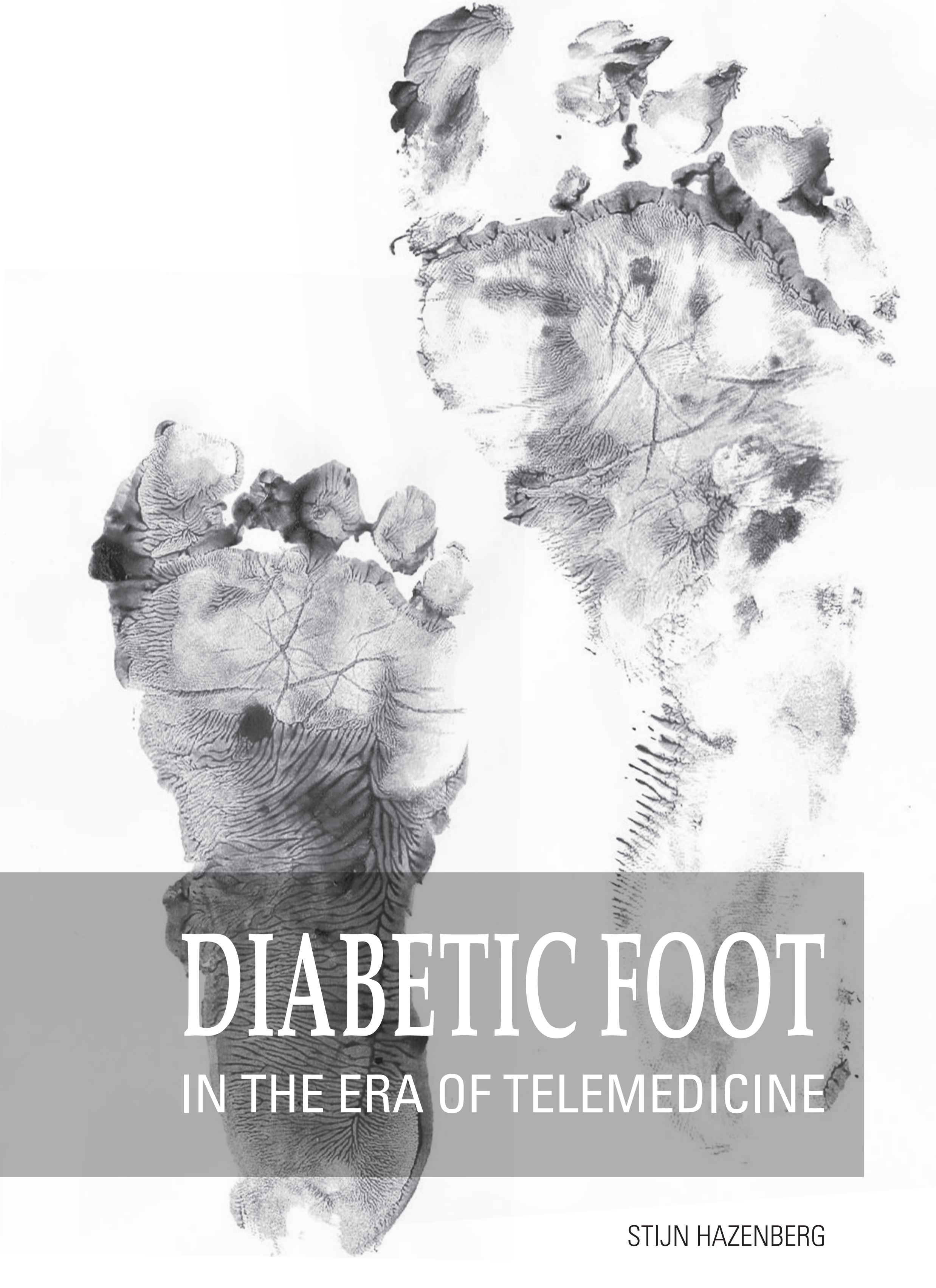

DIABETIC FOOT

IN THE ERA OF TELEMEDICINE

STIJN HAZENBERG

Diabetic foot in the era of Telemedicine

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DIABETIC FOOT
IN THE ERA OF TELEMEDICINE

DE DIABETISCHE VOET IN HET TELEMEDICINE TIJDPERK
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 13 november 2013 des middags te 2.30 uur

door

Constantijn Eymbert Vincentius Boudewijn Hazenberg

geboren op 25 februari 1977 te Oss

Promotor: Prof.dr. F.L. Moll

Co-promotoren: Dr. J.G. van Baal
Dr. S.A. Bus

CONTENTS

Chapter 1

General Introduction

Background

Worldwide, more than 366 million people have diabetes and the prevalence will increase rapidly in the following decades. More than 550 million people (one adult in 10) are expected to have diabetes in 2030, mainly living in urban areas and low- and middle-income countries.[1] In the Netherlands there will be approximately 1.2 million people with diabetes (www.diabetesatlas.org/map). More than 471 billion USD were spent on global healthcare expenditures to treat diabetes and prevent complications. This will probably exceed USD 595 billion in 2030 (www.idf.org). Foot ulceration continues to be a significant complication in patients with diabetes. The lifetime incidence rate of developing a foot ulcer may be as high as 25%.[2] Foot ulcers can lead to infection and, eventually, amputation with 85% of all non-traumatic lower limb amputations being preceded by a foot ulcer.[3] Globally, every 30 seconds a lower limb is lost because of diabetes.[4] These devastating complications have a significant negative impact on health related quality of life[5-7], and impose a heavy economic burden (expenditure on foot care adding up to 33% of total costs for diabetes care).[8-11] Risk identification, education, proper foot care, a multidisciplinary treatment of foot ulcers, provision of appropriate footwear, and close monitoring are fundamental for effective preventive management of the diabetic foot[9,12] and can reduce amputation rates by 49-85%[13].

International guidelines recommend to screen diabetic patients with a high risk for developing a foot ulcer every 1-6 months.[13] High risk patients are those with a history of ulceration or amputation, presence of peripheral neuropathy, peripheral arterial disease and foot deformity.[14,15] However, we believe that in many regions and centres these follow-ups occur less frequently. Furthermore, in a high-risk category of patients, problems most often arise in between visits to the foot clinic or local health care professional. Therefore, self-assessment of patients in their own home environment is important and can also play a role in the prevention of foot disease. Self-monitoring is, however, not easy and may be hampered by the consequences of diabetes. First, most high-risk patients have peripheral neuropathy, which causes a lack of (protective) sensation and the inability to notice any trauma to the foot. Furthermore, many patients live alone, have visual impairment (e.g. retinopathy), physical impairments (e.g. limited joint mobility) or cognitive impairments, or lack knowledge about the disease.[15-17] These patients should have frequent proper inspection of their feet and may benefit from screening on a weekly or even daily basis in order to diagnose ulceration or pre-signs of ulceration at an early stage.

The role of telemedicine and rationale of this thesis

Telemedical systems have been developed for diagnostic, therapeutic, and educational purposes in many different medical specialities, such as dermatology, radiology, cardiology, orthopaedics, pathology, rehabilitation, and surgery. Several applications have been developed for the diabetic foot. This includes the use of mobile phone and video interaction to support foot care[18-20] and the home-monitoring of foot temperatures using infrared thermometry, which has been shown to contribute to the prevention of foot ulcers.[21-23]

Diagnostic support using digital photography in the home environment is another telemedical tool that may fulfil the need for frequent foot assessment and may be a missing aspect in the screening of patients who are at high risk for developing foot complications. For this purpose, a conventional digital camera may be used. However, this poses several disadvantages. It generally requires another person to take photographs of the feet, which is a problem for the prevalent group of diabetic patients that live alone. Furthermore, feet cannot be positioned in a standardized way, the orientation of the camera with respect to the foot varies, and ambient lighting conditions are not controllable, all factors that can negatively affect image quality. To overcome these drawbacks, we have developed, in collaboration with several industrial partners, a photographic foot imaging device. The device is a noninteractive diagnostic tool for at-home usage that provides high-quality digital photographs of the plantar surfaces of both feet. These photographs are sent automatically over the internet to a central database server, from where a foot specialist can download them for remote assessment. The patient can operate the device and it takes photographs under standardized conditions with respect to foot positioning, camera orientation, and lighting.

The intended purpose of the photographic foot imaging device is early recognition of (pre-) sings of foot disease, so that patients can be directly referred for treatment. If proven successful in early recognition and subsequent referral of patients, foot ulcers and further devastating complications such as infection and amputation may be prevented. The technique would probably target best the highest risk category of patients, those with history of ulceration and living alone or being impaired in self-assessment of their own feet. A successful approach will probably improve patient mobility and health-related quality of life, and improve autonomy, especially in patients living in remote areas where distances to health-care centres are long and where reducing the frequency of visits to the foot clinic may be a great benefit.

The technique of photographic imaging of the foot in the home environment may be complementary to existing home-monitoring approaches such as infrared thermography. This technique has been shown to be effective in diagnosing, through increased foot temperatures, signs of inflammation and was shown effective in significantly reducing the risk of ulceration in diabetic patients.[21-23] However, the technique has the limitation that it measures only one component of the spectrum of signs of infection, while other conditions related to diabetes such as autonomic neuropathy or vascular disease can also affect foot temperature. Furthermore, infrared thermography may be limited in predicting severity of infection or the outcome of treatment.[24]

Purpose and outline of this thesis

The general aim of this thesis is to expand the knowledge base on the use of telemedical tools in the management of foot disease in patients with diabetes mellitus. A more specific aim of the studies described in this thesis was to evaluate the value of photographic foot imaging for the assessment and early diagnosis of foot ulcers and pre-signs of ulceration, and, in combination with dermal thermography, the diagnosis of foot infection in diabetic patients. Supportive aims were to develop and improve the telemedical system for optimal foot imaging and data transfer, to evaluate validity and reliability of assessing signs of foot disease from photographs, to evaluate the feasibility of the system in the home environment, and to explore and review the currently existing telemedical approaches for the management of diabetic foot disease.

In **Chapter 2** we describe the technical development of the photographic foot imaging device along the objective of providing high-quality photographs for assessing signs of diabetic foot disease. The results of this study guided us in further improvement of the system to a final version that is used for the subsequent studies.
The results of our study on the validity and reliability of assessing the presence of foot ulcers and pre-signs of ulceration in diabetes patients from photographs produced with the device are described in **Chapter 3**.
The aim of the 4-month follow-up study described in **Chapter 4** was to demonstrate the feasibility of using the photographic foot imaging device for the diagnosis of foot disease in the home environment of high-risk patients with diabetes.
In the literature, different telemedical approaches have been described to support the remote monitoring and treatment of the diabetic foot. To study the refereed literature and determine the value of these applications for the telemedical management of the diabetic foot, a systematic review was conducted and presented in **Chapter 5**.
In **Chapter 6**, we describe the findings of a study on the validity and reliability of diagnosing signs of diabetic foot infection from photographic assessments, from infrared thermography, and the combination of these two.
Finally, in **Chapter 7** the main findings of this thesis are presented and some methodological considerations are discussed. Additionally, the clinical implications of these studies and future perspectives are described.

Parts of this introduction are based on a paper in the Netherlands Medical Journal, Nederlands Tijdschrift voor Geneeskunde 2010.[25]

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Chapter 2

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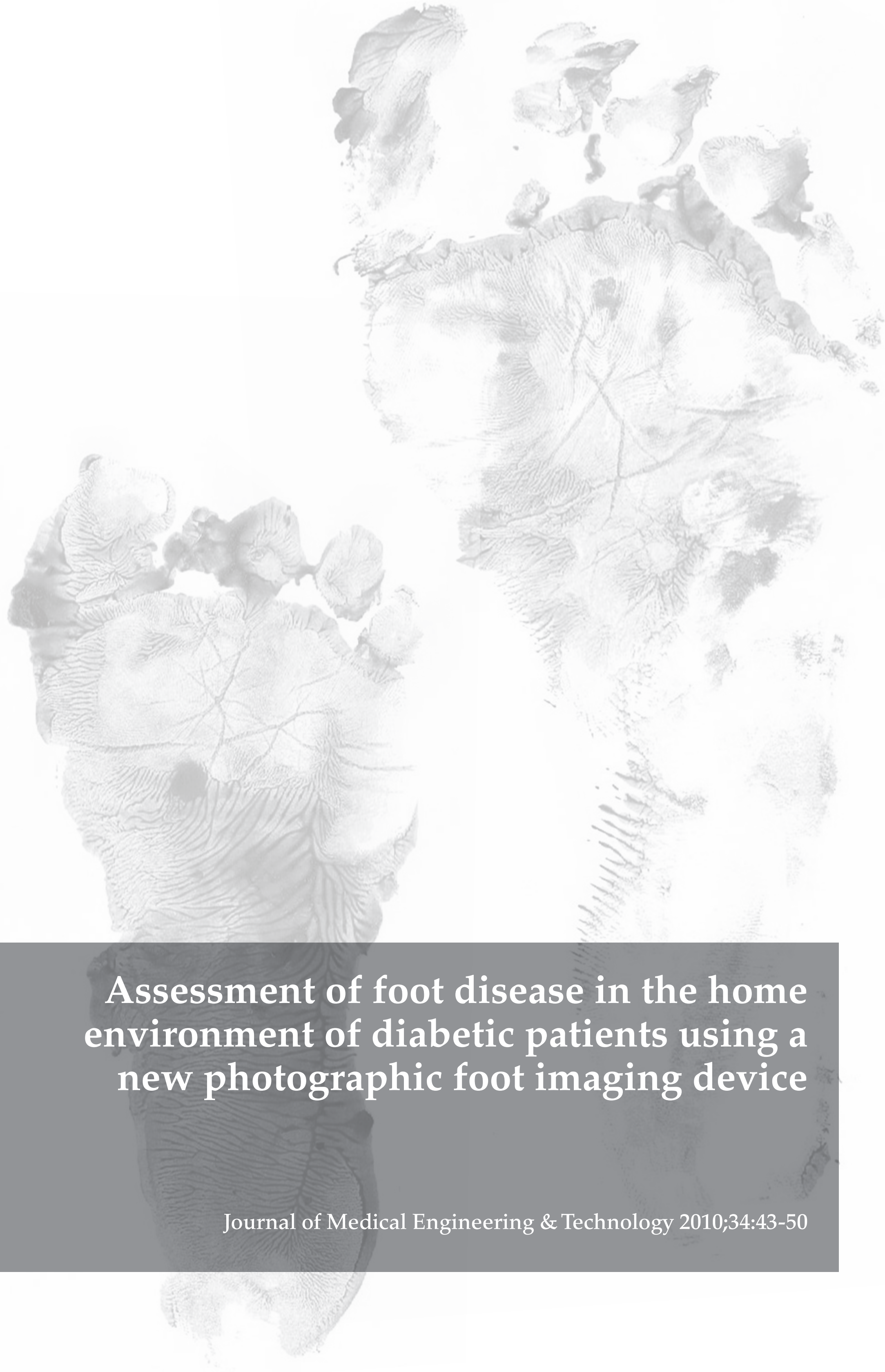


