow-up time measured from start of treatment in specialist health care to end of follow-up was 67 days (SD ± 185.4) for the total sample (including those who healed, amputated, died and lost to follow up). Mean follow-up time was 130 days. The median time measured from start of treatment in specialist health care to ulcer healing, including only those who healed, was 75.5 days (SD 123.4). Mean healing time was 113 days.

Cumulative incidence curve. Cumulative incidence curves of healing time stratified by duration of ulcer are shown in Fig 2. Patients in the upper tertile of time from ulcer onset to referral by general practitioner to specialist health care (≥ 52 days after ulcer onset) had increased healing time compared to earlier referral. There was no significant difference between the tertiles of time from referral by general practitioners to start of treatment in specialist health care.

Cumulative incidence curves of healing time stratified by severity of ulcer (levels of grade and stage), are seen in Fig 3, which shows an increased healing time for patients with a high severity of ulcer compared to the two other categories of grades and stages.

Univariate competing risk regression analysis. The total duration of the ulcer from ulcer onset to start of treatment in specialist health care showed no significant association with healing time (SHR 0.62, CI 0.30–1.28). When duration of ulcer was divided into two periods, there was no association with time from general practitioners' referral to specialist health care to

Table 3. Ulcer characteristics of patients with a diabetic foot ulcer according to UT classification system at baseline.

Stage		Grade 1	Grade 2	Grade 3	Total
A	*Clean wound*	16 (15.2)	1(1.0)	1 (1.0)	18 (17.1)
B	PAD -, infection +	8 (7.6)	10 (9.5)	11 (10.5)	29 (27.6)
C	PAD +, infection -	8 (7.6)	5 (4.8)	6 (5.7)	19 (18.1)
D	PAD +, infection +	5 (4.8)	10 (9.5)	24 (22.9)	39 (37.1)
Total, n, (%)		37 (35.2)	26 (24.8)	42 (40.0)	105 (100)

PAD: Peripheral arterial disease.

Grade 0: Pre-or post-ulcerative lesion, Grade 1: Superficial wound, not involving tendon, capsule or bone, Grade 2: Wound penetrating to tendon or capsule, Grade 3: Wound penetrating to bone or joint.

White area: low severity, Light Grey area: medium severity, Dark grey area: high severity.

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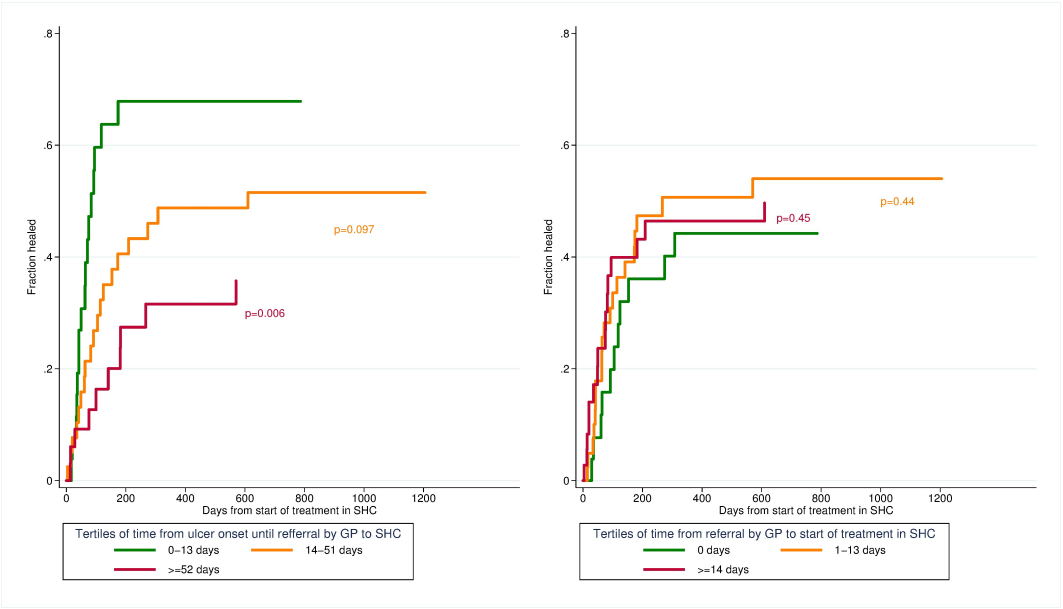

Fig 2. Cumulative incidence curves of healing time stratified by duration of ulcer. P-values from univariate competing risk regression.

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start of treatment and healing time, but there was a strong association between the time from patient-reported ulcer onset to referral by general practitioner to specialist health care with healing time. Patients who were referred to specialist health care by a general practitioner 52 days or more after the onset of ulcer had a 67% (SHR 0.33, CI 0.15–0.72) decreased rate of healing compared to those referred earlier. Older age and vascular surgical treatment were also associated with a decreased rate of healing time (Table 4, model 1).

High ulcer severity ulcer had 87% (SHR 0.13, CI 0.06–0.28) decreased rate of healing compared to low severity. Ulcer of medium severity had 55% decreased rate of healing compared to ulcer with low severity (SHR 0.45, CI 0.24–0.85) (Table 4, model 1). Competing risk analyses with amputation as the endpoint showed a significant association for ulcer severity with three times higher risk of amputation in the category with high severity compared to the category with low severity (SHR 3.15, CI 1.49–6.66) (results not shown in tables). We did not observe any significant associations between total duration of ulcer and risk of amputation or between time from patient-reported ulcer onset to referral by general practitioner to specialist health care and risk of amputation (results not shown in tables). We did however observe a significant association between time from general practitioners' referral to specialist health care to start of treatment and risk of amputation with a lower risk of amputation among those who waited more than 14 days compared to those who had their first appointment the same day as they were referred (SHR 0.41, CI 0.18–0.94). Among the 26 patients having their first appointment the same day as they were referred, 54% ended up with a minor or major amputation.

Multivariate analysis. Estimated SHRs increased slightly for patients who had an ulcer $\geq$ 52 days from 0.33 to 0.38 when the following variables were included in the same model: time from patient-reported ulcer onset to referral by general practitioner to specialist

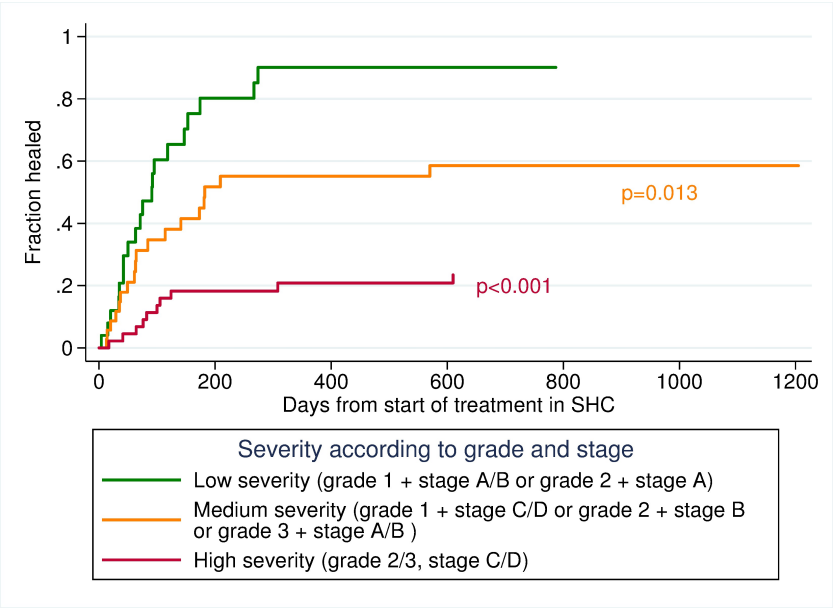

Fig 3. Cumulative incidence curves of healing time stratified by severity of ulcer. P-values from univariate competing risk regression.

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health care, time from referral from general practitioner referral to start treatment in specialist health care and ulcer severity (Table 4, model 2). When age, sex, HbA1c, coronary disease, vascular surgical treatment and neuropathy were entered into the model, the SHRs for time from patient-reported ulcer onset to referral by general practitioner to specialist health care, time from referral from general practitioner to start of treatment in specialist health care and ulcer severity did not change markedly. Age and vascular surgical treatment were associated with reduced healing time in the univariate analysis, but the association did not remain significant after adjustment in the multivariate analysis (Table 4, model 3). For ulcer severity, the association was still significant after adjustment for both duration of ulcer and potential confounders. The significant association between time from referral from general practitioner to start of treatment in specialist health care and risk of amputation observed in the univariate competing risk model was no longer significant after adjustment for severity of the ulcer.

Discussion

Time from patient-reported ulcer onset to referral by general practitioner to specialist health care and the two highest levels of ulcer severity were independently associated with healing time for diabetic foot ulcer while controlling for age, sex, HbA1c, coronary disease, vascular surgery treatment and neuropathy.

The results show that duration of ulcer before starting specialist health care treatment influenced healing time, with time from onset of ulcer to referral by the general practitioner as the main contributor to the association. The waiting time between referral and start of treatment in specialist health care did not show a significant association with healing time and SHR's

Table 4. Subdistribution hazard regression model to calculate the association between duration of ulcer, severity of ulcer and healing time.