Assessment of foot disease in the home environment of diabetic patients using a new photographic foot imaging device

Journal of Medical Engineering & Technology 2010;34:43-50

ABSTRACT

The objective of this study was to compare live and photographic assessments of clinical signs of diabetic foot disease using a new photographic foot imaging device. High quality colour photographs of the plantar foot surface were collected in 20 diabetic feet using a prototype device and in 19 diabetic feet using a definitive version of the device with optimized illumination settings. All photographs were assessed independently by four observers for presence of ulceration, abundant callus, or absence of signs and compared with live and repeated photographic assessments of the feet by the same observers. Agreement between assessments was moderate to good for all outcomes using the prototype device (56-92%) and improved using the definitive version of the device (74-100%). The data seem to suggest that important signs of diabetic foot disease can be diagnosed from high quality photographs using the photographic foot imaging device. Intended for use as telemedical monitoring device in the patients' home, frequent remote assessments may potentially contribute to the early recognition and treatment of foot disease, which may prevent further complications.

Introduction

The World Health Organisation estimates that more than 180 million people worldwide have diabetes mellitus and this number will more than double by 2030. Chronic non-healing ulcers of the lower extremity as complication of the disease continue to be a significant problem in patients with diabetes. Causal pathways to diabetic foot ulceration usually involve the presence of peripheral neuropathy, increased biomechanical stress on the foot, external trauma, and peripheral arterial disease. The yearly incidence rate of ulceration is 2.2% in the overall diabetic population and 5.0% to 7.5% in diabetic patients with peripheral neuropathy.[1] Foot ulcers may lead to infection and, eventually, amputation with 85% of all non-traumatic lower limb amputations being preceded by a foot ulcer.[2] Diabetic foot ulcers have a significant negative impact on health related quality of life[3,4], especially if amputation follows an episode of ulceration[5]. Furthermore, the economic burden associated with the treatment of diabetic foot ulceration is enormous.[6,7] For this reason, any initiative that may contribute to the prevention of diabetic foot ulceration and thus to the decrease of the incidence of lower-limb amputation, should be supported and implemented in diabetic foot care.

Risk identification, education, proper foot care, a multidisciplinary approach, and the provision of appropriate footwear are fundamental for effective preventive management of the diabetic foot.[6,8] Professional foot care in patients at high risk for ulceration is recommended once every three months.[9] However, we believe that in many regions and centres these follow-ups occur less frequently. Furthermore, in a high risk category of patients such as those with a previous foot ulcer, problems most often arise in between visits to the foot clinic or local health care professional. Other conditions impair the patients' own ability to assess the condition of the foot which increases the risk of developing an ulcer.[10] These conditions include visual impairment, living alone, cognitive problems, or lack of knowledge about the disease. Therefore, these patients should have frequent proper inspection of their feet and may benefit from screening on a weekly or even daily basis in order to identify ulceration or pre-signs of ulceration at an early stage. Early recognition of these signs may, if referred and treated adequately, prevent or delay the onset of adverse outcomes.

Early or even immediate recognition of a foot ulcer or pre-signs of ulceration such as abundant callus or blisters, most appropriately takes place in the home environment, preferably using a telemedicine approach. Since the rapid evolution of internet and wireless communication, telemedicine is growing in popularity as a tool to diagnose and treat clinical conditions. Telemedical approaches have been implemented in many different specialties such as internal medicine, radiology, cardiology, dermatology and home health care. Previous studies have documented that the treatment of diabetic foot ulcers can be effectively supported by means of telemedical communication including mobile phone and video consultation in the home-environment[11-14], or remote assessment based on digital images[15,16]. Also for assessment and treatment of non-diabetic (chronic) wounds, interactive and non-interactive telecommunication systems have been shown to be useful.[17-20] Within the context of prevention, self-monitoring of temperature differences between the feet in the home environment has been shown to be efficacious in preventing foot ulceration in diabetic patients.[21,22] To the best knowledge of the authors, the use of digital photography as telemedical monitoring approach to assess the high risk diabetic foot in the home environment for prevention purposes has not been reported before.

For this purpose, conventional digital photo cameras may be used. However, this poses several disadvantages. It generally requires another person to take photographs of the feet, which is a problem for the significant group of diabetic patients at risk for ulceration that live alone. Furthermore, feet cannot be positioned in a standardized way, the orientation of the camera with respect to the foot varies, and ambient lighting conditions are not controllable, all factors that can negatively affect image quality. Finally, for remote assessment, photographs need to be manually uploaded and transferred using an email service provider. Therefore, we have developed a photographic foot imaging device which provides high-quality digital photographs of the plantar surfaces of the feet under standardized conditions with respect to foot positioning, camera orientation, and lighting conditions. This device is fully self-operational and the photographs it produces are sent automatically through the Internet to a central database server from where they can be downloaded and assessed by trained healthcare professionals.

For such a device to become implemented in routine diabetic foot care, it will have to contribute to accurate and reliable assessments of diabetic foot disease, be user-friendly and accepted by patients in the home environment, and its use must be clinically efficacious and cost-effective compared with normal treatment protocols.

In this paper, we describe the technical development of the photographic foot imaging device along the objective to provide indications for the usefulness of the device for assessing signs of diabetic foot disease during two different stages of system development. For this objective, photographic assessments of the feet of 20 diabetic patients by four observers were compared with live assessments and repeated photographic assessments of these feet by the same observers through calculation of agreement scores between assessments.

Methods

Study design

After a prototype of the photographic foot imager was built, several tests were run on a group of diabetic patients with plantar foot ulcers for the purpose of assessing the quality of the photographs. This assessment was done by our clinical research team involving a surgeon, two wound care specialists, and a human movement scientist in collaboration with a group of engineers from the company Demcon (Enschede, The Netherlands), the manufacturer of the device. In this phase of development, specific attention was given to the in-depth focus of the images taking into account the large variability in foot anatomy in these diabetic patients. After several adjustments to the system were made, a prototype version of the device was used for the first phase of the study. In this first phase, the feet of 10 diabetic patients (20 feet in total) with a variety of plantar foot problems were photographed at our outpatient clinic and were assessed both live and from photographs. Based on the agreement found between assessments and comments made by the observers, further adjustments were made to the device and a definitive version of the device was manufactured. This definitive version was used for the second phase of the study in which the feet of 10 new patients (19 feet in total) with a variety of foot problems were photographed and were assessed both live and from photographs. The results on agreement from this second phase and the comparison with the results from the first phase were used to provide indications for the usefulness of the photographic foot images for diagnosing important clinical signs of diabetic foot disease.

Subjects

A total of 20 diabetic patients were included in this study, 10 for the first study phase and 10 for the second study phase. All patients were diagnosed with diabetes mellitus type 1 or 2. Most patients regularly visited the outpatient diabetic foot clinic for foot care, and some patients were hospitalized. The plantar foot condition of the patients varied from the presence of ulceration, the presence of pre-signs of ulceration such as callus, fissures, blisters, redness, or a combination of these signs, to the absence of any clinical signs. All patients gave written informed consent to participate in this study which was approved by the ethics committees of our hospital and the University Medical Centre in Groningen (The Netherlands).

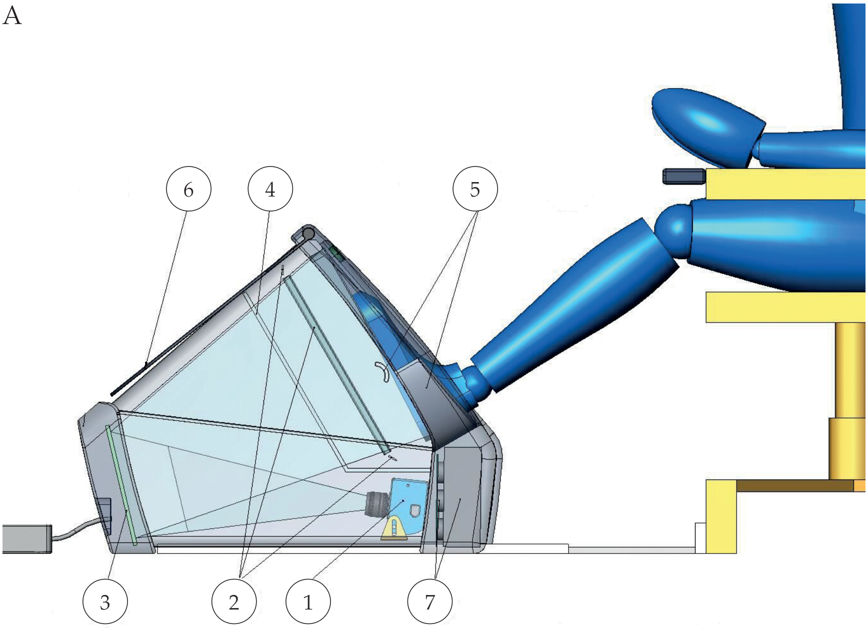
Photographic foot imaging device

The photographic foot imaging device provides high quality digital colour photographs of the plantar surface of the foot and is shown in Figure 1. The device comprises a camera module, light sources, mirror, glass plate, foot supports, a lid, a computer and plastic housing. The camera module consists of an industrial camera featuring a charge-coupled device (CCD) image sensor. The foot soles are imaged from an optical distance of about 1m in order to minimize geometric image distortions caused by the three-dimensional foot shapes and the variability in their lateral and axial (re-) positioning. In order to reduce the physical size of the device while maintaining the 1m optical distance between camera and feet, a high-quality mirror was employed to "fold" the imaging light path. The setting of lens diaphragm was chosen to provide sharp images of all parts of the plantar foot surface taking into account the aforementioned variability in foot geometry and positioning. Image resolution was four pixels per millimetre (1.25 megapixels in entire field of view), which was considered sufficient based on pilot testing using several images of diabetic feet.

The foot plantar surfaces are illuminated by a number of high-power white light emitting diodes (LEDs) which are arranged around each foot surface and can be switched to flash in groups. The device produces three colour images from each pair of feet. For the first image, all LEDs are switched to flash so that the foot surfaces are illuminated with diffuse light. This diffuse illumination suppresses the brightness modulations that would be caused by the shadow effect of the foot contours as seen in directed light, and it therefore results in an optimal rendering of the skin colour with even brightness (Figure 2). The second and third image are taken with only those LED groups switched on that are positioned close to the inner and the outer side of the foot, respectively. This directed light results in small-scale shadowing which enhances the perception of the three-dimensional contours of the skin, likely providing important clues about the skin condition (Figure 2).

The exact design of the LED groups used for directed illumination turned out to be crucial if one wants to obtain useful images for all patients without having to readjust the LED positions for each individual case. Because the observers stated that the quality of the pictures produced by our prototype foot imager did not meet expectations, adjustments were made regarding directed illumination. For this reason, the study consisted of two phases. For the first phase of this study, the LEDs were equipped with reflectors that illuminated the foot surface with a fairly parallel beam of light under a small angle. This produced a very strong enhancement of the skin contours in the images. However, due to differences in the three-dimensional shape of the foot across patients, for many patients shadowing occurred over considerable parts of the foot plantar surface, limiting the usefulness of the image for assessment. For the second phase of this study, the reflectors were removed and the LEDs were aimed at a slightly more perpendicular angle relative to the foot surface. This prevented unwanted shadowing of parts of the foot while maintaining visibility of skin contours in the images. Examples of diffuse and directed light images in both the first and second phase are shown in Figure 2. In order to minimize day-to-day variability in

A



B

Figure 1. (A) Schematic cross section of the photographic foot imaging device showing the most important features, including (1) camera module, (2) light sources (LEDs), (3) mirror, (4) glass plate, (5) foot supports, (6) lid, and (7) computer. (B) Photograph of the device showing the adjustable foot supports bars and the remote control switch.

image contrast and brightness, grey-coloured triangular reference areas positioned along the perimeter of the foot and imaged with each photograph taken, were used for image calibration based on the camera's response to the contrast and brightness levels of these reference areas.