	Total (n = 105) ulcer healed (n = 48)	Model 1 SHR (95% CI) Unadjusted	Model 2 SHR (95% CI) Mutually adjusted	Model 3 SHR (95% CI) Full model
Time from patient-reported ulcer onset to start of treatment in specialist health care				
0–27 days	33/16	1		
28–59 days	28/18	1.58 (0.81–3.08)		
≥ 60	40/13	0.62 (0.30–1.28)		
Time from patient-reported ulcer onset to referral by general practitioner to specialist health care				
0–13 days	26/17	1	1	1
14–51 days	40/19	0.57 (0.29–1.11)	1.00 (0.52–1.93)	1.16 (0.51–2.62)
≥ 52 days	33/10	0.33 (0.15–0.72)	0.38 (0.17–0.86)	0.42 (0.18–0.98)
Time from referral by general practitioner to start of treatment in specialist health care				
0 days	26/11	1	1	1
1–13 days	41/20	1.33 (0.66–2.67)	1.45 (0.68–3.09)	1.56 (0.62–3.90)
≥ 14 days	36/16	1.30 (0.61–2.76)	1.76 (0.83–3.77)	1.84 (0.70–4.84)
Severity of ulcer classified after UT classification system				
Low severity	20/25	1	1	1
Medium severity	18/35	0.45 (0.24–0.85)	0.45 (0.23–0.91)	0.45 (0.23–0.88)
High severity	10/45	0.13 (0.06–0.28)	0.14 (0.06–0.30)	0.14 (0.05–0.43)
Age	105/48	0.98 (0.96–1.00)		1.00 (0.98–1.03)
Sex				
Male	74/35	1		1
Female	31/13	0.85 (0.46–1.58)		0.66 (0.36–1.23)
HbA1c	105/48	0.98 (0.82–1.18)		1.12 (0.87–1.44)
Coronary disease				
No	57/26	1		1
Yes	48/22	0.85 (0.49–1.48)		1.04 (0.55–1.96)
Vascular surgery treatment				
Yes	26/5	0.24 (0.10–0.59)		0.59 (0.19–1.79)
No	79/43	1		1
Neuropathy				
Yes	69/35	1.33 (0.70–2.51)		1.05 (0.53–2.07)
No	36/13	1		1

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were actually greater than 1. reflecting a tendency to higher probability of healing among those who waited ≥14 days for an appointment. This could possibly partly be explained by the observed inverse association between waiting time and risk of amputation, with significantly higher risk of amputation among those who waited 0 days compared to those who waited ≥14 days, leaving fewer patients behind to experience healing. Among the 26 patients who had their first appointment in specialist health care the same day as the referral, 61.5% had a wound in stage C or D and 54% ended in amputation, indicating very severe ulcers. The lack of an association between total duration of ulcer and healing time could possibly also be explained by the tendency to an association in the opposite direction for the second part of the duration time.

Margolis and colleagues (2002) [3] evaluated the association between different risk factors and healing time among 31,106 participants with neuropathic foot ulcers. They found that increased wound duration before initial treatment start in specialist health care was one of the major factors associated with reduced healing. However, these results were not supported in a UK study of 449 participants with diabetic foot ulcers [4]. These authors speculated whether this was caused by the fact that the date of ulcer onset simply was recorded by month. In the Eurodiale study, the variation between countries was considerable, with inconclusive results concerning healing time [2, 23]. In a recent British report (2016), findings indicated that the ulcer healing time increased compared to shorter interval if the interval to first assessment by specialist was > 2 months after ulcer onset [7]. Although the number of patients in our study was relatively small, we found that longer duration of ulcer before specialist health care treatment was associated with decreased healing rate. Our results underscore that the interval from patient-reported ulcer onset to specialist health care referral by a general practitioner seems more important than the interval between referral and the start of specialist health care treatment. In the Norwegian health care system, general practitioners are responsible for coordinating medical follow-up [24]. However, we did not find that more superficial DFU took longer for referral, but rather the opposite. Fifty percent of patients with low severity of the ulcer had an ulcer duration of 0–13 days before referral to SHC while only 16% of patients with high severity had 0–13 days duration before referral. In the group with high severity, 34.9% of the patients waited 52 days or more before referral. It is difficult to explain the reasons for this finding. It might be that patients with more severe ulcers waited for a long time before contacting the GP or that the GP tried to treat the ulcer before referring the patient to the specialist health care. We lack information of both these aspects. However, the data give valuable information of the importance of early referral to specialist health care to avoid severe complications. Therefore, it is important to communicate to patients and health care professionals in primary health care that referral pathways and adequate access to general practitioner services are crucial. Reduced function and further adverse complications can be prevented if ulcers are identified at an early stage [8, 10, 25]. A better follow-up strategy in primary health care and models that facilitate communication across different care levels should be considered.

Delayed specialist health care treatment start was seen in many patients, although guidelines stress the importance of early treatment to avoid adverse complications [10, 11]. In our cohort, 38.1% of patients had a duration of ulcer ≥ 60 days (2 months) prior to the start of specialist health care treatment. This is comparable with the results of the Eurodiale study involving 14 countries, where over 27% of participants were treated for >3 months before initial specialist health care treatment [8], while only 7.7% among patients with DFU in England and Wales had more than 60 days (2 months) delayed referral time to specialist health services [7]. Although substantial differences among countries exist, current guidelines were not followed when treating a significant number of patients [8, 11]. Our study showed a strong association between delayed referral to a specialist unit and healing time after adjustment for potential confounder with clear implications for routine care. Treatment is effective, guidelines are available and early intervention seems to reduce the burden of an adverse outcome.

The present cohort has a higher incidence of amputation and relative low incidence of ulcer healing compared to other studies [6, 8, 23]. In total, 52% of the ulcers leading to amputation were affected by infection, peripheral artery disease and ulcers penetrating to bone and joint These more severe risk factors may have had an impact on the relative high incidence of amputation. One other possible explanation might be that our definition of healing did not include minor amputation, which is in contrast to some other studies [6, 26]. In these studies, minor amputation could be regarded as a strategy leading to healing.

Ulcers of the highest and medium stage and grade were strongly associated with decreased rate of healing. Both peripheral arterial disease, independently and in combination with infection, are known predictors of ulcer healing leading to prolonged healing time. Patients with the combination of PAD, infection and ulcer penetrating to bone or joint were also more likely to undergo amputation than those with less severe ulcer stage [2, 23, 27]. In our cohort, PAD, infection and ulcer penetrating to bone or joint with amputation as an endpoint were seen in 20 of the patients. Given the association between severity of ulcer and healing time, early screening of people with a new ulcer is imperative to assess the severity and initiate adequate treatment to reduce the risk of amputation [2, 27].

We found an association between severity of ulcer and duration of ulcer, but the duration of ulcer and severity of ulcer still showed significant associations with healing time after mutual adjustment and adjustment for potential confounders. First, the persistent associations after adjustment for duration of ulcer indicate that ulcer severity at the first specialist health care consultation was important for healing time, regardless of how long the ulcer had lasted before the first consultation. In other words, an ulcer with a severe grade and severe stage has an increased healing time, even if it did not last long before start of treatment. Second, the independent association for duration of ulcer indicates that duration of ulcer affects healing through mechanisms other than greater ulcer severity. Other possible factors might be the quality of general practitioners' treatment and a lack of health awareness among this patient group.

There are several limitations in this retrospective cohort study. First, the sample size is relatively small, which limit the statistical power. However, these results may still provide new knowledge about independent predictors for healing time and implications for further research. Second, in total 69.5% of the potential participants were included in the study. Non-participants might have been in worse health status, and this could potentially lead to selection bias. The increased healing time associated with duration of ulcer before start of treatment in specialist health care and severity of ulcer in the present study might therefore have been underestimated. Third, we acknowledge that the UT classification system omits reference to ulcer area. In our study we were not able to examine the impact of ulcer areas on healing due to missing data on ulcer size (cm^2) (41.9%). In the time period that data were collected, it was not common to use pictures to measure ulcer area, which may explain the high occurrence of missing. As the UT classification system provides a standard description of an ulcer and help predict outcomes we decided only to use the UT classification system in the analyses. Fourth, the possible impact of early amputation as a strategy to obtain healing would be interesting to investigate, but this was not possible since follow-up was terminated at the time of minor or major amputation. Therefore, we do not know the healing time for patients who experienced ulcer healing after a minor amputation. Fifth, the incidence of amputation was high in this study, especially among those who had their first appointment in specialist health care the same day as they were referred by the GP, causing a non-significant increased rate of healing among those who waited longer for an appointment after referral was sent by the GP. In a population with a lower incidence of amputation, it might be more likely to observe an increased rate of healing with shorter waiting time, but the strength of the association would be weakened if patients with more severe ulcers have shorter waiting time. Sixth, information on how long the patient waited before he/she contacted a general practitioner was unavailable for most patients and could therefore not be included in the analysis. Finally, data on whether the general practitioner had treated the ulcer before the patient was referred to specialist health care was also lacking. Such information could provide important information on the causes of delayed referral, and further studies are necessary to assess the importance of these factors.

In summary, duration of diabetic foot ulcer before the start of treatment in specialist health care and ulcer severity influenced healing time independently of each other. Early identification of the ulcer by the patient and the general practitioner, as well as early referral by a general practitioner to specialist health care are important for ulcer healing and have clear implications for routine care. Grade and stage severity are important predictors for healing time. Early screening might identify patients needing extra support in treatment and follow-up care.

Supporting information

S1 File. Data set in excel format.
(XLS)

S2 File. Strobe checklist.
(DOCX)

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References

1. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. The Lancet. 2005; 366(9498):1719–24.
2. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: Focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia. 2008; 51(5):747–55. https://doi.org/10.1007/s00125-008-0940-0 PMID: 18297261
3. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: the association of wound size, wound duration, and wound grade on healing. Diabetes Care. 2002; 25(10):1835–9. PMID: 12351487
4. Ince P, Game FL, Jeffcoate WJ. Rate of healing of neuropathic ulcers of the foot in diabetes and its relationship to ulcer duration and ulcer area. Diabetes Care. 2007; 30(3):660–3. https://doi.org/10.2337/dc06-2043 PMID: 17327337

5. Sanders AP, Stoeldraaijers LG, Pero MW, Hermkes PJ, Carolina RC, Elders PJ. Patient and professional delay in the referral trajectory of patients with diabetic foot ulcers. Diabetes research and clinical practice. 2013; 102(2):105–11. https://doi.org/10.1016/j.diabres.2013.09.016 PMID: 24145054
6. Orneholm H, Apelqvist J, Larsson J, Eneroth M. High probability of healing without amputation of plantar forefoot ulcers in patients with diabetes. Wound Repair & Regeneration. 2015; 23(6):922–31.
7. Clinical Audit and Registries Management Service, Health and Social Care Information Centre. National Diabetes Foot Care Audit Report 2014–2015. England and Wales; 2016. Available from: http://content.digital.nhs.uk/catalogue/PUB20343/nati-diab-foot-care-audit-14-15-rep.pdf.
8. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. Delivery of care to diabetic patients with foot ulcers in daily practice: results of the Eurodiale Study, a prospective cohort study. Diabetic medicine. 2008; 25(6):700–7. https://doi.org/10.1111/j.1464-5491.2008.02445.x PMID: 18544108
9. Graue M, Dunning T, Hausken MF, Rokne B. Challenges in managing elderly people with diabetes in primary care settings in Norway. Scandinavian journal of primary health care. 2013; 31(4):241–7. PubMed Central PMCID: PMCPMC3860301. https://doi.org/10.3109/02813432.2013.854445 PMID: 24205973
10. Bus S, Netten J, Lavery L, Monteiro-Soares M, Rasmussen A, Jubiz Y, et al. IWGDF Guidance on the prevention of foot ulcers in at-risk patients with diabetes. Diabetes/metabolism research and reviews. 2015.
11. The national Institute for Health and care Exellence (NICE). Diabetic foot problems: prevention and management. NICE guideline (NG19). https://www.nice.org.uk/guidance/ng192015.
12. Monteiro-Soares M, Boyko E, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Risk stratification systems for diabetic foot ulcers: a systematic review. Diabetologia. 2011; 54(5):1190–9. https://doi.org/10.1007/s00125-010-2030-3 PMID: 21249490
13. Monteiro-Soares M, Boyko E, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Predictive factors for diabetic foot ulceration: a systematic review. Diabetes/Metabolism Research and Reviews. 2012; 28(7):574–600. https://doi.org/10.1002/dmrr.2319 PMID: 22730196
14. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care. 1998; 21(5):855–9. Epub 1998/05/20. PMID: 9589255
15. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Harkless LB, Boulton AJ. A Comparison of Two Diabetic Foot Ulcer Classification Systems. The Wagner and the University of Texas wound classification systems. Diabetes care. 2001; 24(1):84–8. PMID: 11194247
16. Game F. Classification of diabetic foot ulcers. Diabetes Metab Res Rev. 2016; 32 Suppl 1:186–94. Epub 2015/10/13.
17. The Norwegian Directorate of Health. National professional guidelines: Diabetes—Prevention, diagnosis and treatment (IS-1674). http://www.helsebiblioteket.no/retningslinjer/diabetes/11.komplikasjoner/11.9-diabetiske-fotproblemer; 2011.
18. Lavery LA, Armstrong DG, Walker SC. Healing rates of diabetic foot ulcers associated with midfoot fracture due to Charcot's arthropathy. Diabetic Medicine. 1997; 14(1):46–9. https://doi.org/10.1002/(SICI)1096-9136(199701)14:1<46::AID-DIA291>3.0.CO;2-T PMID: 9017353
19. Boulton AJM, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Kirkman MS, et al. Comprehensive foot examination and risk assessment a report of the task force of the foot care interest group of the American diabetes association, with endorsement by the American association of clinical endocrinologists. Diabetes care. 2008; 31(8):1679–85. https://doi.org/10.2337/dc08-9021 PMID: 18663232
20. Rayman G, Krishnan ST, Baker NR, Wareham AM, Rayman A. Are We Underestimating Diabetes-Related Lower-Extremity Amputation Rates? Diabetes care. 2004; 27(8):1892–6. PMID: 15277413
21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American statistical association. 1999; 94(446):496–509.
22. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. American journal of epidemiology. 2009:kwp107.
23. van Battum P, Schaper N, Prompers L, Apelqvist J, Jude E, Piaggesi A, et al. Differences in minor amputation rate in diabetic foot disease throughout Europe are in part explained by differences in disease severity at presentation. Diabetic Medicine. 2011; 28(2):199–205. https://doi.org/10.1111/j.1464-5491.2010.03192.x PMID: 21219430
24. Ministry of Health and Care services. The primary health and care services of tomorrow—localised and integrated; 2015. Available from: https://www.regjeringen.no/en/dokumenter/meld.-st.-26-20142015/id2409890/?q=fremtidens&ch=1.
25. Bakker K, Apelqvist J, Schaper N. Practical guidelines on the management and prevention of the diabetic foot 2011. Diabetes/metabolism research and reviews. 2012; 28(S1):225–31.

26. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia. 2007; 50(1):18–25. https://doi.org/10.1007/s00125-006-0491-1 PMID: 17093942

27. Brownrigg J, Apelqvist J, Bakker K, Schaper N, Hinchliffe R. Evidence-based management of PAD & the diabetic foot. European Journal of Vascular and Endovascular Surgery. 2013; 45(6):673–81. https://doi.org/10.1016/j.ejvs.2013.02.014 PMID: 23540807

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III

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An integrated wound-care pathway, supported by telemedicine, and competent wound management—Essential in follow-up care of adults with diabetic foot ulcers

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ABSTRACT

Introduction: Diabetic foot ulcers are a feared complication of diabetes. Care delivered via telemedicine is suggested to be a more integrated care pathway to manage diabetic foot ulcers than traditionally delivered healthcare. Our aim was to explore patients' experiences with telemedicine follow-up care as compared to traditional care.
Methods: Interpretive description was used as an analysis strategy. Data were collected using individual semi-structured interviews in the context of a larger ongoing clustered randomized controlled trial. Twenty-four patients (13 in the intervention group; 11 in the control group), aged 38–88 years were purposively recruited from the RCT in order to obtain a diverse sample in terms of group composition (intervention vs. control), age, gender, marital status, setting, and comorbidities present. The control group received traditional care.
Results: Three themes emerged from the interpretive analysis: *competence of healthcare professionals*, *continuity of care,* and *easy access*. This was independed of types of follow-up that had limited impact on the patients' follow-up experiences. Competence of healthcare professionals and continuity of care were crucial, because they can either enhance or jeopardize wound care. If these two latter factors were absent, patients would lose confidence in the wound care process. If this happened, patients pointed out that the expert knowledge of a specialist clinic was essential to receive good care. When telemedicine functioned optimally, telemedicine was an advantage in the treatment, because the images quickly captured changes in the wound healing that immediately could be corrected. Easy access is important for patients, but the importance of accessibility appears to be primary when the other two factors were present.
Conclusion: The best wound care pathway for patients with diabetes foot ulcers is depended on a combination of competence and professional skills in wound management, and continuity of care. If telemedicine is functioning as intended, it can be an important additional tool.

1. Introduction

Diabetic foot ulcers severely affect patients' quality of life [1]. They are worrisome complications of diabetes, as they can take months to heal and can lead to osteomyelitis and amputation [2].

In Norway, and in other countries, home care nurses in collaboration with the general practitioner (GP) have the primary responsibility for treatment and follow- up of patients with ulcers in collaboration with the specialist health care service [3–5]. However, in the current system it is reported that the collaboration between primary health care and specialist health service is not sufficient [6]. In particular, problems exist related to lack of competence in wound management among home care nurses and GPs, the GPs and municipalities' roles in treatment and follow –up care are unclear, and capacity problems exist in the specialist health service as well as varying and unclear referral practices between primary

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Table 1
Characteristics of the participants.

	Telemedicine follow- up N = 13	Traditional follow-up N = 11
Sex		
Men	10	8
Women	3	3
Age		
30–39	–	1
40–49	1	2
50–59	3	–
60–69	4	3
70–79	2	4
>80	3	–
Mean (r)	62.6 (47–88)	60.4 (38–76)
Type of diabetes		
Type 1	2	4
Type 2	11	7
Marital status		
Married/cohabitant	11	10
Widow/widower	1	1
Single	1	–
Employment		
Work full-time/Part-time	5	4
Retried	7	3
Sick leave	1	–
Disabled	–	4
Co-morbidities	–	–
Coronary disease	3	3
Peripheral artery disease	2	2
Neuropathy	7	4
Rheumatism	1	1
None		
Geographical distance from settlement to hospital, km. median (r)	11.4 (0.5–72.6)	10.7 (2.6–30.6)

– and specialist health care service [7–9]. A particular challenge is related to lack of good communication technology between the two levels. Lack of collaboration between levels, with the consequence that the patient does not receive timely treatment can lead to severe consequences for the patients [8]. Diabetic foot ulcers are one of the leading causes of hospital admission for people with diabetes and the most common cause of lower limb amputation [9,10].