With the patient seated, both feet are placed in the imaging device. The foot is immobilized by placing the heel of the foot in a heel cup and by resting the foot against a 20 mm wide, medial to lateral foot support which can be adjusted along the length of the foot depending on the location of the foot region of interest (Figure 1B). Due to the support bar, a small part of the foot sole is not visible in the images (figure 2). However, earlier tests had shown that without support bars most patients find it extremely difficult to position their feet correctly, because of the presence of neuropathy, which affects propriocepsis and limited joint mobility as complications of the disease. An anti-reflection coated glass window prevents dust entering the device. The photographic foot imaging device is independently operational by the patient in the home environment once installed. One imaging procedure takes only a few minutes to complete. Photographs are taken by pressing a button on a remote box connected to the system via a cable (Figure 1B). By closing the lid of the device after imaging the foot, the photographs are sent automatically via the Internet to a database server from where the pictures can be downloaded, all through a secure communication protocol, and assessed.

Protocol and analysis

Each patient was photographed sitting in a comfortable position on a normal chair in front of the device with the knees bent slightly. After the feet were positioned and immobilized in the device, one diffusely illuminated and two directly illuminated photographs were taken.

Directly following photographic imaging of the feet, live assessment of the feet was done by four independently operating observers: two wound care specialists and two surgeons. All observers were diabetic foot care specialists working with the diabetic foot on a day-to-day basis. Photographic assessment was performed two weeks and again four weeks post imaging, by the same four observers. Assessments were done and scored using simple clinical report forms, which included space to write down comments regarding photographic quality and ease of assessment. IrfanView Graphic Viewer (Version 3.99) was used to upload and assess the photographs on a 19 inch CRT (Cathode Ray Tube) monitor (maximal resolution 1600 x 1200/75 Hz). Each foot was assessed for the presence of a foot ulcer, abundant callus, redness (erythema), fissures, blisters, or the absence of any of these signs. A foot ulcer was defined as a full-thickness lesion penetrating through the dermis and into the subcutis. Abundant callus, redness, blisters and fissures were assessed since they are important clinical pre-signs of ulceration. Abundant callus was defined as callus formation requiring referral and treatment within three days. For each of the foot signs, the foot region was identified and reported on the CRFs.

Figure 2. Example photographs of diabetic feet with an ulcer taken with the photographic foot imaging device using the three different lighting conditions: diffuse (left pane), medial directed (middle pane), and lateral directed (right pane). The top row show example photographs taken with the prototype device during the first study phase, the bottom row photographs taken with the definitive device during the second study phase.

Agreement between live and photographic assessments and between repeated photographic assessments was calculated in percentages per outcome for the total number of observations by the four observers. A percentage agreement between 40% and 60% was classified as moderate, between 60% and 80% as good, and between 80% and 100% as excellent agreement. Disagreement between live and photographic assessments was defined as false positive and false negative observations. A false positive observation was defined as the observation of any clinical sign on the photographs observed as 'absence of signs' during live assessment, or the observation of an ulcer on the photograph observed as any other clinical sign during live assessment. A false negative observation was defined as the observation of any clinical sign during live assessment observed as 'absence of signs' during photographic assessment, or the observation of an ulcer during live assessment observed as any other clinical sign during photographic assessment. Furthermore, a descriptive analysis was made of the observers' comments regarding the quality of the photographs and the ease with which the different clinical signs could be assessed.

Results

The total number of feet assessed was 20 in the first study phase and 19 in the second study phase. The total number of observations for redness, fissures and blisters was too small for separate analysis. Therefore, these signs are represented together in the category 'other signs' in table 1.

Agreement scores between live and photographic assessments for the group of observers and per outcome are shown for the first and second study phase in table 1. Percentage agreement for the diagnosis of an ulcer was 90% in both the first study phase (10 out of 11) and the second study phase (19/21). Agreement for the diagnosis of abundant callus was 64% (36/56) in the first and 82% (27/33) in the second study phase. Agreement for absence of signs was 56% (30/54) in the first and 74% (28/38) in the second study phase. False positive scores were mainly observations of absence of signs during live assessment observed as abundant callus during photographic assessment: 18/54 (33%) in the first and 10/38 (26%) in the second study phase. False negative scores were mainly observations of abundant callus during live assessment observed as absence of signs during photographic assessment: 17/56 (30%) in the first and 5/33 (15%) in the second study phase.

Table 1. Agreement and disagreement (shown in numbers) between live and photographic assessments per outcome for the total number of observations from the group of four observers in the first and second study phases.

	Photographic assessment				
Outcome	**Ulcer**	**Abundant callus**	**Absence of signs**	**Other**	**Total**
Live assessment					
First study phase					
Ulcer	**10**	0	0	1	11
Abundant callus	*3*	**36**	17	0	56
Absence of signs	0	*18*	**30**	*6*	54
Other signs	0	0	3	**6**	9
Total	13	54	50	13	130
Second study phase					
Ulcer	**19**	2	0	0	21
Abundant callus	0	**27**	5	1	33
Absence of signs	0	*10*	**28**	*0*	38
Other signs	0	2	0	**4**	6
Total	19	41	33	5	98

Agreement in observations is displayed with numbers in boldface, false positive observations are displayed in italic and false negative observations are underlined.

Agreement scores between the repeated photographic assessments for the group of observers and per outcome are shown for the first and second study phase in table 2. For all outcomes, the agreement scores were higher in the second study phase than in the first study phase: 100% (19/19) versus 92% (12/13) for ulcer, 98% (40/41) versus 78% (42/54) for abundant callus and 97% (32/33) versus 82% (41/50) for absence of signs, respectively.
All four observers commented that the quality of the photographs was better in the second than in the first study phase. All four observers further commented that the quality of the photographs was sufficient for assessment of clinical signs: spatial resolution, in-depth focus, brightness and image contrast of the photographs were considered sufficient. The three different illumination settings were found helpful in most cases to obtain more information on the characteristics of the ulcer, such as depth. The investigators found the photographic foot imaging device to be user-friendly, requiring only minimal instructions for operation, which is important since the intended use of the system is in the patients' home, where it will be operated by the patient. Compared with live assessment of diabetic feet, the observers felt limited by the fact that the photographic assessment did not allow the opportunity to feel or smell the feet of the patient or to allow the direct assessment of ulcer depth. A further limitation commented by the observers was the uncertainly they felt in defining the amount of callus seen on the photograph as 'abundant' and therefore a referral for treatment.

Table 2. Agreement and disagreement (shown in numbers) between repeated photographic assessments shown per outcome for the total number of observations from the group of four observers in the first and second study phase.

	Photographic assessment 2				
Outcome	**Ulcer**	**Abundant callus**	**Absence of signs**	**Other**	**Total**
<u>**Photographic assessment 1**</u>					
First study phase					
Ulcer	**12**	0	0	1	13
Abundant callus	0	**42**	12	0	54
Absence of signs	2	3	**41**	4	50
Other	1	0	3	**9**	13
Total	15	45	56	14	130
Second study phase					
Ulcer	**19**	0	0	0	19
Abundant callus	1	**40**	0	0	41
Absence of signs	0	1	**32**	0	33
Other	0	1	0	**4**	**5**
Total	20	42	32	4	98

Agreement in observations are displayed with numbers in boldface.

Discussion

The purpose of this study was to describe the technical development of a new photographic foot imaging device along the objective to provide indications for the usefulness of the device for assessing signs of diabetic foot disease. This was done by comparing live and photographic assessments and by comparing repeated photographic assessments of the feet of diabetic patients by a group of four observers at two different developmental stages. The agreement found between live and photographic assessment for ulcer, abundant callus, and absence of signs was moderate to excellent in the first study phase (56-90%) and increased to high or excellent in the second study phase (74% - 90%). Between repeated photographic assessments of the same outcomes, agreement was good to excellent in the first study phase (78% - 92%), which improved substantially to excellent agreement in the second study phase (97% - 100%). These data seem to indicate that important clinical signs of diabetic foot disease can be diagnosed from high quality photographs by trained observers using the photographic foot imaging device.

The photographic foot imaging device was developed in two stages, the first in which a prototype version of the imaging device was used and the second in which a definitive version of the device was used. Both the comments of the four observers and the agreement scores indicate an improvement in image quality from the first to the second study phase. This is likely the result of the optimized illumination settings in the definitive version of the device with which the large variability in three dimensional foot shape across patients could be better covered. However, additionally, a learning effect in assessing foot disease from photographs among the observers may have been present between the first and second study phase and this may have been influential in the outcomes found. All observers frequently use photographic images in daily foot care for registration and presentation purposes, but none use these images regularly as a diagnostic tool. Nevertheless, we suggest that only trained professionals working with the diabetic foot on a day-to-day basis should be involved in photographic assessments of diabetic foot.

To our best knowledge, this is the first report on the use of digital photography as a telemedical diagnostic tool for the assessment of diabetic foot ulcers and pre-signs of ulceration. Several studies in different fields of medicine have reported on the usefulness of photographic assessments in characterizing chronic wounds for oedema, erythema, necrosis or granulation when compared with live assessments and these studies found good agreement scores.[18,19,23,24] No other studies were found in the literature on the assessment of abundant callus from digital photographs. Despite fairly good agreement results in the present study, all observers mentioned some difficulty in judging whether the present callus should be considered abundant and would require referral for treatment. Therefore, the assessment of callus seems more sensitive to variation, which may affect inter-observer reliability.

The results from this study are encouraging with regard to the use of the photographic foot imaging device as a monitoring tool for diabetic foot disease in the home environment of at-risk diabetic patients. If proven feasible for day-to-day monitoring in the home environment in future studies, this approach may contribute to the early recognition of signs of diabetic foot disease. We hypothesize that with the early recognition, referral and treatment of pre-signs of ulceration foot ulcers may be prevented. Furthermore, with the early recognition, referral and adequate treatment of foot ulcers in this patient group, we hypothesize a lower risk for further complications such as infection and amputation. If future clinical trials confirm these hypotheses, this approach could become an important part of prevention programs of diabetic foot disease, providing better patient mobility, improved health related quality of life, and lower treatment costs. We expect the approach to be cost-effective since the investment made for the photographic foot imaging device, estimated at €2,000 – €3,000 per device including installation, is relatively small compared with the direct costs for foot ulcer or amputation treatment (€5,000 - €40,000).[25] Additionally, the use of the device may decrease transportation costs and number of visits to the clinic. If the device is proven effective, this will improve patient autonomy, in particular in those patients with significant co-morbidities or those living in remote areas. Apart from using the device for prevention, it may also find application as a telemedical support tool in the treatment of foot ulcers, as many studies have previously shown that this can be effective. Clearly, further research using the photographic foot imaging device is needed before definitive conclusions about the efficacy of this approach can be drawn.

The study was limited to the evaluation of ulceration, abundant callus and absence of signs, even though redness (erythema) and blisters are also important clinical signs of diabetic foot disease. However, the sample size in this study was too small for including these less frequently occurring signs in this analysis. Furthermore, using the device, photographic assessments were limited to the plantar surface of the foot while a recent report showed that about 50% of all ulcers seen in specialized diabetic foot clinics appear on the dorsum of the foot.[26] Even though this may indicate the need for multiplanar photography in future designs of the device, the plantar foot surface remains the primary target for assessment, because (a) plantar foot ulcers are generally less predictable than dorsal ulcers because of their more complex aetiology; (b) some signs such as callus and blisters are more common on the plantar foot surface due to biomechanical influences; and (c) the plantar surface is not directly visible to the patient.

In conclusion, we have developed a photographic foot imaging device which produces high-quality photographs of the plantar surface of the foot which meet our expectations regarding the assessment of foot ulcers and pre-signs of ulceration in diabetic patients. The data seem to suggest that the photographic foot imaging device is a useful tool for the diagnosis of important foot problems in diabetic patients. The validity and reliability of assessments using this device in a larger patient sample, its usability as a monitoring tool in the home environment, and the effectiveness of the approach in preventing ulceration and further complications, requires further investigation. These investigations are needed before the photographic foot imaging device can become an accepted diagnostic tool in the home of diabetic patients at high risk for foot ulceration.

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Chapter 3

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The validity and reliability of diagnosing foot ulcers and pre-ulcerative lesions in diabetes using advanced digital photography

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ABSTRACT

Background

The goal of this study was to determine the validity and reliability of assessing the presence of plantar foot ulceration and pre-ulcerative lesions in diabetes patients from digital photographs that were produced using a new photographic foot imaging device.

Methods

In 32 diabetic patients who had a foot ulcer or were at high-risk of ulceration (a total of 60 feet), high quality photographic images of the plantar foot surface were collected. Each foot was assessed live, from photographs 2 weeks later, and again 4 weeks later for the presence of an ulcer, abundant callus, or the absence of signs. Each foot was assessed by four independently operating foot care specialists. Agreement scores were calculated using κ values (range, 0-1). Sensitivity and specificity scores were also calculated.

Results

Foot ulceration was cumulatively scored 59 times, callus 78 times, and absence of signs 149 times during live assessment. Agreement with photographic assessment was very good for ulcer (κ 0.87) and absence of signs (κ 0.83) and good for callus (κ 0.61). Sensitivity and specificity were high for ulcer (88% and 98%, respectively), callus (69% and 89%, respectively), and absence of signs (both 90%). Intra-observer agreement between repeated photographic assessments was good to excellent for all outcomes and observers (κ between 0.70 and 1.00). Inter-observer agreement for photographic assessments was good for ulcer (κ 0.72-0.88) and absence of signs (κ 0.59-0.75) and moderate to good for callus (κ 0.48-0.73). For live assessment, inter-observer agreement scores were only slightly higher.

Conclusions

The data illustrate that diabetic foot ulcers and pre-ulcerative lesions can be diagnosed in a valid and reliable manner by trained professionals from digital photographs produced with the foot imaging device. This supports the intended use of the device as a telemedical monitoring tool in the home environment for early detection of diabetic foot disease and prevention of severe complications in high-risk diabetic patients.