Telemedicine is suggested to be one solution used to facilitate the creation of a more integrated healthcare service, with the aim of increasing access, quality, patient satisfaction, and treatment efficiency in patients with diabetic foot ulcers [4,11,12]. Telemedicine has been available in different healthcare disciplines and for various disease groups for decades. In wound care, much literature exists on imaging technology and feasibility of the technology. However, studies that have focused specially on diabetic foot ulcer and telemedicine are scarce. A systematic review from 2014 [13] assessing the effect of telemedicine compared to traditional care among patients with leg and foot ulcer concluded that the evidence is inconclusive due to lack of studies and poor methodological quality of the studies. The authors concluded that RCT studies with larger samples and longer follow-up time are needed. In Denmark, a recently published RCT [14] study including 401 patients with diabetic foot ulcers found no difference in terms of wound healing or amputation. However, they found a higher mortality rate among patients receiving telemedicine follow-up versus traditional care. Based on that, the authors question the role of telemedicine in monitoring diabetic foot ulcers, especially to subgroups of patients that may have poorer outcomes with telemedicine monitoring. In contrast, a large RCT study in UK [15] including 3230 patients with diabetes, chronic obstructive pulmonary disease or hearth failure found that telehealth was associated with lower mortality. The latter study did not include patients with diabetic foot ulcer. Hence, more studies are needed to evaluate the effects of telemedicine follow up compared to traditional care as well as how the incorporation of telemedicine impacts on the experiences of patients receiving such care. Also, few studies have explored patients' experiences with treatment for diabetic foot ulcers and their satisfaction with telemedicine [4,16]. The few existing reviews of implementation of this technology examined patients' satisfaction with telemedicine and included various patient groups, but not patients with diabetic foot ulcers [17–19]. These reviews concluded that the majority of studies varied in quality and had many methodological problems.

There is a need to supplement previous research by exploring the patients' perspective on wound management as patients' experiences are an important contributor to improve the quality of health care services. In-depth knowledge of patients' experiences can help evaluate whether use of telemedicine is an appropriate way to improve the service. In the present study, we employed a qualitative approach, and patients included were part of a larger ongoing cluster randomized controlled trial (RCT) (Clin.Trial.gov: NCT01710774). This trial is investigating whether telemedicine follow-up care for patients with diabetic foot ulcers who receive home care in collaboration with specialist healthcare is an equivalent alternative to traditional outpatient clinical follow-up in a specialist healthcare setting. The main trial outcome for the larger RCT is healing time.

The telemedicine intervention consists of an interactive wound platform, which uses a web-based ulcer record combined with a mobile phone that allows counseling and communication among nurses in community and specialist healthcare. Use of wound images in combination with written assessments of the wound might replace or supplement existing treatment follow-up. Both groups receive treatment in primary and specialist healthcare, and the purpose of patients receiving telemedicine follow-up is to reduce the number of consultations in the outpatient clinic in the specialist health care. More responsibility can then be transferred to primary healthcare that is in line with national guidelines [6,20]. By obtaining knowledge of patients' experiences receiving telemedicine and comparing and contrasting these experiences

Table 2
Main topics covered by the interview guide.

Intervention group	
1.	The patient's experiences with the foot ulcer and what he did when he discovered the ulcer
2.	The patient's experiences with receiving telemedicine treatment and follow-up from the home care nurse
3.	The patient's experiences with being followed up in specialist healthcare
4.	The patient's' experiences of being involved in wound management and decisions that concerned his treatment
5.	The patient's experiences with healthcare professionals' use of the telemedicine equipment and healthcare professionals' own views on using images in wound care
6.	Whether the patient observed telemedicine collaboration between the home care nurse and specialist healthcare service during follow-up
7.	The patient's perception of whether he takes more responsibility for his own health
8.	The patient's perception of what is the most important task home care nurses and experts at the outpatient clinic have in treatment and care of patients with diabetic foot ulcers
Control group	
1.	The patient's experiences with the foot ulcer and what he did when he discovered the ulcer
2.	The patient's experiences with receiving traditional treatment and follow-up from the home care nurse
3.	The patient's experiences with being followed up in specialist healthcare
4.	The patient's experiences of being involved in wound management and decisions that concerned his treatment
5.	Whether the patient observed any collaboration between the home care nurse or GP and specialist healthcare services during follow-up
6.	The patient's perception of whether he takes more responsibility for his own health
7.	The patient's perception of what is the most important task home care nurses and experts at the outpatient clinic have in treatment and care of patients with diabetic foot ulcers

with those of patients in the control group, we may get new insight into how this technology influences patients' perspectives. Including patients' perspectives may cultivate a more holistic view and more tailored treatment. The aim of our study was therefore to explore the experiences of adults with diabetic foot ulcers receiving telemedicine compared to patients receiving traditional follow-up healthcare delivered in the context of a clustered RCT.

2. Methods

2.1. Study design

Interpretive description (ID), as described by Thorne [21], was used as a strategy in the present study. ID is an inductive analysis approach that addresses clinical research questions in a way that can inform and potentially change practice [21].

2.2. Patients

Twenty-four patients (13 in the intervention group, 11 in the control group), aged 38–88 years, were purposively recruited from the telemedicine RCT trial so that we could obtain a diverse study sample in terms of group (intervention vs. control), age, gender, employment, marital status, settlement, and comorbid conditions (Table 1). Patients in this study were included if their foot ulcers had healed, or at the end of intervention that last maximum for 12 months. The study nurse organized patient recruitment at two clinical sites in Western Norway that are responsible for the larger, ongoing cluster RCT study. The first author (HSS) contacted patients who earlier consented to participate in an interview in order to make an appointment for the present study. One patient declined participation, citing current unfavorable health conditions. At the time of the interview, patients' foot ulcers had healed completely for most of the patients, except for three patients in the intervention group and four in the control group.

2.3. Follow-up of intervention group and control group in the RCT study

Patients in the telemedicine group were followed primarily by home care service. However, every six weeks they visited the outpatient clinic, where their foot ulcer was monitored. At a minimum of once per week, the home care nurse would take a digital image of the patients' ulcers and would send it to the expert wound care team at the outpatient clinic for assessment and feedback. Assessment of the wound image, together with a written assessment, determined whether a patient would require more frequent consultations at the outpatient clinic.

Patients in the control group underwent wound control every 2–4 weeks at the outpatient clinic, with follow-up by the home care service between consultations. However, this did not take place in combination with telemedicine follow-up. For some patients home care follow up was not needed.

Patients in both groups were included in the trial until their foot ulcer healed, but for maximum of 12 months.

2.4. Data collection

All interviews were conducted between March 2014 and May 2015, either in the patients' homes or at their workplace. Each interview lasted between 35 and 55 min.

A semi-structured interview guide was developed, based on the aim of the study, our current contextual understanding of the treatment, and care pathways for patients with a diabetic foot ulcer. The interview guide was piloted with one patient from each group of the trial to assess its usefulness. The guide was perceived as a functional tool, and only minor changes were made.

The interview guide contained eight overall topics with subthemes for the intervention group and seven overall topics with subthemes for the control group (Table 2). The topics were similar for both groups, except for questions related to the patients' experiences with health professionals' use of the telemedicine equipment and users' own views on using digital images and remote assessment in wound care.

2.5. Analysis

Interviews were transcribed verbatim. The analysis process comprised four phases: [1] researcher immersion in the transcripts, [2] coding and developing of themes, [3] comparing and contrasting themes within the groups, and [4] comparing and contrasting themes between the groups (telemedicine vs. control). By follow these phases, it was possible to obtain comprehensive insight into the data, which in turn afforded us the opportunity to examine the similarities and differences that emerged from the data. Each author analyzed the data individually, and then all authors con-

vened to discuss the data. This was done to ensure credibility and obtain consensus at the interpretation of the individual themes that emerged during the four-phase analysis process.

Immersion in the transcripts began immediately after each interview, in which field notes were prepared containing observations of the setting and overall impressions from each interview. The first author then transcribed all interviews directly after completion of each interview. Each transcript ended with preliminary interpretations of the text, which were used for further analysis. This enabled us to get an overall impression of the data. The transcripts were then read in their entirety in order to get a sense of the whole.

In the second phase, we used open coding. Here, we chose codes to match closely to the language inherent to the data. The different codes were then sorted into groups of data that seemed to be thematically related. In this process, different tentative themes were identified; these were used as a basis for further analysis.

We used a constant comparison method [21] to compare the different parts of and patterns in each interview and to compare the intervention and control groups. In phase three, first we performed a "within-group comparison" by assessing the telemedicine intervention patients for similarities and differences. The same was done with the data from the patients in the control group. Then, we performed a "between-group" analysis by comparing themes from the intervention and controls groups. Both positive and negative patterns emerged from both group analyses. Further analysis revealed remarkable similarities between the two groups (intervention vs. control) and between members within each group. By comparing and contrasting these positive and negative patterns within and between groups, it was possible to conduct a more holistic analysis. This in turn enabled us to identify the final themes within the overall dataset common to both groups.

In the final phase of analysis, we identified three themes; competence of healthcare professionals, continuity of care, and easy access to healthcare services, that appeared to play an essential role in patients treatment and follow-up care.

2.6. Ethical considerations

The study was approved by the Western Norway Regional Committee for Medical and Health Research Ethics (2011/1609/REK vest). All participants received written and oral information about the study. Participation was voluntary, and each patient signed an informed consent form.