Introduction

Foot ulceration represents a significant problem in patients with diabetes mellitus. The yearly incidence rate in the overall population with diabetes is 2.2% and in those patients with peripheral neuropathy 5.0%-7.5%.[1,2] Foot ulcers can lead to infection and, eventually, amputation with 85% of all non-traumatic lower limb amputations being preceded by a foot ulcer.[3] The economic burden of diabetic foot ulceration and its sequelae is substantial.[4] For this reason, adequate treatment and, preferably, prevention of foot ulcers are of paramount importance if we are to reduce this large patient and economic burden. Risk identification, education, proper foot care, a multidisciplinary approach, and the provision of appropriate footwear have been shown to be fundamental for effective preventive management of the diabetic foot.[5] Any novel concept that may further contribute to the prevention of these serious foot problems should be supported and implemented in diabetic foot care.

International guidelines recommend the provision of foot care in patients at risk for ulceration at least once every three months.[6] However, we believe that in many regions and centres follow-ups in these patients occur less frequently. Regardless of the frequency, in a high risk category of patients, for example those with a previously healed foot ulcer, it is very likely that problems arise in-between visits to the foot clinic or health care professional. Furthermore, many diabetic foot patients are limited in their ability to assess the condition of the foot because they have visual impairment or limited joint mobility, live alone, have cognitive problems, lack adherence, or lack knowledge about the disease, which further increases the risk of developing an ulcer.[7] These patients may benefit from more frequent screening, i.e. on a weekly or daily basis, for the early recognition of foot problems. If diagnosed problems are referred and treated adequately, this may prevent or delay the onset of adverse outcomes. The most efficient way to monitor the feet of these patients on a frequent basis seems to be through the use of a telemedical approach in the home environment.

For this purpose, we have developed in collaboration with several industrial partners a photographic foot imaging device as a non-interactive diagnostic tool for use in the home-environment.[8] The system provides high-quality photographs of the plantar surface of the foot, which are sent automatically over the internet to a central database server from which they can be downloaded and assessed by a trained professional. Such a system has an advantage over conventional digital photography. It does not require another person to take photographs of the foot, it takes photographs under standardized conditions (foot orientation and ambient lighting) which improves image quality, and it does not require the manual upload of photographs to a server. Previous studies have documented that treatment of diabetic foot ulcers in the home environment can be effectively supported by means of a telemedical approach, including mobile phone and video technology.[9-12] However, these approaches have not yet been described for the diagnosis, early recognition, and prevention of diabetic foot disease.

Any tool can only be useful when outcomes of assessments are in agreement with outcomes from live assessments of the patient and from repeated assessments using the tool. There are only few studies that report on the validity and reliability of assessments of chronic wounds using a telemedical approach.[13-16] None of these studies have focused specifically on the diabetic foot or on diagnosing important pre-signs of ulceration such as callus and redness (erythema). Therefore, the aim of this study was to determine the validity and reliability of assessing the presence of foot ulcers and pre-signs of ulceration in diabetes patients from photographs produced with the photographic foot imaging device.

Patients and Methods

Subjects

A total of 32 patients (26 men, six woman; mean age, 64 years) participated in this study. All patients were diagnosed with diabetes mellitus and had a plantar foot ulcer or were at risk for developing a foot ulcer. Our intention was to recruit a sample of patients with a large variety of foot signs present, representative of the population of patients treated in our clinic. The study was approved by the local ethics committee, and each subject provided informed consent before the start of the study.

Photographic foot imaging device

The imaging device provides high-quality digital photographs of the plantar surface of the foot and is shown in Figure 1. The device has been described in detail elsewhere.8 In short, the device comprises an industrial camera in a plastic housing that provides images at a resolution of 4 pixels/mm^2. A mirror is used to "fold" the imaging light path from the camera in order to reduce the physical dimensions of the device. The foot plantar surfaces are illuminated by a number of high-power white light emitting diodes (LEDs). These LEDs can be flashed in groups to produce one diffusely illuminated and two directly illuminated images (from either the medial or lateral side) of the feet to enhance the perception of the three-dimensional contours of the foot (Figure 2). A glass plate prevents dust or other debris from entering the device. The foot is immobilized with a posterior heel cup and a plantar foot support across the midfoot, which can be adjusted depending on the location of a particular region of interest. Photographs are taken by pressing a remote switch button connected to the system.

Protocol

All patients were assessed and photographed at our outpatient clinic. Each patient sat in front of the device on a normal chair with the feet positioned against the foot supports. After the photographs were taken, the feet were assessed live at a separate location in the hospital. Both photographic imaging and live assessment were performed before foot treatment took place (e.g. debridement) to mimic the situation in which the system is used in the home. Photographs were assessed two weeks and again four weeks after live assessment. Photographs from different feet were presented to the observer in random order to reduce the chance of photographic memory of the foot or lesion. All assessments, live and photographic, were done by four independently operating diabetic foot care specialists – two surgeons and two wound consultants – working in the same diabetic foot centre. One surgeon was a vascular surgeon with 14 years of experience with treating the diabetic foot; the other was a surgical resident with 4 years of specific experience. Both wound specialists were trained in nursing and as a cast technician and later specialized as wound consultants. One consultant had 14 years of experience in treating diabetic feet, the other 10 years.

Photographs were opened using an IrfanView graphic viewer version 3.99 (www.irfanview.com) on a 19-inch cathode ray tube monitor (maximal resolution 1,600 x 1,200 pixels). Each foot was assessed for the presence of six different outcomes: foot ulcer, redness (erythema), abundant callus, blister, fissure, and the absence of any sign. A foot ulcer was defined as a full-thickness lesion penetrating through the dermis. Abundant callus was defined as callus formation requiring referral and treatment within 3 days. Redness was diagnosed as sign of infection (rubor), blister as a collection of fluid underneath the epidermis, and fissure as a crack-like lesion of the skin. Assessments were done using basic report forms. For each foot sign, the corresponding foot region (i.e. heel, medial or lateral midfoot, each of five metatarsals, or each of five toes) was reported.

Figure 1. (**Left panel**) Side view of the photographic foot imaging device with the feet of a subject positioned in the heel supports. (**Right panel**) Front view of the device showing the interior of the device including the foot supports.

Using ImageJ software (National Institutes of Health, Bethesda, MD), the size (i.e. area) of each diagnosed foot ulcer was measured from the photographic images according to the formula for an ellipse.

Data analysis

For a comparison between assessments to score as a 'match', both the sign and the foot region had to be identical. In case an observer scored abundant callus more than once per foot and more than one match or mismatch was present, this was scored only once.

The agreement between live and photographic assessment was calculated per outcome (sign) for each observer and for the total number of observations from the four observers. Disagreement was analysed as false-positive or false-negative observations. A false-positive observation was defined as (a) an observation of an ulcer on the photograph observed as any other outcome during live assessment or (b) an observation of pre-ulcerative lesion on the photograph observed as absence of a sign during live assessment. A false-negative observation was defined as (a) an observation of an ulcer during live assessment observed as any other outcome on the photograph or (b) an observation of pre-ulcerative lesion during live assessment observed as absence of a sign on the photograph. Sensitivity and specificity of diagnosing outcomes from the photographic images were also calculated. For this purpose, 2x2 tables had to be created from the agreement scores for each outcome. This was done by grouping all observations that were not "positive" (i.e., the outcome) as "negative" observations. Intra-observer agreement was calculated per outcome and for each observer between the first and second photographic assessments. Inter-observer agreement was calculated per outcome for all possible six pairs of observers, both for live and photographic assessments.

Figure 2. Example photographs of the feet of a study patient with an ulcer on the head of the first metatarsal bone. Photographs were produced with the photographic foot imaging device using three different lighting conditions: (**left panel**) diffuse illumination, (**middle panel**) medially directed illumination, and (**right panel**) laterally directed illumination.

Statistical analysis

Agreement between assessments was calculated statistically using Cohen's kappa (κ) values, which are measures of agreement between two observations in excess of the agreement by chance. The κ is expressed as a fraction of 1, with <0.20 representing poor, 0.21 – 0.40 fair, 0.41 – 0.60 moderate, 0.61 – 0.80 good, and 0.81 – 1.00 very good agreement.[17] All statistical analyses were done using SPSS version 14.0 software (SPSS, Chicago, IL).

Results

In 32 patients, a total of 60 feet were photographed (four patients had unilateral above-the-ankle amputation). A foot ulcer was cumulatively scored 59 times, abundant callus 78 times, and absence of signs 149 times by the four observers during live assessment (Table 1).

Table 1. Number of observations in 60 feet during live assessment and both photographic assessments per observer and per outcome.

	Ulcer	Abundant callus	Absence of signs	Redness	Blister	Fissure
Live assessment						
Observer 1	18	20	36	2	0	0
Observer 2	13	23	36	1	1	0
Observer 3	15	17	39	2	1	1
Observer 4	13	18	38	0	1	4
Cumulative	59	78	149	5	3	5
Photographic assessment 1						
Observer 1	14	21	39	2	0	0
Observer 2	12	24	37	1	1	0
Observer 3	19	8	39	2	1	6
Observer 4	13	18	37	0	1	5
Cumulative	58	71	152	5	3	11
Photographic assessment 2						
Observer 1	14	21	39	2	0	0
Observer 2	12	24	37	1	1	0
Observer 3	19	14	36	2	1	3
Observer 4	14	19	37	0	1	3
Cumulative	59	78	149	5	3	6

Redness (erythema), blisters, and fissures were underrepresented with less than five cumulative observations each. As a result, these signs were disregarded for analysis on agreement and pooled as "other" category for analysis of false-positive and -negative observations. The median size for the nine ulcers that were diagnosed by each of the four observers was 1.4 cm^2.
Agreement scores between live and photographic assessment are shown in Table 2. For foot ulcer, agreement was very good (overall κ = 0.87, range between observers κ = 0.76 - 0.95). For abundant callus, agreement was good (overall κ = 0.61, range κ = 0.48 - 0.72). For absence of signs, agreement was very good (overall κ = 0.83, range κ = 0.64 - 0.97). Both the false-negative and false-positive observations for foot ulcer were mainly observations of callus (Table 3). False-negative and -positive observations for callus were mainly observations of absence of signs.
Sensitivity and specificity scores are shown in Table 3. For ulcer, sensitivity was 88% and specificity 98%; for abundant callus, these were 69% and 89%, respectively; and for absence of signs, these were 90% and 90%, respectively.
Intra-observer agreement scores are shown in Table 2. Agreement was excellent for foot ulcer (overall κ = 0.97, range between observers κ = 0.91 – 1.00). For abundant callus, agreement was very good (overall κ = 0.87, range κ = 0.70 – 1.00). For absence of signs, agreement was excellent (overall κ = 0.95, range κ = 0.89 – 1.00).
Inter-observer agreement scores for the six pairs of observers are shown in Table 4.

Table 2. Agreement between live and photographic assessments and intra-observer agreement for repeated photographic assessments expressed in κ values per observer and per outcome.

	Ulcer	Abundant callus	Absence of signs
Live vs. photographic assessment			
Observer 1	0.76	0.69	0.83
Observer 2	0.95	0.48	0.64
Observer 3	0.85	0.57	0.86
Observer 4	0.95	0.72	0.97
Overall	0.87	0.61	0.83
Photographic assessment 1 vs. 2			
Observer 1	0.91	0.82	0.89
Observer 2	1	1	1
Observer 3	1	0.7	0.91
Observer 4	0.95	0.91	1
Overall	0.97	0.87	0.95

With live assessment, inter-observer agreement was good to very good for foot ulcer (κ = 0.74 – 0.88), moderate to good for abundant callus (κ = 0.52 – 0.73), and good for absence of signs (κ = 0.62 – 0.73). With photographic assessment, inter-observer agreement was good for foot ulcer (κ = 0.72 – 0.80), moderate to good for abundant callus (κ = 0.48 – 0.63), and good for absence of signs (κ = 0.59 – 0.75).

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Table 3. Total agreement and disagreement between live and photographic assessment expressed in cumulative numbers for all observers together and per outcome.

	Photographic assessment			
	Ulcer	Abundant callus	Absence of signs	Other
Live assessment				
Ulcer	53	<u>6</u>	<u>1</u>	0
Abundant callus	*5*	54	<u>14</u>	5
Absence of signs	*1*	*14*	134	0
Other	0	*4*	0	9
Sensitivity	53/60 (88%)	54/78 (69%)	134/149 (90%)	9/13 (69%)
Specificity	234/240 (98%)	198/222 (89%)	136/151 (90%)	282/287 (98%)

Sensitivity and specificity of diagnosing outcomes using the photographs are expressed in ratios and percentages for each outcome. False-positive observations are displayed in italic style; false-negative observations are underlined.

Table 4. Inter-observer agreement for live assessment and for the first photographic assessment between all six pairs of observers, expressed in κ values per outcome.

	Ulcer	Abundant callus	Absence of signs
Observer pair			
Live assessment			
1 vs. 2	0.75	0.73	0.73
1 vs. 3	0.88	0.52	0.64
1 vs. 4	0.76	0.63	0.70
2 vs. 3	0.77	0.54	0.62
2 vs. 4	0.82	0.63	0.69
3 vs. 4	0.74	0.73	0.71
Photographic assessment			
1 vs. 2	0.77	0.52	0.59
1 vs. 3	0.77	0.63	0.67
1 vs. 4	0.72	0.57	0.75
2 vs. 3	0.75	0.56	0.63
2 vs. 4	0.80	0.59	0.67
3 vs. 4	0.77	0.48	0.64

Discussion

The results of this study showed that agreement between live and photographic assessments was very good for the diagnosis of a foot ulcer and absence of signs and good for callus. Sensitivity and specificity scores for these outcomes were high. Furthermore, the variability in agreement scores among the four observers was relatively small. Intra-observer agreement scores between repeated photographic assessments ranged from good to excellent for all outcomes and observers. Inter-observer agreement was good for ulcer and absence of signs and moderate to good for callus. Only small differences in the range of inter-observer agreement scores were found between live assessments and photographic assessments. Overall, these results show that valid and reliable assessments of the presence of foot ulcers and pre-ulcerative lesions on the plantar foot surface in diabetic patients could be made by trained professionals from the digital photographs produced by the photographic foot imaging device.