3. Results

The most important requirement expressed by adults with diabetic foot ulcers was to feel secure about or have confidence in their ulcer treatment and follow-up. Fear of amputation or new wounds were fundamental for the patients in both groups. Consequently, experiences of security and confidence were fundamental premises for how they experienced the treatment and follow-up care. Some felt confident they were receiving care that would benefit wound healing. Others felt doubtful that the care they were receiving would promote wound healing. The type of service (telemedicine vs. traditional) seemed less important in terms of how the patients experienced follow-up care. They emphasized *competence of healthcare professionals, continuity of care,* and *easy access to healthcare services* as the most important elements that helped them gain security and confidence about the wound care they were receiving. Both competence of healthcare professionals and continuity of care were seen as essential for providing high-quality foot ulcer care. The presence of both elements would contribute to improve the quality in handling of the foot ulcer, whereas their absence would not. The analysis also revealed positive process with telemedicine follow-up care. For instance, with the patients in the telemedicine intervention, taking an image with the mobile phone could quickly capture changes in healing. In a matter of minutes, the home care nurse can take mobile phone images of an ulcer and forward them to the expert team at the outpatient clinic, allowing both of them to evaluate the ulcer and discuss what treatment course to take. Although easy access to wound care was generally important for all the patients, the importance of accessibility appears first when competence of healthcare professionals and continuity of care were present.

3.1. Competence of healthcare professionals

With respect to competence of nurses, patients stated that knowledge of ulcer management and ability to teach patients about proper ulcer care were important contributors to the quality of care and patients' sense of security. These sentiments were true for both telemedicine patients and control patients. Meeting nurses and other health professionals who had specialized skills in ulcer treatment, gave them a sense of security that they were receiving high-quality foot ulcer care and that severe complication could be avoided such as osteomyelitis and amputation. Patients viewed frequent assessments by a doctor important only if their wound was not healing as expected.

The patients viewed home care nurses and nurses at the outpatient clinic differently. At the outpatient clinics, all patients (both intervention and control) were assessed by expert wound care specialists. Regarding these meetings, all but two patients described themselves as being "*in secure hands*" due to available expertise and rapid referral, if needed, which was not possible in home care settings. Most patients commonly stated: *"They [*specialists*] know how to treat ulcers."* However, several patients also stated that it was important for them to learn about proper wound care from the nurse wound specialists at the outpatient clinic. This gave them a feeling of being empowered, because acquiring appropriate wound care knowledge would help them prevent their ulcer from worsening, prevent recurrence of the ulcer, and prevent new ulcers from forming. As one patient said:

> "*If they only treat the ulcer but do not facilitate learning, there is a risk that the patients will come back with a new ulcer*" (IG19).

Contrasting with their experience at the specialist clinics, the patients stated that they encountered large differences in knowledge and experience among home care nurses. This situation made them feel either secure or insecure, depending on the nurse's expertise in wound care. Patients who received care from home care nurses having extensive ulcer management experience described them as possessing a strong commitment and interest in the ulcer healing process. They viewed these nurses as highly skilled, competent in foot ulcer care, and qualified to treat their ulcers. Often, they used descriptions like, "*engaged,*" "*enthusiastic,*" "[having] *great interest in wounds.*"

On the other hand, patients treated by home care nurses who clearly lacked competence in wound management had a very different perception of their nurses. Not surprisingly, nurses who lacked skills and a professional attitude made patients feel uneasy with their treatment. Patients were afraid that these nurses overlooked important signs of ulcer deterioration. Both control patients and telemedicine patients expressed the same concerns. This sentiment was conveyed by one man in his 70s as follows:

> "*I do not trust the home care nurses. They are so uncertain. They ask me what to do! I say that I cannot decide that. I feel that I am more of a [*wound care*] specialist than they are. If changes occur in the ulcer, I have the impression they do not know this is happening,*

because they have not seen the ulcer for 14 days. They have no information about the ulcer treatment process; they do not know what has been done with it. None of the home care nurses who have treated the ulcer have competence in ulcer treatment" (CG 2).

Another patient stated:

"*I had to explain to the home care nurses how they should treat my foot ulcer, because they treated the ulcer very differently. I knew more about wound care than the nurses*" (IG9).

These representative quotes show how lack of competence in home care service affected whether the patients felt secure with the care they were receiving.

3.2. Continuity of care

3.2.1. Receiving ulcer treatment from fewer nurses made patients feel more secure

The patients described various experiences when several nurses were involved in performing the follow-up ulcer management care. Regardless of treatment group (telemedicine or control), the number of nurse caregivers influenced whether the patients felt secure with the ulcer care they were receiving. In general, they preferred care from fewer nurses, because they felt that, with fewer caregivers, the nurses would *be more familiar with their particular ulcer*, would be more up-to-date on the ulcer healing process and treatment procedure, would be more knowledgeable about ulcer treatments, and would have better communication with the outpatient clinic. If this was not possible, patients felt it was important to have only one nurse oversee treatment, so that responsibility over the treatment was not distributed among several nurses. Patients said this arrangement worked well and promoted good communication among the nurses. Being certain that nurses communicated among themselves about the ulcer progress and treatment was very important and was emphasized as necessary in order for the patients to feel secure with the ulcer treatment in primary healthcare. As one 60-year-old man expressed it:

It was fantastic to be followed up by two nurses. They were up-to-date on the ulcer, they were competent, and both had read and followed the procedures that were sent from the outpatient clinic. They had a very positive commitment to wound management. For me, it was very stimulating and very reassuring (CG7).

One man in the intervention group described follow-up care by home care nurses like this:

"*It was one nurse who had primary responsibility for ulcer treatment and follow-up and communicating with the outpatient clinic. She was available when she was needed, both for me and the other nurses. It was a brilliant way to do it*" (IG5).

Patients followed up by many different home care nurses did not experience such a positive experience. In their case, no one person oversaw their ulcer treatment. Moreover, the nurses involved were not up-to-date on the ulcer's progress. One patient with a complicated, slow-healing ulcer described his experience with home care nurses in the following way:

"*What was so sad is that a new nurse came almost every time, and when I asked them how the ulcer looked like, they would say that they had no idea. They had not seen the ulcer for one to 1.5 months. Few images were taken. I feel not very secure when they cannot tell me how the ulcer is healing*" (IG 12).

3.2.2. Telemedicine can benefit patients

The patients in the two groups (telemedicine vs. control) had very similar experiences. It seemed, however, that care delivered via telemedicine could counteract some of the challenges the patients experienced during the treatment process. Still, this depended on whether telemedicine was carried out as intended.

Telemedicine patients who had positive experiences with their telemedicine care stated that images of the ulcer combined with a written assessment contributed positively to ulcer treatment, because the images reinforced the written assessment of the foot ulcer. Several of the telemedicine patients used the adage, *"one image speaks more than a thousand words,"* to describe their positive experience. The patients stated that the telemedicine protocol worked well, because it gave them the assurance that if something was wrong with their ulcer, it would be quickly caught by the outpatient clinic expert team, who assessed the images. This sense of confidence in the treatment scheme was expressed by one man as follows:

"*The digital communication between the outpatient clinic and the home care nurse, and image transfer gave [*me a feeling of*] security that, if there was some changes in the ulcer healing, the health professionals at the outpatient clinic would catch it" (IG19).*

Patients also noted that taking wound images was a good tool, because it helped the home care nurses be more observant and improved their wound care knowledge and skills. This notion is exemplified in the following quotation:

"*[*The fact*] that the home care nurses take images of the ulcer has made them very observant. They do what they should [*do*]" (IG5).*

The patients also observed that the act of taking and sending images of the ulcers to and having them assessed by the outpatient clinic also gave the home care nurses a sense of security. One 62-year-old man expressed this in the following way:

"It was reassuring for the home care nurses to communicate with the expert team at the outpatient clinic, because they received feedback on whether they were on the right path or not" (IG20).

The communication between the home care nurses and outpatient clinic also improved, because the assessed image and treatment procedure were sent directly to the home care nurses through the shared web-based ulcer record used both by experts in the outpatient clinic and home care nurses. That allowed direct communication between the two levels. In the control group, however, the treatment procedure was given to the patient.

The use of images in telemedicine also increased the sense of security of patients who received follow-up care from many nurses with varying expertise. One woman expressed this sense of enhanced security in the following way:

"*There were many nurses involved [*in my wound care*] who lacked wound skills compared to [*those at*] the outpatient clinics. It therefore was of great comfort for me that images [*of my ulcer*] were taken and sent to the outpatient clinic for assessment"* (IG 4).

These examples show that telemedicine can support a treatment intervention in a positive way. However, if telemedicine was not carried out as planned—for example, images were not taken or not sent, or outpatient clinic did not assess the images—telemedicine did not benefit the patients. Some of the telemedicine patients mentioned that some home care nurses did not take images of their ulcers due to lack of mobile skills, during sick leave and vacation. Others reported that the outpatient clinic did not respond to the home care nurses' request to assess the images. One man in his 50s observed the following:

"*The home care [*nurses*] did not take any images of the foot ulcer. They did not start [*taking*] images before the wound was healed (IG17).*

3.3. Easy access and close proximity to home care service

Easy access and proximity to the service appeared to be important for the patients. For some patients, this was an excellent care pathway; for others, easy access and proximity were less relevant. These perceptions were independent of whether the patients received telemedicine care or not. If home care service was available and of sufficient quality, patients preferred to receive ulcer treatment and follow-up from a home care nurse rather receive frequent control at the outpatient clinic. As two patients put it:

> *"If the home care nurses have the necessary expertise and communicate well with the outpatient clinic via the images, I see no reason to travel often to the outpatient clinic" (IG20).*

> *"There are two home care nurses who had the responsible for the ulcer treatment, one each time. I experienced them as being competent and professional. And it is sufficient to have two follow-up checks per month at the outpatient clinic"* (CG16).

Employed participants and sick patients emphasized that receiving treatment close to home afforded flexibility in choosing both the time and place of treatment, which reduced traveling time to and waiting time at the outpatient clinic. For employed patients, this allowed them to go to work during wound healing.

On the other hand, if the home care service lacked competence and continuity, the patients decided to decline the home care service and instead receive all treatment and follow-up at the outpatient clinic. Two patients commented:

> "*I would rather use the car and drive to the clinic instead of getting treatment from the home care nurses, because the follow-up by the home care nurse made me unsecure "* (IG 9).

> *"I have declined home care [*because*] many nurses lacked competence. I was followed up at the outpatient clinic, but I did the wound care myself between the consultations"* (CG15).

These patients stated that travel time to and waiting time at the outpatient clinic were less important. This may indicate that easy access and proximity were less significant factors than competence and continuity, because the latter contributed most to a feeling of security, a factor that was strongly emphasized by the patients. Some patients also requested more frequent checks at the outpatient clinic, but said that this option was not possible because of capacity problems at the outpatient clinics.

4. Discussion

The aim of this qualitative study was to explore the experiences of adults with diabetic foot ulcers receiving telemedicine compared to patients receiving traditional follow up in the context of a clustered RCT study. The discussion will be structured around the main themes identified.

4.1. Competence of the health care professionals

This study has shown very clearly that competence in wound management of health professional was of great importance for patients' experience of security during wound care. Nurses' competence at the outpatient clinic emerged as very essential to the patients, because expert knowledge and skills in wound care made the patients confident that if changes in the wound occurred this would be detected and necessary action taken. Patients also stated that effective teaching of patients about wound care occurred mainly at the outpatient clinic by specialist nurses and was less frequently done at home by home care nurses. This perception is in line with other studies that concluded that specialists in wound treatment have a key role in empowering patients in self-wound care [22].

The level of acquired wound-care knowledge and skills varied among the home care nurses, according to the patients. This perception corroborates findings from other studies [3–5]. Independent of group affiliation (both in intervention and control group), patients who were treated by home care nurses lacking competence felt insecure about their wound management. An important issue was that these patients wanted to receive all their treatment at the outpatient clinic, but this was not feasible due to capacity problems. Nevertheless, for these patients, the outpatient clinic turned out to be an important confidence factor for them, because they received confirmation of whether their wound management received through home care was adequate. Education of home care nurses to ensure appropriated treatment practice is of importance and one of the cornerstones in foot management [23]. The home care nurses interact with people at high risk of severe complications and lack of awareness with regard to treatment and follow-up care practice can lead to unnecessary poor outcomes and hospitalizations [24]. In our study, the patients reported that learning mainly occurred at the outpatient clinic. Thus, improved knowledge among the home care nurses can indirectly empower patients through teaching them about how to recognize foot problems, promote appropriate self-care, and thus contribute equivalent to the expert team in patient education. That can change the current perception among the patients and prevent foot ulcer in people with diabetes [24]. However, a cautious approach of telemedicine monitoring in patients with severe foot ulcer diseases should be considered [14], especially if lack of wound knowledge and training in telemedicine equipment are shortcomings among the staff involved.

When few nurses in home care service were responsible for the wound care, patients' sense of security and confidence increased, and this seemed to be an important issue in wound management for patients. Correctly implementing telemedicine seems to further contribute to this increase. Most patients receiving telemedicine felt that it was a useful adjunct to the other treatment they received. This apparently enhanced their feelings of security, resulting in assurance that the expert team at the outpatient clinics and home care nurses used mobile phone images appropriately. Patients reported that this enhanced wound-management competence among the home care nurses. Current evidence shows that using telemedicine in combination with communication with other healthcare professionals, enhanced competence in wound management among the home care nurses [4,5,25,26]. Using telemedicine, the home care nurses collaborated closely with the nurses at the outpatient clinics. The collaboration involved continual feedback on performed work via discussions and reports from nurses at the outpatient clinics that seem to strengthened patient confidence. This finding is in line with other studies [4,5,27]. Similar collaboration in traditional follow-up in which there is no formal cooperation among levels of care was not experienced in the same way by the patients.

We observed in our settings that use of telemedicine could be questionable in a number of circumstances. Some of the patients receiving telemedicine reported that the nurses failed to take any mobile phone images, and some nurses lacked the necessary mobile-device skills. Similar issues have been reported in other studies [26,28]. If telemedicine is to have any benefit for the patients and operate successfully, these barriers must be removed. Several studies have emphasized that innovative technologies need to be integrated in the stakeholders' routine practice. The technologies must be easy and as fast as possible to use, with necessary initial training and continuously support. If not, there is a major risk of failure [25,26,29].

4.2. Continuity of care

Our analyses also showed that continuity of care in wound management is another confidence-building factor that is essential to patients. Freeman and colleagues [30] described three dimensions of continuity of care: interpersonal continuity, informational continuity, and management continuity. The *interpersonal dimension* refers to the ongoing therapeutic relationship between providers and patients. The *information dimension* refers to the links of information between episodes of care and transitions, and communication between provider and patient. These two dimensions are identifiable in our data.

Patients in both groups reported that they preferred being followed up by a limited number of home care nurses. This is consistent with the findings of other studies [31–33]. Indeed, receiving care from just a few home care nurses increases patient well-being and security [31]. Constancy of a small number of home care nurses can increase their chances of detecting subtle changes in the ulcer-healing process, thereby avoiding severe complications such as osteomyelitis and amputation. This was a major concern for the patients in this study.

Although continuity of care in primary healthcare has a positive effect on outcomes [32], it can be difficult to implement due to variable shift schedules, and contextual and individual factors [31,33]. The patients of our study were familiar with those issues. Telemedicine can reduce the uncertainty or anxiety that these types of issues can create, because telemedicine can promote continuity of care via efficient information exchange, regardless of which home care nurse follows up the patient. So, any uncertainty a patient may experience can be remedied by the fact that home care nurses have quick access to wound care specialists, who analyze the ulcer images and prepare a written assessment of the ulcer. This enables the nurses to appropriately treat the ulcer in a timely fashion. Patients receiving traditional care did not report similar experiences. This is consistent with other studies that show that telemedicine can increase exchange of knowledge and information between healthcare professionals, between levels of care, and between patients and healthcare professionals [34].

However, continuity of care cannot be viewed as being independent of caregiver skill and knowledge of wound management. Woodward and colleagues [35] found that consistently applied knowledge and skills of several healthcare professionals and consistent care management were important for ensuring continuity of care in home care settings. This was the case in our study as well. Taken together, consistent service and care delivery by knowledgeable and skilled home care nurses were factors that fostered the patients' confidence that they were receiving quality care.

4.3. Easy access

Easy access was an important factor in wound treatment, but it depended on whether competence and continuity of care were established. This outcome was regardless of whether the patient received telemedicine or not. When both factors were presented, follow-up in the primary health care was an excellent care pathway. Thus, it is not necessary to charge the specialist health service with a service that can be done equally well in the primary health care. This is in line with the lowest effective service level (LEON) principle that the services should take place in close connection to the home environment [20]. Telemedicine seem to be an additional factor that may contribute to increase patient satisfaction at LEON level. This will reduce the number of consultations at the outpatient clinic. In this way, resources can be better channeled to patients who need more frequent follow-up by the expert team in specialist healthcare.

Follow-up by the home care nurses gave a flexibility in the wound care that did not happen to the same degree at the outpatient clinic. This flexibility was an important factor for patients who were employed, because they wanted to use the least amount of time on treatment and travel. Without this flexibility, patients reported that they would not be able to go to work. However, for patients who were uneasy with receiving home care follow-up, traveling to and waiting at the outpatient clinic were of little importance. These patients are concerned about feeling safe and secure and having confidence in their treatment. One solution could be to allow the patient to a greater extent be involved to determine ways to be treated. Being involved in their own care pathway and participate in decisions regarding their own health can provide better quality of wound care. This is emphasized in national guidelines [20].

The use of individual face-to-face interviews with the patients was effective in collecting relevant data. The possibility of using a focus group interview instead was a relevant alternative that was discussed, but was not selected because patients lived in different municipalities, often were older on average, had reduced mobility and health, and often depended on help from relatives or healthcare professionals to get from one place to another.

This study included a sample size of 24 patients purposely selected from an ongoing RCT. We believe that this sample size was large enough to sufficiently achieve the aim of the study.

The patients participating in the trial were also a selected group of patients based on inclusion criteria. Their experience might differ from more seriously ill patient populations, who were excluded from participation in the trial.

5. Conclusions and implications for practice

Our study shows that an effective wound care pathway for patients with diabetic foot ulcers depended on professionals' competence and professional skills in wound management and on continuity of care. The interaction between the two factors not only promotes more integrated care, but also bolsters patients' confidence in their ulcer care. Telemedicine can be an important supplement in that process, but its efficacy will depend on whether telemedicine is used as intended. Education and practical training in the use of telemedicine should be given to all health care professionals in the primary health care and not simply to a few [25]. Also clear guidelines for delegation of responsibility in case of sickness and vacation among key staff must be clarified. The quality of the service can thus be strengthened and lack of documentation be avoided.

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Competing interests

None.

Summary points

What was already known?

- In the current system, the care pathway for patients with diabetes foot ulcers is not optimal.
- Previous telemedicine research in wound care has primarily focused on technology development and feasibility.
- Few studies have explored patients with foot ulcers experiences with use of telemedicine.

What this study adds:

- The best wound care pathway for patients with diabetes foot ulcers is depended on a combination of competence and professional skills in wound management, and continuity of care.
- Professional competence and skills in would management is essential for a flexible health service enabling more patients to be treated in home based care.
- Telemedicine seem to be an important supplement to create a more integrated wound care pathway, but is depended whether telemedicine is implemented as intended.