In the comparison between live and photographic assessments, foot ulcer as outcome showed the best agreement scores and overall the best sensitivity and specificity scores, callus the lowest, and absence of signs in-between these scores. Good agreement and high sensitivity and specificity are particularly important for foot ulcers considering the severity of the problem. The false-negative observations for foot ulcer were mainly observations of callus on the photographs. In these cases an ulcer may have been present underneath the callus. Furthermore, despite the advanced imaging options with different illumination settings, the difficulty reported by the observers in accurately assessing depth and texture of a small ulcer on the photographs in some cases may have resulted in different interpretations, such as callus with internal bleeding (pre-ulcerative lesion). Clearly, in live assessment a wider range of options (e.g., touch, smell, and multiple viewing angles) is available to assess the foot than in photographic assessments, which may explain these false-negative observations. However, because the patient with abundant callus would still be referred for treatment within a few days, the consequences of these observations may not be dramatic. The lowest agreement scores were found for abundant callus, likely because of the reported difficulty by the observers in characterize the callus as "abundant" requiring referral for treatment. Disagreement in diagnosing callus was equally divided over false-positive and -negative scores, mainly constituting observations of absence of signs. Similarly, disagreement found between live and photographic assessments in observing absence of signs was mainly attributable to false observations of callus in these cases. However, with the normal growth of callus over time, we do not foresee problems with classifying callus at a certain instant as abundant when monitored over a longer period using the foot imaging device

To the best knowledge of the authors, this is the first study on the diabetic foot to provide insight into the accuracy of using digital photography to diagnose important signs of foot disease. Several studies assessed the validity of remote photographic assessments of dermatological lesions and reported agreement rates with live assessment between 59% and 83%.[18,19] Other studies used digital images to assess wound characteristics and concluded that accurate wound evaluation and monitoring is possible with this approach.[13-16] In individuals with spinal cord injury, decisions that were based on photographic assessments of pressure ulcers agreed in 78% to 100% of cases with decisions based on live assessments.[20] The results from the current study are in good agreement with these previous findings in subjects without diabetes and further support the potential value of photographic-based imaging in the diagnosis and treatment of ulcers.

Good intra- and inter-observer reliability in photographic assessments is important when digital photography will be used as home monitoring tool and photographs will be assessed by different healthcare professionals. The medical literature does not provide information on the reliability of photographic assessments of foot disease in diabetic patients. To identify pressure sores from photographs in elderly hospitalized patients, one study showed that inter- and intra-observer agreement scores between six experienced nurses was good (0.69 and 0.84, respectively)[21] and comparable to agreement scores in the current study. Both this previous study as well as the current study suggest that specific experience is necessary to obtain such good results in observer agreement. For the same reasons as mentioned above in the comparison of live and photographic assessments, the inter-observer agreement scores for abundant callus were lower than for the other outcomes. Surprisingly, inter-observer agreement scores for photographic assessments were only slightly lower than scores for live assessments. Although the live assessments of the foot were somewhat unrealistic because they took place before foot treatment (i.e., debridement), these findings apparently show that lack of consensus of what constitutes a foot ulcer or abundant callus contributes more to the outcome on agreement than the circumstances in which the foot was assessed (live or from photograph).

Demonstrating that valid and reliable assessments can be made from digital photographs produced with the device is a first step in the integration of this approach as telemedical home monitoring tool in clinical practice. Next, the device needs to be proven usable in the home environment. Furthermore, its use has to be proven (cost)-effective over regular treatment in preventing severe complications in high-risk diabetes patients. Proven efficacy of the approach will, if implemented, likely improve patient mobility and health related quality of life, and it will reduce the economic burden for diabetic foot treatment. Furthermore, foot monitoring may provide a feeling of safety with patients knowing that their feet are frequently checked by a healthcare professional. Also, it will likely improve autonomy in patients with significant co-morbidities or those living in remote areas if the frequency of visits to the foot clinic can be reduced by using this telemedical approach.

The study was limited by the fact that the total number of patients with blisters, fissures, and erythema was too small to draw relevant conclusions on these outcomes. Early recognition of these signs is important, though, to prevent further complications in the diabetic foot as previous studies on the use of skin temperature monitoring have shown.[22,23] Sufficiently sized studies in a dedicated sample of patients are needed to assess the validity and reliability of diagnosing these signs from photographic images. Second, photographic imaging was limited to the plantar foot surface. Recently it was shown that about 50% of all ulcers treated in specialist clinics appear on the foot dorsum.[24] Therefore, the possibility of imaging the foot dorsum may be implemented in future designs of the device. Nevertheless, the plantar surface remains the primary target surface because many lesions such as callus and blisters are more common on the plantar than dorsal foot surface and because the plantar surface is not directly visible to the patient. Finally, the study outcomes may be specific to the professional background of the observers, their experience, and the setting they all worked in, namely the same multidisciplinary team. In support of this, the results from one study on the use of digital images in the diagnosis and treatment of wound healing problems showed that the agreement between live and photographic assessments was significantly associated with the experience level of the observer.[25] Future studies should demonstrate how well the current results apply to professionals with a different background or experience.

Conclusions

The data from this study showed that foot ulcers and pre-ulcerative lesions can be assessed by trained professionals in a valid and reliable manner from digital photographs produced by the photographic foot imaging device. These finding are important to support the use of the device as a telemedical home monitoring tool for the early recognition of foot disease in high-risk diabetes patients. Future studies will have to expand on these findings by determining the validity and reliability of diagnosing other important pre-signs of ulceration such as blisters and erythema using digital photography. Furthermore, the usability and (cost) effectiveness of the approach will have to be proven before it can be widely implemented in foot care for high-risk diabetes patients.

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Chapter 4

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Telemedical home-monitoring of diabetic foot disease using photographic foot imaging

A feasibility study

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ABSTRACT

We assessed the feasibility of using a photographic foot imaging device (PFID) as a tele-monitoring tool in the home environment of patients with diabetes who were at high risk of ulceration. Images of the plantar foot were taken three times a week over a period of four months in the home of 22 high-risk patients. The images were remotely assessed by a diabetic foot specialist. At the end of the study, 12% of images were missing, mainly due to modem or server failures (66%), or non-adherence (11%). All three referrals for diagnosed ulcers and 31 of 32 referrals for abundant callus resulted in treatment. Health-related quality of life (EQ-5D visual analogue scale), increased from 7.5 at baseline to 7.9 at end of follow-up, but not significantly. Mean scores on a visual analogue scale for different usability domains (independence, ease of use, technical aspects, and value) ranged from seven to nine. The study demonstrates the feasibility of using the PFID for the early diagnosis of foot disease, which may prevent complications in high-risk patients with diabetes.

Introduction

As a complication of diabetes mellitus, foot disease imposes a heavy burden on both the patient and society.[1] Early recognition of signs of foot disease is essential in preventing complications, especially in patients at high risk of foot ulceration. However, most complications occur between visits to a health-care professional. Furthermore, many patients are limited in assessing the condition of their own feet because they have visual impairment, live alone, have cognitive problems, lack adherence or lack knowledge about the disease, which increases ulcer risk.[2] Therefore, a telemedical diagnostic method for use in the home environment may be useful.

Previous studies have documented that the treatment of diabetic foot ulcers can be supported in the home environment through mobile phone and video interaction.[3-5] Furthermore, home-based communication technology applied to chronic disease management can improve functional and cognitive patient outcomes and reduce health-care spending.[6] However, such telemedical approaches have not been used for the early recognition of foot disease in diabetic patients. Skin temperature monitoring is the only home-based method that has been proven effective in the prevention of foot ulcers.[7-9] However, several important early signs of ulceration and ulceration itself, cannot be diagnosed using foot temperature monitoring. For these cases, photographic imaging of the foot could be beneficial.

We have developed a photographic foot imaging device (PFID) which provides high-quality digital photographs of the plantar surface of the foot.[10] The images can be remotely assessed by a diabetic foot specialist. Imaging can be performed several times a week and when signs of foot disease are diagnosed, patients can be directly referred for treatment. Assessment of signs of diabetic foot disease from photographs taken with the PFID has been shown to be valid and reliable.[11]

If the PFID is to be used in clinical practice, it has to be feasible in patients at high risk of developing foot ulcers. The aim of the present study was to demonstrate the feasibility of using the PFID for the diagnosis of foot disease in the home of high-risk patients with diabetes.

Methods

A prospective four-month monitoring study was conducted. Twenty-two subjects with diabetes (18 males) at high-risk of foot ulceration (i.e. presence of peripheral neuropathy with foot deformity and/or prior foot ulceration) were evaluated. All patients were recruited at the outpatient clinic of two specialized diabetic foot centres, the Ziekenhuisgroep Twente in Almelo, the Netherlands (18 patients) and the Mathias Spital in Rheine, Germany (4 patients). The mean age of the subjects was 60 years (SD 11) and the mean duration of diabetes mellitus was 18 years (SD 12). Fourteen patients had type 2 diabetes and eight had type 1. All subjects had peripheral neuropathy as confirmed by the diagnosis of loss of protective sensation using the Semmes-Weinstein monofilaments. All patients had at least one clinically diagnosed foot deformity (i.e. Charcot osteo-arthropathy, claw toes, hallux valgus, pes planus, pes cavus, toe amputation or limited joint mobility). Seventeen patients had a history of one or more plantar foot ulcers. According to the PEDIS classification, none of the patients had peripheral arterial disease at the time of study entry.[12] Exclusion criteria were an amputation at a level beyond the metatarsal bones of either foot, or the intention to be absent for longer than seven consecutive days (e.g. vacation) during the four-month follow-up period. The study protocol was approved by the appropriate ethics committee and all subjects signed an informed consent form before the start of the study.

Photographic foot imaging device

A total of 14 photographic foot imaging devices were used to assess the 22 patients (8 devices were used in consecutive patients). The PFID comprised a camera module, light sources, mirror, glass plate, foot supports and a computer, all in a plastic housing (Figure 1).[10] The camera module contained an industrial camera with a charge-coupled device (CCD) image sensor producing digital photographs at resolution of 4 pixels/mm^2. Photographs were taken with one diffusely illuminated, one medially illuminated and one laterally illuminated image to enhance the perception of the contours of the foot. The foot was immobilized in the device with a posterior heel cup and an adjustable plantar foot support. Photographs were taken by pressing a remote switch connected to the system. After closing of the lid of the PFID, photographs were automatically transmitted as non-compressed, TIFF files to a database server. The system could be operated by the patient alone. A modem connection to the Internet at the patients' home was required. If such a connection was not present, it was installed for the study.

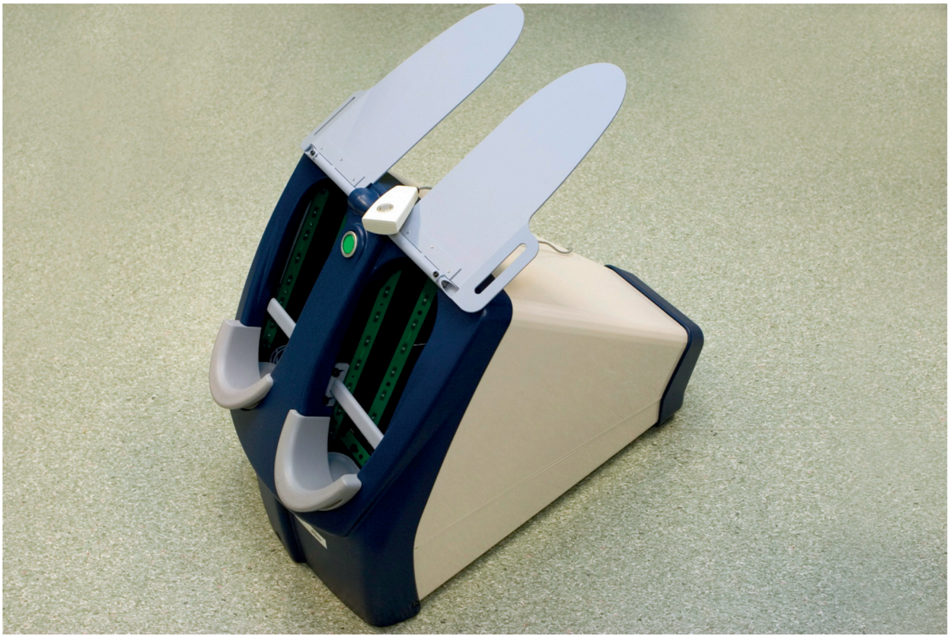

Figure 1. The photographic foot imaging device.

Protocol

Patients underwent a baseline assessment at the outpatient clinic where demographic and medical history data were collected and where a lower extremity examination took place, by the same trained researcher in each of the two centres. Health-related quality of life (HRQoL) was assessed at baseline using the EQ-5D. The EQ-5D consists of a descriptive system and a visual analogue scale (VAS). The descriptive system comprises five dimensions of health: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Scores on each dimension are rated on a three-point Likert scale (no problems/some or moderate problems/extreme problems) presenting respondents' health state. A health state may be converted into a single summary index (or utility) by applying a formula that attaches different weights to each of the levels in each dimension. This scoring method has been developed to assign each possible health state a utility score in which 1 represents the best possible health state (no problems on all 5 items) and 0 represents the worst health state possible. The formula is based on the valuation of EQ-5D health states from general population samples. Scores on the EQ-5D VAS records the respondent's self-rated health where the endpoints are labelled 'Worst imaginable health state' and 'Best imaginable health state' (score 0-10).