Author contributions

H.S.S., M.M.I., M.K. designed the study. H.S-S. collected the data. H.S.S., M.M.I., M.G., S.S. and M.K. contributed to data analysis. H.S.S., M.M.I., M.G., S.S. and M.K. contributed to drafting the manuscript and read and approved the final manuscript.

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References

[1] L. Ribu, B.R. Hanestad, T. Moum, K. Birkeland, T. Rustoen, A comparison of the health-related quality of life in patients with diabetic foot ulcers, with a diabetes group and a nondiabetes group from the general population, Qual. Life Res. 16 (2) (2007) 179–189.
[2] P. van Battum, N. Schaper, L. Prompers, J. Apelqvist, E. Jude, A. Piaggesi, et al., Differences in minor amputation rate in diabetic foot disease throughout Europe are in part explained by differences in disease severity at presentation, Diabet. Med. 28 (2) (2011) 199–205.
[3] L. Ribu, A. Wahl, How patients with diabetes who have foot and leg ulcers perceive the nursing care they receive, J. Wound Care 13 (2) (2004) 65–68.
[4] J. Clemensen, S.B. Larsen, M. Kirkevold, N. Ejskjaer, Treatment of diabetic foot ulcers in the home: video consultations as an alternative to outpatient hospital care, Int. J. Telemed. Appl. 1 (2008).
[5] B. Nyheim, A.T. Lotherington, A. Steen, Nettbasert sårveiledning, Kunnskapsutvikling og bedre mestring av leggsårbehandling i hjemmetjenesten (web-based wound counseling. Developing new knowledge and improved management of leg ulcers in primary health care), Nordisk tidsskrift for helseforskning, (2010) 6 1 40–55.
[6] Ministry of Health and Care Services, The Coordination Reform—Proper treatment—at the right place and right time, In: Ministry of Health and Care Services, Editor. Report No 47 to the Storting (2008–2009), Oslo: Ministry, 2009.
[7] M. Iversen, M. Hausken, K. Vetlesen, Forsprosjekt. Diabetes fotsår. Utvikling av nye telemedisinske systemer/produkter. (Project. Diabetic foot ulcer. Development of new telemedical system/products), Stavanger: Stavanger universitetssjukehus, (2012) 1–20.
[8] M. Graue, T. Dunning, M.F. Hausken, B. Rokne, Challenges in managing elderly people with diabetes in primary care settings in Norway, Scand. J. Prim. Health Care 31 (4) (2013) 241–247.
[9] P.A. Lazzarini, D. Clark, R.D. Mann, V.L. Perry, C.J. Thomas, S.S. Kuys, Does the use of store-and-forward telehealth systems improve outcomes for clinicians managing diabetic foot ulcers? A pilot study, J. Aust. Wound Manage. Assoc. 18 (4) (2010).
[10] National Board of Health, Diabetic foot ulcers-a health technology assessement summary, In: Health NBo, Editor: Health technology assessemen, (2011) 3–16.
[11] R. Currell, C. Urquhart, P. Wainwright, R. Lewis, Telemedicine versus face to face patient care: effects on professional practice and health care outcomes, Cochrane Database Syst. Rev. 2 (2) (2000) CD002098.
[12] C. Chanussot-Deprez, J. Contreras-Ruiz, Telemedicine in wound care: a review, Adv. Skin Wound Care 26 (2) (2013) 78–82.
[13] L.V. Nordheim, M.T. Haavind, M.M. Iversen, Effect of telemedicine follow-up care of leg and foot ulcers: a systematic review, BMC Health Serv. Res. 14 (1) (2014) 565.
[14] B.S. Rasmussen, J. Froekjaer, M.R. Bjerregaard, J. Lauritsen, J. Hangaard, C.W. Henriksen, et al., A randomized controlled trial comparing telemedical and standard outpatient monitoring of diabetic foot ulcers, Diabetes Care 38 (9) (2015) 1723–1729.
[15] A. Steventon, M. Bardsley, J. Billings, J. Dixon, H. Doll, S. Hirani, et al., Effect of telehealth on use of secondary care and mortality: findings from the Whole System Demonstrator cluster randomised trial, BMJ 344 (2012) e3874.
[16] M.V. Trondsen, Managing Everyday Life: A Qualitative Study of Patients' Experiences of a Web-Based Ulcer Record for Home-Based Treatment Healthcare, Multidisciplinary Digital Publishing Institute, 2014.
[17] F. Mair, P. Whitten, Systematic review of studies of patient satisfaction with telemedicine, BMJ 320 (7248) (2000) 1517–1520.
[18] K. Kidholm, J. Oates, Regions of Europe WorkIng together for HEALTH, 2010.
[19] D.R.E. Scott, D.F. McCarthy, D.P. Jennett, T. Perverseff, D. Lorenzetti, B. Rush, et al., Telehealth outcomes: a synthesis of the literature and recommendations for outcome indicator, J. Telemed. Telecare 13 (2007) 1–38.
[20] Ministry of Health and Care Services, The primary health and care services of tomorrow –localised and integrated. In: Services MoHaC, Editor: Oslo, Ministry of Health and Care Services, 2015.
[21] S.E. Thorne, Interpretive Description, Left Coast Press, Walnut Creek, 2008.
[22] F.A. Sloan, M.N. Feinglos, D.S. Grossman, Receipt of care and reduction of lower extremity amputations in a nationally representative sample of US elderly, Health Serv. Res. 45 (6p1) (2010) 1740–1762.
[23] K. Bakker, J. Apelqvist, N. Schaper, Practical guidelines on the management and prevention of the diabetic foot 2011, Diabetes Metab. Res. Rev. 28 (S1) (2012) 225–231.
[24] J. Dorresteijn, D. Kriegsman, W. Assendelft, G.D. Valk, Patient education for preventing diabetic foot ulceration, Cochrane Database Syst. Rev. 12 (2014).
[25] B.-C.H. Kolltveit, E. Gjengedal, M. Graue, M.M. Iversen, S. Thorne, M. Kirkevold, Telemedicine in diabetes foot care delivery: health care professionals' experience, BMC Health Serv. Res. 16 (1) (2016) 1.
[26] B. Rasmussen, L. Jensen, J. Froekjaer, K. Kidholm, F. Kensing, K. Yderstraede, A qualitative study of the key factors in implementing telemedical monitoring of diabetic foot ulcer patients, Int. J. Med. Inf. 84 (10) (2015) 799–807.
[27] F. Verhoeven, K. Tanja-Dijkstra, N. Nijland, G. Eysenbach, L. van Gemert-Pijnen, Asynchronous and synchronous teleconsultation for diabetes care: a systematic literature review, J. Diabetes Sci. Technol. 4 (3) (2010) 666.
[28] T. Finch, F. Mair, C. May, Teledermatology in the UK: lessons in service innovation, Br. J. Dermatol. 156 (3) (2007) 521–527.
[29] M. Muller, S. David-Tchouda, J. Margier, M. Oreglia, P.Y. Benhamou, Comment on Rasmussen et al., A Randomized Controlled Trial Comparing Telemedical and Standard Outpatient Monitoring of Diabetic Foot Ulcers, Diabetes Care, (2015) 38 1723–1729, Diabetes Care, (2016) 39 1 e9–e10.
[30] G.K. Freeman, M. Woloshynowych, R. Baker, M. Boulton, B. Guthrie, J. Car, et al., Continuity of Care 2006: What Have We Learned Since 2000 and What are Policy Imperatives Now, National Co-ordinating Centre for NHS Service Delivery and Organisation R & D (NCCSDO), London, 2007.
[31] E.R. Gjevjon, T.I. Romøren, B.Ø. Kjøs, R. Hellesø, Continuity of care in home health-care practice: two management paradoxes, J. Nurs. Manag. 21 (1) (2013) 182–190.
[32] D. Russell, R.J. Rosati, P. Rosenfeld, J.M. Marren, Continuity in home health care: is consistency in nursing personnel associated with better patient outcomes? J. Healthc. Qual. 33 (6) (2011) 33–39.
[33] S. Waibel, D. Henao, M.-B. Aller, I. Vargas, M.-L. Vázquez, What do we know about patients' perceptions of continuity of care? a meta-synthesis of qualitative studies, Int. J. Qual. Health Care (2011), mzr068.
[34] F. Verhoeven, L. van Gemert-Pijnen, K. Dijkstra, N. Nijland, E. Seydel, M. Steehouder, The contribution of teleconsultation and videoconferencing to diabetes care: a systematic literature review, J. Med. Internet Res. 9 (5) (2007) e37.
[35] C.A. Woodward, J. Abelson, S. Tedford, B. Hutchison, What is important to continuity in home care? Perspectives of key stakeholders, Social Sci. Med. 58 (1) (2004) 177–192.

Appendix I-II

Referanse nr.				