After baseline assessment, an engineer from the manufacturer of the device (DEMCON Advanced Mechatronics, Oldenzaal, the Netherlands), installed the device in the patients' home. The foot support was adjusted if needed. Patients received a user manual and the imaging procedure was explained.

For a period of four months, patients were asked to image both feet three times a week, on Monday, Wednesday, and Friday, immediately after getting out of bed. The images were downloaded from the database server and assessed by a diabetic foot specialist (surgeon) the same day that they were acquired. If the photographs were not available on the server, the patient was telephoned by the surgeon and asked about the reason for non-availability. If forgotten or otherwise not performed by the patient, this was considered non-adherence with the protocol. If the green LED on the device was flashing, this indicated a modem connection failure. In all other cases, a failure was regarded as a server failure. In case of non-adherence, the patient was asked to image their feet so that photographs for that day were available. In case the patient could not be contacted and it appeared later that there was no clear reason for missing images on the server, this was considered non-adherence. All outcomes were scored on a clinical report form.

An image viewer (IrfanView Graphic Viewer) was used to display the photographs on a 19 inch CRT (Cathode Ray Tube) monitor (maximum resolution 1600 x 1200 pixels). If a foot ulcer or redness was diagnosed, the patient was referred for treatment within 24 hours. If abundant callus, a blister, fissure or other pre-sign was diagnosed, the patient was referred for treatment to the outpatient clinic within the following three days. Patients were contacted and appointments were scheduled on the day of diagnosis. Patients were treated by a foot care specialist who was unaware of the indication for referral. All referrals for treatment were scored on a clinical report form. A referral was considered justified if treatment of the diagnosed foot problem took place (e.g. callus removal or prescription of antibiotics). This was assessed by viewing patient records after the visit to the clinic. In case no signs of foot disease were seen on the photograph, patients were not contacted for feedback.

At the end of the four-month follow-up, patients completed a questionnaire on the usability of the PFID and the scanning procedures. Most outcomes were scored on a VAS, with 0 representing the worst possible outcome and 10 representing the best possible outcome. Other outcomes were scored in a binary fashion (yes/no). HRQoL was again assessed using the EQ-5D.

Statistical analysis

Descriptive statistics were performed for outcomes on justified referrals, missing data and non-adherence. Paired t-tests were used to compare mean scores between baseline and four-month assessment for HRQoL. All tests were performed using a standard package (SPSS version 14.0).

Results

The mean duration of follow-up was 111 days (SD 36, range 23–152 days). One patient died because of cardiac arrest after 28 days follow up. Another patient developed an infection between the third and fourth metatarsal phalangeal joint after 23 days follow up, which was not diagnosed on the photographs. The patient visited the outpatient clinic because of inter-digital swelling, local pain, and fever. He was admitted to hospital and treated with intravenous antibiotics. The patient was excluded from further follow-up in the study.

All patients reported that it took less then 6 min to complete the imaging task (65% of patients reported a mean duration between 1 and 3 min). The time required to download a complete set of three images from the server and assess the photographs was less than one min per patient. In all cases that a sign of foot disease was diagnosed, the patient was contacted on the same day for referral.

Missing data

Missing data and failures in the communication process are summarised in Table 1. Based on a cumulative follow-up period in the 22 patients of 349 weeks, a total 1022 image sets were expected to be available for assessment, excluding the 25 image sets on days that a patient had a scheduled leave of less than one week. A total 122 image sets were missing (12% of the total). Most of the missing data was due to modem failures (68 image sets), which occurred mostly in the first three patients because of wireless connection problems caused by the distance between the PFID and the modem. After ensuring that the PFID was placed close enough to the modem,

Table 1. Outcomes for missing data, communication failures, (justified) referrals and HRQoL.

Parameter	Outcome
Missing data / communication process failures	**No (%)**
Total	122
Connection / modem failure	68 (56)
Server failure	12 (10)
Non-adherence to protocol	13 (11)
Short hospital admission	9 (7)
Visit to outpatient clinic	6 (5)
Leave for illness of family member	5 (4)
Unknown	9 (7)
Referrals based on photographic assessment	**No (justified)**
Ulcer	3 (3)
Abundant callus	32 (31)
Blister	1 (0)
HRQoL (18 patients)	**Mean (SD)**
EQ-5D VAS score at baseline	7.5 (1.5)
EQ-5D VAS score at end of follow-up	7.9 (1.8)*
EQ-5D utility score at baseline	0.79 (0.29)
EQ-5D utility score at end of follow-up	0.82 (0.20)#

Not significant compared with baseline assessment, *P = 0.31, # P = 0.12

this problem was solved and subsequently occurred only occasionally. A server failure was the cause of 12 missing image sets, of which most were the result of a server breakdown during one full day. Non-adherence was the cause of 13 missing image sets.

Justified referrals

In all three cases that a foot ulcer was diagnosed, treatment of the ulcer took place, see Table 1. Of the 32 referrals for abundant callus, 31 were treated (callus removal). One patient was referred because of the diagnosis of a blood blister. However, the blister was not present when the patient was seen in the clinic three days later and thus treatment did not take place.

Usability

The outcomes on usability are summarised in Table 2. For the 10 items for which a VAS score was used, mean scores were 7 (for technical aspects) to 9 (for ease of use, clarity of instructions and confidence in remote assessment).

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Table 2. Usability questionnaire: scoring items, scoring scales and outcomes.

Questions	Scale	Mean (SD) score*
How pleasant was the 'remote contact' with your doctor through the device?	VAS 0-10	8 (2)
How independent were you in operating the device?	VAS 0-10	8 (4)
How clear were the scanning instructions?	VAS 0-10	9 (2)
How user-friendly was the device?	VAS 0-10	9 (2)
How well did you succeed in taking pictures of your feet?	VAS 0-10	8 (4)
How quickly did you receive support with technical problems?	VAS 0-10	7 (4)
How well were technical problems solved?	VAS 0-10	7 (4)
How easy was the installation of the device?	VAS 0-10	7 (4)
How satisfied are you about the monitoring with the device?	VAS 0-10	8 (3)
How confident were you that a professional was remotely inspecting your feet?	VAS 0-10	9 (2)
Statements	**Scale**	**Score***
Monitoring with the device saves me time in the treatment of my foot problems	Yes/No	16/4
Monitoring with the device saves me expenses in the treatment of my foot problems	Yes/No	16/4
I feel more safe with more frequent screening of my feet using the device	Yes/No	18/2
I am less dependent on family/ friends for help with my feet using the device	Yes/No	12/8
I prefer to use the device if it would become part of regular treatment for diabetic patients	Yes/No	19/1

* 20 patients; two patients did not reach the end of follow and therefore did not complete the questionnaire

For the five items which were scored in binary fashion, agreement ranged from 12 out of 20 patients (for independence from family) to 19 out of 20 patients (for preference on using the device in regular treatment).

Health-related quality of life

Complete data on HRQoL was obtained from 18 of 22 patients. At baseline, seven of 18 patients reported no or few problems on all health dimensions. Eleven patients reported severe problems on at least one dimension. Nine of 18 patients reported a change in one or more dimensions between end of follow-up and baseline: in five patients scores were better and in four patients scores were worse at the end of follow-up. The mean self-rated overall health (EQ-5D-VAS) was 7.5 (SD 1.5) at baseline and 7.9 (SD 1.8) at the end of follow-up. The difference of 0.4 points was not significant ($P = 0.31$). The mean health state utility was 0.79 (SD 0.28) at baseline and 0.82 (SD 0.20) at end of the follow-up ($P = 0.12$).

Discussion

We assessed the feasibility of using the PFID as home-monitoring tool in high-risk patients with diabetes. Only 12% of the image sets were missing, which is much less than with the use of UMTS mobile phone video technology.[5] Most of the missing image sets were due to preventable modem failures in the first few devices set out for testing. Non-adherence with the imaging protocol was small, probably because the patients were closely monitored and directly contacted when image sets were not available. The time needed for patients to image the foot and for the surgeon to download and assess the images was short. Nearly all referrals for treatment were justified, although the number of severe complications such as ulceration or infection was small. Perceived usability was high which was in agreement with patient satisfaction scores on web-based consultation systems for chronic wound care.[13] Finally, HRQoL was slightly improved during the four-month follow-up period with the device, although not significantly. These results show that the use of the PFID is a feasible approach for home monitoring and the diagnosis of ulcers and pre-ulcerative lesions in the diabetic foot.

The present study is one of the first to examine the feasibility of using digital photography as a home monitoring tool for the early diagnosis of diabetic foot disease. The majority of feasibility studies on the use of telemonitoring for foot care have been conducted in non-diabetic patients.[14] These studies generally show that patients are satisfied with the use of telecare, but they prefer a combination with conventional health care.[15] However, most feasibility studies focus only on the validity and/or reproducibility of the approach and not on patient-perceived usability, technical or communication aspects, and non-adherence. The validity and reliability of assessments with the PFID have been tested previously.[11] The present study provides a more comprehensive analysis of feasibility in high-risk patients.

Demonstrating the feasibility of this approach is an important step towards its integration into diabetic foot practice. Approaches may be valid, reliable, and effective, but if they are not feasible for use in the homes of patients, proper implementation may be unsuccessful. The participants in the present study were representative of the high-risk population eligible for telemedical monitoring. The investment needed to apply this method, about €3000 per patient, is only a fraction of the cost of foot ulcer or amputation treatment (€5 – 40,000).[16] If proven (cost) effective in preventing severe foot complications, the use of the PFID in daily care may lead to improved autonomy and well-being, in particular for those patients living alone or in remote areas, and to reduced health-care costs.

Imaging using the PFID is limited to the plantar foot surface, even though many wounds and other lesions occur on the dorsal surface or between digits, as one patient in the study showed.[17] Other methods such as skin temperature monitoring may be sensitive enough to diagnose these complications.[7-9] Therefore, future designs of the device preferably include dorsal photography and skin temperature monitoring. Second, even though sample size and follow-up time were sufficient to assess several aspects of feasibility, the number of patients included was too small to draw relevant conclusions on clinical aspects such as justified referrals and changes in HRQoL. The number of severe complications was small, but this may be a positive effect of using the device in the early diagnosis of pre-ulcerative lesions. Finally, the study design did not allow the opportunity to asses self-referrals by the patient in comparison to referrals based on remote assessment using the PFID. Clearly, a prospective controlled trial using a larger sample size and a longer follow-up is required.

The present study demonstrates the feasibility of using the PFID as a home monitoring tool for the early diagnosis of signs of foot disease in high-risk patients with diabetes. The next stage is to examine the (cost-) effectiveness of this approach in preventing severe complications.

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Chapter 5

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A systematic review of telemedicine applications for the diabetic foot

Submitted

ABSTRACT

Objectives

To assess the medical-scientific literature on the feasibility, effectiveness, value, and limitations of using telemedicine approaches for the management of diabetic foot disease.

Design

Systematic review.

Search Strategy

The MEDLINE database was searched for original research articles on telemedical approaches used for the prevention, assessment and treatment of foot disease in patients with diabetes mellitus. All study designs were included and the search was limited to English language papers.

Participants

Patients with diabetes mellitus and signs of foot disease.

Interventions/modalities

Dermal thermography, hyperspectral imaging, digital photographic imaging, and video/audio communication tools. Primary and secondary outcome measures: validity, reproducibility, feasibility, usability, and (cost-) effectiveness of the telemedical approach.

Results

The search yielded 882 articles of which 30 were eligible. Ten articles were on the use of dermal thermography as home monitoring tool, of which 3 randomized controlled trials showed this method to effectively diagnose foot temperature changes and significantly reduce the incidence of foot ulcers compared to usual care. Seven studies showed that the use of hyperspectral imaging can predict ulcer healing as well as ulcer development. Nine studies showed the value of photographic imaging to accurately and reliably assess foot ulcers, ulcer area, and callus, and showed this modality to be feasible for use in the patient's home. Video-assisted treatment of diabetic foot ulcers in the home environment showed to be a feasible tool in four studies.

Conclusions

This systematic review shows that telemedicine for the diabetic foot is still in its infancy, but several promising technologies are available that may be of additional value for the prevention, assessment, and/or treatment of foot disease in diabetic patients. The cost-effectiveness of dermal thermography and feasibility and/or effectiveness of other modalities should be proven for them to become more widely accepted and used in diabetic foot care.

Introduction

Foot complications in diabetes are worldwide a major medical, social and economic problem. The lifetime risk of developing a foot ulcer is approximately 25%[1], with the most devastating and costly outcome being a lower limb amputation, which is nearly always preceded by a foot ulcer. Health-care expenditure on diabetic foot care adds up to one third of total expenditure on diabetes care[2,3], and the direct costs of a foot ulcer that results in amputation may be on average $US 40,000[4]. The prevention of these lower limb complications of diabetes would have major positive impact on morbidity, mortality, and patient well being, and would lead to large savings on healthcare expenditure.

Frequent inspection of the foot is an important cornerstone of prevention. Once an ulcer has developed, monitoring of the ulcer is important to assess treatment efficacy, to predict healing, and to respond swiftly in case a complication such as foot infection develops. Therefore, in ulcer treatment patients are often seen every week or every other week at the outpatient foot clinic. Once healed, guidelines recommend that patients are screened at least once every 1-6 months.[5] However, foot ulcers mostly occur in-between clinic visits, when the patient is at home. Therefore, patient self-monitoring is important to timely identify signs of foot disease. Self-monitoring is, however, not easy and may be hampered when patients are physically limited because of limited joint mobility, visual impairment, or obesity, or when they lack sufficient knowledge about the disease.[6-8] A previous study showed that self-inspection of the plantar foot with the aid of a mirror provided no significant benefit in ulcer risk compared with usual care that did not involve such self-inspetion.9 Foot inspection by a relative may be troublesome as well since many patients live alone and relatives may also be limited in their ability to inspect the patient's foot.

For these reasons, the development of tools that can effectively contribute to monitoring the patient's foot may be a great asset for diabetic foot management. Because of rapid developments in telecommunication technology and the widespread availability of internet, telemedicine has become increasingly popular in monitoring and treating patients, even though the first telemedicine application was first used in psychiatric consultations almost 55 years ago.[10] Telemedical systems have been developed for diagnostic, therapeutic, and educational purposes in many different medical specialities. Although telemedicine still has to be proven to be cost-effective in a large number of applications[11], it is used to improve efficiency and effectiveness of care and patients well-being and autonomy in a world with rapidly changing socio-economic perspectives in health care[12].

Telemedicine applications are also used in diabetes care, for example in supporting self-monitoring of glucose that has been proven feasible and acceptable.[13] Several applications have been developed for the diabetic foot. This includes the use of mobile phone and video interaction to support foot care[14-16],the use of imaging devices[17-22], and dermal thermography[9,23,24] for ulcer monitoring and diagnosis of foot disease. Nevertheless, very few applications seem to be implemented in diabetic foot care.

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The purpose of this systematic review was to assess the refereed literature on telemedicine in the diabetic foot to determine the feasibility, (cost-) effectiveness, value, and limitations of currently available telemedicine applications for the management of the diabetic foot and to discuss, based on this assessment, future directions in foot care and research.

Methods

The population of interest for this review was patients with diabetes mellitus and foot disease. The intervention considered was any telemedical tool or medical tool that may potentially serve as telemedical application. Main outcomes were validity, reproducibility, feasibility, usability, and (cost-) effectiveness in the prevention, monitoring/assessment, or treatment of diabetic foot disease.

The literature search was performed using the MEDLINE database on the 4th of July 2013. The search was not limited by date. The search string used is shown in Appendix A. Only original research articles written in the English language were considered. One reviewer (CH) assessed all obtained references by title for eligibility for inclusion. Two reviewers (CH and SB) independently assessed abstracts of selected references. The same reviewers independently assessed full-paper copies of references that were selected based on abstract to determine final inclusion in the review. Disagreement between reviewers was discussed and a final decision made based on consensus.

Extracted information from each paper was summarized in a table. This information included study design, characteristics of the study population, type and description of intervention/diagnostic test, outcome category (prevention, monitoring/assessment, or treatment), and the results and conclusions from the study. Studies were categorized in diagnostic and intervention studies. Intervention studies were classified according to guidelines from the National Institute for Clinical Excellence.[25]

Results

In total 882 references were identified in the database search of which 83 were considered potentially eligible for inclusion based on assessment of title. Thirty-nine of these 83 references were considered eligible based on assessment of abstract. After full-paper review, 30 papers were selected for final inclusion. Detailed results of these 30 studies are summarized in the table shown in Appendix B. Table 1 shows the distribution of included papers across different types of telemedicine approaches and different outcome categories (i.e. prevention, monitoring/assessment, or treatment). Most studies involved assessing the area of a foot ulcer.

The four main telemedicine approaches that were evaluated were:

Dermal thermography: Infrared thermography: technology detecting radiation in the infrared range of the electromagnetic spectrum (thermal sensors capture the emitted

or reflected thermal radiation from objects), and liquid-crystal thermography: technology using (layers of) thermochromic liquid crystals, each changing colours within a determined temperature interval which can be read and which provides information concerning the temperature distribution
Hyperspectral imaging: technology that uses the near-infrared range of the electromagnetic spectrum to quantify tissue oxygenation by measuring oxygen delivery (oxyhemoglobine) and oxygen extraction (deoxyhemoglobine), and to generate maps of microcirculatory changes at depths of up to several centimetres. Medical applications using hyperspectral imaging are often called near-infrared spectroscopy.
Photographic imaging: digital photography
Audio/video communication: telephone, video-telephone, and videoconference modules

Dermal thermography

Most papers on telemedical applications for the diabetic foot are on dermal thermography and deal with the prediction and prevention of neuropathic foot ulceration (Table 1).

On infrared thermography, the literature search identified three randomized controlled trials (RCT), two longitudinal studies, one retrospective (cohort) study, one diagnostic study, and one case report. Many of these studies were from the same research group. In a longitudinal study of 25 patients who were measured with a hand-held infrared skin temperature probe (Exergen DT 1001®), Armstrong and Lavery measured a significantly higher temperature in the foot with an ulcer than in the contralateral foot, both at initial presentation and after healing of the ulcer.[26] Using the same probe, the same authors showed in a retrospective study that temperature differences between the left and right foot increased from patients with asymptomatic sensory neuropathy (0.1°F), to patients with new-onset neuropathic ulcers (5.6°F), to patients with Charcot arthropathy (8.3°F).[27] In a large longitudinal study on 332 patients with diabetic foot infection, Armstrong *et al*. used the Thermo-Trace™ hand-held infrared probe and showed no significant change in left-right foot temperature difference between the start of intravenous therapy and at discontinuation of therapy (a mean 11.7 (SD 7.5) days after baseline): 2.81°F (SD 5.75) versus 2.43°F (SD 4.84) respectively.[28]
In the 3 RCTs, patients randomized to the intervention group measured their sub-surface foot temperatures at-home on a daily basis using the TempTouch® (Xilas Medical) infrared probe. In case a temperature difference >4°F between corresponding regions in the left and right foot occurred for two consecutive days, participants were instructed to contact the study nurse and dose their activity until temperatures normalized. The control group had standard follow-up and treatment, which did not include foot monitoring with infrared thermography. Ulceration rate after 6 months follow-up was 2% in the intervention group versus 20% in the control group (p=0.01, OR=10.3) in Lavery *et al*.[24] For the other two RCT's these rates were 4.7% vs. 12.2%, respectively (p=0.038, OR=3.0) in Armstrong *et al*.[23], and 8.5% vs. 29.3%, respectively (p=0.008, OR=4.48) in Lavery *et al*.[9] In the latter RCT, an

additional control group of high-risk diabetic patients performed self-assessment of the plantar foot twice a day using a mirror. Ulceration rate in this group was 30.4%, which was significantly higher than in the intervention group (p=0.0061, OR=4.71).[9] The same study showed a higher voluntary withdrawal from the study in the intervention group (10.2%) compared with the standard group (5.2%) and group that performed self-assessment (3.6%).
Nagase *et al*. presented the use of infrared thermography as a novel framework of classifying plantar temperature distributions according to the foot angiosome concept.[29] In 129 diabetic patients without a foot ulcer, they showed a wider variation of plantar thermographic patterns compared to 32 non-diabetic healthy volunteers: 87.2% of diabetic patients were variously allocated to 18 out of the 20 categories of temperature distribution compared to 65% of healthy volunteers who were allocated to two typical categories. The more variable thermographic patterns in the diabetes group were explained by the individual irregularity of blood supply at the angiosome level (due to stenosis of arteries or A-V shunt between angiosomes). One case report showed an elevated skin temperature using infrared thermography at the site where osteomyelitis later developed, which was normalized after osteomyelitis resolved.[30]
On liquid-crystal thermography, one cohort study was found on ulcer prevention and one diagnostic study on assessing/monitoring ulcers. Benbow et al. found a significantly higher mean plantar foot temperature in neuropathic diabetic patients who went on to develop a plantar foot ulcer, compared to patients who did not develop an ulcer (30.5°C vs. 27.8°C, p<0.01).[31] Roback et al. assessed left-right foot temperature differences based on visual assessments of colour differences using the SpectraSole Pro 1000 and compared this,with clinical examination (standard examination according

Table 1. Distribution of included papers in the review across type of technology and across outcome categories

	Number of papers	Reference
Type of technology		
Dermal thermography		
Infrared	8	9, 23, 24, 26-30
Liquid-crystal	2	31, 32
Hyperspectral imaging	7	33-39
Photographic imaging	9	17-22, 40-42
Audio/video (+image)	4	14-16, 43
Outcome		
Ulcer prevention	8	9, 21, 23, 24, 27, 29, 31, 39
Ulcer assessment	16	17-20, 22, 26, 32-38, 40-42
Infection assessment	2	28,30
Ulcer treatment	4	14-16, 43

to Swedish guidelines). Foot status was classified according to the severity of problem areas (group 1: no visible problem areas, 2: one or few minor problems, 3-5: several and/or large problem areas). Twenty-seven clinical examinations were classified in group 3-5, of which 74% were identified by the measured temperature distribution of the feet.[32]

Hyperspectral imaging

One cohort study, five longitudinal studies, and one retrospective study on hyperspectral imaging were identified in our search.[33-39] Most studies were on assessing and monitoring foot ulcers for healing purposes[33-38] and one study on the prediction of foot ulceration[39]. These studies used hyperspectral imaging to assess tissue oxygenation at or near the ulcer according to measured oxyhemoglobin and deoxyhemoglobin levels. From these levels, a healing index was calculated to determine the potential for healing. Three studies monitored the healing of between 21 and 73 diabetic foot ulcers and reported sensitivity levels between 80% and 93%, specificity levels between 74% and 86%, and positive predictive values between 82% and 93%.[33,35,38] Three other studies observed a significant reduction in oxyhemoglobin level prior to ulcer closure in those ulcers that healed, compared to unchanged oxyhemoglobin levels in ulcers that did not heal.[34,36,37] A negative slope in the rate of change of oxyhemoglobin concentration was indicative for healing in all foot ulcers. The retrospective study analysed 21 sites that had ulcerated during follow up and showed that the occurrence of these ulcers could be predicted using hyperspectral imaging with a sensitivity of 95% and specificity of 80% in a mean of 58 days before skin breakdown became apparent.[39]

Photographic imaging

Six diagnostic studies and three longitudinal studies on the use of digital photographic imaging were identified in our search. Eight studies were on the assessment of foot disease[17-20,22,40-42], one study on ulcer prevention[21]. Four papers report on the accuracy with which the *ulcer area* is measured using digital photography as compared with live assessments.[22,40-42] Two of these studies show a strong association between ulcer area measurements from photographs and from live assessments based on ulcer boundary drawings, with correlation coefficients >0.95.[22,40] The two other studies showed an inter-observer variation in ulcer area measurements from photographs of 16% and 11.9%, compared to 27% based on live assessments.[41,42] Intra-observer variation showed to be 3.3%.[41]

Two photographic imaging devices have been designed to monitor the diabetic foot in the home environment: Bus et al. showed that with using a photographic foot imaging device a good agreement between live and photographic assessment and between repeated photographic assessments could be obtained for diagnosis of different (pre-) signs of ulceration.[17] This was further elaborated on by Hazenberg et al. who showed assessments from photographs to be in good agreement with live assessment for the presence of ulcers (kappa 0.87), abundant callus (kappa 0.61), and for absence of any sign (kappa 0.83). Outcomes were also reliable between repeated photographic assessments (kappa 0.70-1.00).[20] Inter-observer agreement for photographic assessments was good for ulcer and for absence of signs, and moderate for abundant callus.[20] In another study by the same group, Hazenberg *et al*. showed a good feasibility of using the photographic foot imaging device in the home environment: patient adherence was high, referrals based on photographic assessment justified, perceived usability was good.[21] In two papers, Foltynski *et al*. reports descriptive data of at-home usage of the TelediaFos system, such as the total number of assessed wound pictures, the length of the monitoring period, and change in ulcer area after four and 12 weeks follow up.[18,19] Furthermore, patients perceived the usability of the system between moderate and good[19].

Video/audio communication

The use of video and/or audio communication to support at home treatment of diabetic foot ulcers was assessed in one case-control study[43], and three case series[14-16]. One case-control study showed no significant difference in ulcer healing between weekly telemedicine consultations using video interaction and face-to-face treatment: in 12 weeks, 75% of ulcers healed in the intervention group versus 81% (p=0.546) in the control group.[43] The 3 small case series assessed the feasibility of using a mobile phone to link the physician and home visiting nurse to support ulcer treatment.[14-16] Clemensen and Larsen *et al*. reported that patients were satisfied with the treatment support because it was timesaving, nurses were capable of handling the technical skills, and physicians found the equipment easy to use and feasible to prescribe treatment from a distance.[14] In the two other studies, the same authors described details regarding the video consultation procedure: duration ranged from 5-18 minutes, major audio problems occurred 3 times of 15 consultations, and connection problems occurred 7 times.[16] Furthermore, patients were satisfied and felt safe with this remote treatment, the visiting nurse felt supported, and physicians felt a good basis for decisions with using the tool.[15]

Discussion

This systematic review discusses the existing medical-scientific literature on (potential) telemedical approaches for the diabetic foot. The findings of this review show that there are several promising technologies available which may be of additional value in the prevention, assessment, and/or treatment of diabetic foot disease. Most of them, however, are still in an early stage of development and require a stronger scientific base before they can be deployed in the patient's home as telemedical tool.