DEL I
GENERELLE OPPLYSNINGER

1.	Har pasienten blitt behandlet for fotsår før 01.01.2009?
	Ja ☐ Dato Nei ☐
	Hvis ja, antall ganger:

2.	Har pasienten blitt behandlet for nye fotsår i perioden 01.01.2009 -31.12.2011?
	Ja ☐ Nei ☐
	Hvis ja, hvor mange: Type sår:

3.	Dato for første konsultasjon ifm fotsåret i perioden 01.01.2009 -31.12.2011?
	Dato:

4.	Dato for siste konsultasjon ifm det første fotsåret i perioden 01.01.2009 -31.12.2011?
	Dato:

5.	Alder ved første konsultasjon:

6.	Antall uker fra henvising til mottatt time i spesialisthelsetjenesten?
	Uker:

7.	Dato pasienten rapporterte å ha fått fotsåret? før første konsultasjon
	Dato/år: eller måned/år:

8.	Dersom hjemmesykepleie - hvor lenge har pasienten vært behandlet i hjemmesykepleien før pasienten fikk time i spesialisthelsetjenesten for fotsåret sitt?
	Uker: eller måneder:

9.	Dersom fastlegen behandler fotsåret - hvor lenge har pasienten vært behandlet av fastlegen før pasienten fikk time i spesialisthelsetjenesten for fotsåret sitt?
	Uker: eller måneder:

10.	Hvem henviste pasienten?	
	Fastlegen	☐
	Spesialist	☐
	Andre	☐ spesifiser:

11.	Antall innleggelser på sykehus relatert til første fotsår i perioden 01.01.09-31.12.11:	
	Dato:	Årsak:
	Dato:	Årsak:
	Dato:	Årsak:

12.	Totalt antall konsultasjoner på poliklinikken i forbindelse med første fotsår:	
	2009	Antall konsultasjoner:
	2010	Antall konsultasjoner:
	2011	Antall konsultasjoner:

13.	Geografisk avstand mellom bopel og poliklinikk		
	Fra:	Til:	Antall km:

DEL II
DEMOGRAFISKE DATA

14.	Kjønn:	Mann ☐
		Kvinne ☐

15.	Fødselsår:

16.	Arbeidstilknytning:	
	Jobber fulltid/deltid	☐
	Ufør/under attføring	☐
	Pensjonist	☐
	Hjemmeværende (uten lønn)	☐
	Ukjent	☐

17.	Sivil status:	
	Gift/samboer	☐
	Ugift	☐
	Enke/enkemann	☐
	Ukjent	☐

18.	Røyking:	
	Røyker	☐
	Tidligere røyker	☐
	Aldri røykt	☐
	Ukjent	☐

19.	Etnisitet:	
	Etnisk norsk	☐
	Ikke etniske norsk	☐ spesifiser etnisitet:

DEL III
DIABETES-RELATERTE KJENNETEGN

20.	Type diabetes:	
	Diabetes I	☐
	Diabetes II	☐

21.	Debut år diabetes:

22.	Diabetesbehandling:	
	Insulin	☐
	Antidiabetikum.	☐
	Kostregulert	☐

23.	Nærmeste HbA1c i forhold til første konsultasjon perioden 01.01.09-31.12.11:
	Hba1c. data/år:

24.	Makrovaskulær komplikasjon:	
	• Cardiovaskulære sykdommer: ex hypertensjon, tidligere hjerteinfarkt, angina pectoris, hjertesvikt, TIA, slag, opr. for trange kar, claudicatio	☐ spesifiser

25.	Mikrovaskulær komplikasjon:	
	• retinopati, nefropati og neuropati	☐ spesifiser

26.	Charcot foot: Ja ☐ Nei ☐

DEL IV
FOTSÅR - RELATERTE KARAKTERISTIKA - Kliniske

Klassifisering av fotsåret ved første konsultasjon i perioden 01.01.2009 – 31.12.2011

27.	Klassifisering ved innkomst:	
	Ischemisk	☐
	Neuropatisk	☐
	Ischemisk/neuropatisk sår	☐

28.	Sirkulasjonsutredning ved innkomst:		
	Ankel-arm index	Ja ☐ Nei ☐	Resultat:
	Tå trykk måling	Ja ☐ Nei ☐	Resultat:
	Angiografi	Ja ☐ Nei ☐	Resultat:
	Puls a. dorsalis pedis	Ja ☐ Nei ☐	Merknad:
	Puls a. tibialis anterior	Ja ☐ Nei ☐	Merknad:

29.	Nevrologisk undersøkelse ved innkomst:		
	10-g monofilament	Ja ☐ Nei ☐	Resultat

30.	Infeksjon/osteomyelitt:	
	Infeksjon ved diagnose:	Ja ☐ Nei ☐
	Infeksjon underveis i behandlingen:	Ja ☐ Nei☐
	Bakteriologisk u.s. tatt ved infeksjon:	Ja ☐ Nei☐
	Administrering av antibiotika ved infeksjon? • Intravenøst • Per os	Ja ☐ Nei ☐ Ja ☐ Nei☐ antall dager: Ja ☐ Nei☐ antall dager:
	Osteomyelitt ved diagnose:	Ja ☐ Nei ☐
	Osteomyelitt underveis i behandlingen:	Ja ☐ Nei☐
	Administrering av antibiotika for osteomyelitt? • Intravenøst • Per os	Ja ☐ Nei☐ Ja ☐ Nei☐ antall dager: Ja ☐ Nei☐ antall dager:

31.	Karkirurgi ved diagnose:	Ja ☐ Nei ☐ spesifiser type:
	Karkirurgi underveis i behandlingen:	Ja ☐ Nei ☐ spesifiser type:

32.	Antall sår ved innkomst:

33.	Sårlokalisasjon ved diagnose:	
	Tå regionen	☐ spesifiser:
	Metatarsal område	☐ spesifiser:
	Midt fot/hindfot område	☐ spesifiser:
	Multiple områder	☐ spesifiser:
	Plantar	☐ spesifiser:
	Plantar metatarsal	☐ spesifiser:
	Hæl	☐ spesifiser:

34.	Sårets størrelse ved diagnose:
	Lende: mm
	Bredde: mm
	Dybde: mm

35.	Sårets utseende ved diagnose:	
	Nekrose	☐
	Infeksjon	☐
	Væskende	☐
	Ødem/hoven	☐
	Puss	☐
	Granulasjon	☐
	Rent	☐

36.	Rapporter pasienten smerter? Ja ☐ Nei☐	
	Administrert smertestillende?	Ja ☐ Nei ☐ Hvis ja, medikament: styrke/dose:

37.	**UT classification ved diagnose**	**Grade 0:** Pre – eller post såområde som er tilhelet	**Grad 1:** Overfladisk sår som ikke involverer sene, capsula (nerve) eller bein	**Grad 2:** Såret penetrerer sene eller capsula	**Grad 3:** Såret penetrerer bein eller ledd
	Stage A: Rent sår				
	Stage B: PAD - infeksjon +				
	Stage C: PAD + infeksjon -				
	Stage D: PAD + Infeksjon +				

DEL V
SÅRBEHANDLING OG VIDERE OPPFØLGING I PERIODEN 01.01.2009 – 31.12.2011

38.		
	Behandling Type bandasje Debridering Callus fjerning	Spesifiser:
	Karkirurgi ved diagnose Ja ☐ Nei ☐	Hvis ja, spesifiser:
	Karkirurgi underveis Ja ☐ Nei ☐	Hvis ja, spesifiser:
	Offloading Ja ☐ Nei ☐	Hvis ja, spesifiser:
	Infeksjonskontroll Ja ☐ Nei ☐	
	Blodprøver Ja ☐ Nei ☐ HbA1c, CRP, Lpk, albumin, kreatinin, ratio, HDL, GFR	Hvis ja, spesifiser hvilke blodprøver og verdi:

39.	Hvilke profesjoner har vært involverte i behandling og oppfølging av pasienten?	
	Diabetes sykepleier	☐
	Sykepleier	☐
	Endokrinolog	☐
	Karkirurg	☐
	Ortopedisk kirurg	☐
	Ortoped ingeniør	☐
	Fotterapeut	☐
	Psykolog	☐

DEL VI
HELINGSTID

40.	Såret grodd?	Ja ☐ Nei ☐	Dato/år:

41.	Amputasjon	Ja ☐ Nei ☐	Dato/år:

42.	Pasienten døde før behandlingen var avsluttet?	Ja ☐ Nei ☐	Dato/år:

43.	Har pasienten blitt fulgt opp av hjemmesykepleien i behandlingsperioden?	Ja ☐ Nei ☐	Antall uker:

44.	Er pasienten død etter tilheling?	Ja ☐ Nei ☐	Dato/år:

DEL VII

NYTT FOTSÅR

Dersom pasienten har fått et nytt fotsår i perioden 01.01.09 – 31.12.11

45.	Nytt fotsår: Ja ☐ Nei ☐

Main topics in the interview guide

Intervention group

1. The patient's experiences with the foot ulcer and what he did when he discovered the ulcer
2. The patient's experiences with receiving telemedicine treatment and follow-up from the home care nurse
3. The patient's experiences with being followed up in specialist healthcare
4. The patient's' experiences of being involved in wound management and decisions that concerned his treatment
5. The patient's experiences with healthcare professionals' use of the telemedicine equipment and healthcare professionals' own views on using images in wound care
6. Whether the patient observed telemedicine collaboration between the home care nurse and specialist healthcare service during follow-up
7. The patient's perception of whether he takes more responsibility for his own health
8. The patient's perception of what is the most important task home care nurses and experts at the outpatient clinic have in treatment and care of patients with diabetic foot ulcers

Control group

1. The patient's experiences with the foot ulcer and what he did when he discovered the ulcer
2. The patient's experiences with receiving traditional treatment and follow-up from the home care nurse
3. The patient's experiences with being followed up in specialist healthcare
4. The patient's experiences of being involved in wound management and decisions that concerned his treatment
5. Whether the patient observed any collaboration between the home care nurse or GP and specialist healthcare services during follow-up
6. The patient's perception of whether he takes more responsibility for his own health
7. The patient's perception of what is the most important task home care nurses and experts at the outpatient clinic have in treatment and care of patients with diabetic foot ulcers