Dermal thermography

Three randomized controlled trials showed that home monitoring of foot temperatures using infrared thermography can contribute to significantly reducing the incidence of diabetic foot ulcers.[9,23,24] In all three trials, intervention and control groups were similar at baseline, care providers and outcome assessor were blinded to treatment allocation, study groups were treated equally except for the intervention, and drop-out was <20%. In two of the RCT's, the method of randomization was described and an independent person assigned patients.[9,23] Patients were not blinded to the intervention. Our conclusions on effectiveness confirms those of a recent systematic review and meta-analysis that the use of at-home temperature-monitoring is an effective way to predict and prevent diabetic foot ulceration.[44] Effect sizes found were large, among the largest of any intervention that has been assessed for prevention of foot ulcers in diabetes.[1] It is therefore remarkable and rather disappointing to observe that such monitoring is hardly adopted in clinical practice. There may be some scepticism among physicians regarding the usability and effect of such at-home temperature monitoring in their own clinical and geographical settings. Furthermore, in several settings, reimbursement issues for implementing the approach may play a role. The 3 RCT's on the topic originate from the same research group. Furthermore, no data has been found on the usability of the infrared temperature probe used. One RCT reported reasons for withdrawal from the study (highest in the intervention group) with 'too much to do' being the main reason.[9] Except local cost calculations of foot complications[45], no data have been published on cost-effectiveness of the approach. Confirmation of the positive outcomes on at-home dermal thermography in well-designed trials in other settings by other authors is needed, together with proving the usability and cost-effectiveness of the approach to improve the widespread acceptance and use in diabetic foot care of this promising approach.

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Liquid-crystal thermography may be a promising tool for the prediction of diabetic foot ulceration.[31] However, in this cohort study by Benbow et al. only baseline foot temperatures were measured and compared between feet that ulcerated and those that didn't during follow up. A threshold temperature that may predict ulceration could not be established from this data. Furthermore, conclusions only apply to the group without peripheral vascular disease (PVD), because in the group with PVD only one ulcer developed. Although Roback *et al*. concluded that liquid-crystal thermography is easy to use and provides valuable diagnostic information in early stages of foot disease,[32] foot complications were poorly defined, and no data was found on usability. Liquid-crystal thermography is easy to use and at low cost. However, the thermometers used in above studies were quite large, while smaller thermometers exist. Future studies should assess the effectiveness of the approach in the home setting.

Hyperspectral imaging

Six studies on the use of hyperspectral imaging in foot disease showed that this technique can accurately predict the healing of diabetic foot ulcers and therefore seems promising to support treatment of foot disease. However, most studies included only a small number of ulcers, and treatment or follow-up strategies that influenced healing and outcome were not reported.[33,34,36,37] In one study reporting the results of a large sample size (66 patients, 54 ulcers), the type of ulcer was not defined.[35] Ulcer healing is different in (neuro-)ischemic or infected ulcers than in neuropathic ulcers, which may affect the predictability of healing with hyperspectral imaging. A retrospective study on the same group of 66 patients, of which 21 went on to develop an ulcer, showed that hyperspectral imaging can also accurately predict the occurrence of foot ulcers, even 58 days in advance of tissue damage.[39] Although the authors concluded that the use of hyperspectral imaging can possibly prevent foot complications, such statements need to be supported by well-designed clinical studies.[39] Thus, clinical effectiveness studies are needed. Furthermore, hyperspectral imaging is currently still an experimental and expensive technique, only suitable possibly for a clinical hospital setting to support treatment of foot ulcers in diabetes patients. Applications for the home environment are far from being developed, and first must be proven cost-effective to be implemented in foot care for high-risk diabetic patients.

Photographic imaging

Photographic imaging of the foot has been mainly used for the diagnosis of ulcers and pre-ulcerative lesions, and to measure ulcer area.[17,20,22,40-42] Three studies on ulcer area measurements included a substantial number of ulcers (30-36) to draw relevant conclusions from[22,40,42], whereas one study included only three ulcers[41]. Two diagnostic studies showed robust data on the diagnosis of ulcers and callus[17,20], however included too few patients to reliably assess other important signs such as blisters, fissures and erythema. The photographic foot imaging device and TeleDiafos system both showed to be feasible for use in the home environment. Feasibility analysis with the TeleDiafos system was assessed in a small group of relatively young patients and patient characteristics were not reported.[18,19] The feasibility study on the photographic foot imaging device included a larger patient sample, but the 4 month follow-up with the system did not lead to a sufficient number of severe complications to draw robust conclusion on efficacy of the system. [21] The limitations of both systems are that only the plantar foot surface is assessed. Future designs of the system should involve dorsal foot imaging since many ulcers are not plantar. Future research should study the validity and reliability of assessing blisters, fissures and erythema as precursor to foot infection. And also with photographic foot imaging, the (cost-) effectiveness of the approach needs to be proven.

Video/audio communication

Video and audio communication as telemedical support tool has received only little attention in the scientific literature.[14-16,43] The treatment of foot ulcers may benefit from this approach and the approach was found to be feasible with potential to expand the delivery of specialized foot care to rural areas, but mostly only small descriptive studies were conducted.[14-16,43] On effectiveness, one case-control study showed no significant difference in healing time and number of ulcers healed between treatment with support of real-time interactive video consultations, and standard treatment.[43] Well-designed studies on the feasibility and effectiveness of video/audio communication are still needed. A potential disadvantage of video or audio consultation, compared for example with photographic imaging, is that both patient and physician need to be available at the same time. Future studies should further explore the value of this approach to telemedical health care for the diabetic foot.

Cost aspects

For all described telemedical approaches, the benefit for the patient and the health care system will have to be evaluated relative to the investments needed to setup and use the telemedical system. Cost-effectiveness is the key aspect here that will determine potential for acceptance and implementation in diabetic foot care. Some telemedical systems are low in cost, such as infrared thermometers. Other systems that in the future may serve a telemedical purpose are expensive, such as hyperspectral imaging. However, the prevention of a foot ulcer or an amputation may save the health care system between US$ 5,000 and 40,000 per event and therefore, effective telemedical approached have a good chance of being cost-effective for the management of diabetic patients with a high-risk of developing serious foot complications.

If proven (cost-) effective and if implemented successfully, telemedical support in the screening, monitoring or treatment of diabetic foot disease can improve patient mobility, autonomy, and health-related quality of life, in particular for patients who may be best served with telemedical support such as those that live alone, have cognitive, visual or physical impairments, or lack knowledge about the disease. Due to the further increasing global internet penetration, such telemedical tools may also serve those patients living in remote areas with limited and time-consuming access to health-care services.

Conclusion

This systematic review shows that the use of and knowledge on telemedicine for the diabetic foot is still in its infancy, but several promising approaches exist that have been shown to be effective in the prevention, monitoring or treatment of diabetic foot disease. For some of these approaches, feasibility and effectiveness are not known yet, while for all approaches it is important that their cost-effectiveness in managing the diabetic foot is demonstrated to achieve wide acceptance and implementation in diabetic foot care.

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Appendix A

Search string used for the Medline database

(“Diabetic Foot”[Mesh] OR“Foot ulcer”[Mesh] OR diabetic foot OR foot ulcer*) AND ("Telemedicine"[Mesh] OR“Home care services” [Mesh] OR "Telenursing"[Mesh] OR“Remote consultation”[Mesh] OR“Community medicine”[Mesh] OR telemed* [tiab] OR tele-med* [tiab] OR telenurs* OR home-environment OR home monitor* OR home-monitor* OR telecommunication* [tiab] OR mobile health OR telerehabilitation [tiab] OR telecare [tiab] OR tele-care [tiab] OR tele-home [tiab] OR telehome [tiab] OR e-health [tiab] OR e health [tiab] OR tele-health [tiab] OR telehealth [tiab] OR remote assessment [tiab] OR remote treatment [tiab] OR remote consultation [tiab] OR telemonitor* [tiab] OR “Cellular phone”[Mesh] OR “Photography”[Mesh] OR photograph* OR“Image processing”[Mesh] OR image processing OR imaging [tiab] OR “Temperature”[Mesh] OR temperature* OR “Thermography”[Mesh] OR thermograph* OR thermometer [tiab] OR “Infrared”[Mesh] OR infrared [tiab] OR video consultation*)

Appendix B

Summary of data from the included papers in the systematic review

Reference	Study design	Study population and characteristics	Intervention (I) and control (C) conditions	Outcome category	Results	Conclusion (C)/ Limitations (L)
			Dermal thermography: *infrared*			
Armstrong *et al.*, 1996[26]	Longitudinal	Patients: 25 with a neuropathic plantar foot ulcer Study duration: 4 months after return to shoe gear Lost to study: 0	Dermal thermometry (Exergen DT 1001®)	Ulcer assessment Feasibility	Temperature difference between foot with ulcer and contralateral foot at initial presentation: 91.1°F vs. 84.2°F (P < 0.0001, 95%CI 5.3 – 8.5 During healing: no significant difference between foot with ulcer and contralateral foot: 83.4°F vs. 85.3°F (t=-1.35) 95%CI -7.5 – 3.9 Vibration perception > 45 V: wider temperature gradients (P = 0.007) Brachial indices < 0.60: wider temperature gradients (P = 0.01)	C: significant difference in skin temperature between foot with ulcer and contralateral foot at presentation, but not during healing and larger in patients with high degrees of neuropathy or peripheral vascular disease L: unclear inclusion of type of ulcers: included patients had neuropathic ulcers, but apparently also (neuro-) ischemic ulcers (brachial indices < 0.60)
Armstrong *et al.*, 1997[27]	Retrospective Cohort	Patients: 143 distributed over 3 groups: 1. Asymptomatic peripheral sensory neuropathy (78) 2. New-onset neuropathic ulcers (44) 3. Charcot artropathy (21) Study duration: presented on diabetic foot centre 1993 - 1995 mean of 22.1 months (SD:6.4)) Lost to study: 0	Dermal thermometry (Exergen DT 1001®)	Ulcer prevention Feasibility	Temperature difference between foot at time of diagnosis: 1. 0.1°F P > 0.05 2. 5.6°F P < 0.0001 3. 8.3°F P < 0.0001 5 re-ulcerated, after initial healing (mean 12.2 months) with increase of temperature difference between foot: 89.6°F vs. 82.5°F P = 0.003	C: at time of diagnosis, significant difference in skin temperature between foot with neuropathic ulcers and Charcot L: no uniform follow up (retrospective study) L: no ischemic ulcers

Lavery *et al.*, 2004[24]	RCT	Patients: I : 41, C: 44 at high risk (history foot ulcer or lower-extremity amputation, or peripheral sensory neuropathy, or foot deformity) Study duration: 6 months Lost to study: 0	I : dermal thermometry, reduce walking activity and contact study nurse in case difference in skin temperature between foot was >4°F (TempTouch®) C: standard therapy	Ulcer prevention Effectiveness	Proportion developing foot complications: I : 1/41 (2%), one ulcer C : 9/44 (20%), 7 ulcers, 2 Charcot P = 0.01 I vs. C: C: odds ratio 10.3 (95%CI 1.2-85.3) Quality of life (SF-36): I vs. C: no difference	C: at-home self-monitoring with dermal thermography may prevent foot complications in high risk patients L: method of randomization not reported L: assignment method not reported L: patient not blinded to intervention L: singe-centre L: compliance not reported
Armstrong *et al.*, 2006[28]	Longitudinal	Patients: 362 with diabetic foot infection: double blind comparison of intravenous ertapenem or piperacillin / tazobactan (SIDESTEP trial) Study duration: discontinuation of intravenous antibiotics Lost to study: I: 30	Dermal thermometry (TempTouch®)	Infection assessment Feasibility	Change mean difference in skin temperature between foot, between baseline and discontinuation of intravenous antibiotic therapy (mean of 11.7 (SD 7.5) days after baseline): -0.37°F P = 0.225 (95%CI = -0.98, 0.23) Correlation baseline skin temperature differential with: White blood cell count r: 0.058 C-reactive protein r: 0.148 Erythrocyte sedimentation rate r: -0.002 Infection severity score (Texas*) r: 0.067 Patients with skin temperature differential >10°F had lower clinical response than those with <10°F 81.4% vs. 94.3% P = 0.007	C: mean difference in skin temperature between infected an non-infected limbs does not predict the severity of an infection or the outcome of treatment C: no correlation between baseline skin temperature differential with white blood count, C-reactive protein, erythrocyte sedimentation rate, or infection severity score L: short follow up after baseline assessment. L: clinical response not defined

Armstrong *et al.*, 2007[23]	RCT	Patients: 225, (number per group not reported) with high risk (history foot ulcer or lower-extremity amputation, or peripheral sensory neuropathy, or foot deformity), DM II Study duration: 18 months Lost to study not reported	I: dermal thermometry (TempTouch®) C: standard therapy	Ulcer prevention Effectiveness	Proportion patients developing a foot ulcer: I: 4.7% C: 12.2% I vs. C P = 0.038 OR = 3.0 (95%CI = 1.0 – 8.5)	C: temperatures differential between feet may predict neuropathic ulceration L: patient not blinded to intervention L: drop-outs not reported L: compliance not reported L: veterans only
Lavery *et al.*, 2007[9]	RCT	Patients: I : 59, C1 : 58, C2: 56 with high risk for ulceration Study duration: 15 months Lost to study 22	I : dermal thermometry, reduce walking activity and contact study nurse in case temperature differential was >4°F (TempTouch®) C1: standard therapy C2: structured foot examination (+ self-assessment twice a day with a mirror)	UP Effectiveness	Proportion patients developing a foot ulcer: I : 8.5% C1 : 29.3% C2 : 30.4% I vs. C1 P = 0.008 OR = 4.48 (95%CI 1.53 – 13.1) I vs. C2 P = 0.0061 OR = 4.71 (95%CI 1.60 – 13.85)	C: home temperature monitoring may reduce the risk for foot ulcers L: patient not blinded to intervention L: drop-outs were not analysed
Nagase *et al.*, 2011[29]	Diagnostic	Patients: 129 non-ulcer diabetic patients, 32 healthy volunteers Study duration: 161 examinations Lost to study: 0	Dermal thermometry – imaging of temperature distribution of plantar skin using angiosome concept (20 different categories of plantar thermographic patterns) (Thermotracer - TH5108ME)	Ulcer prevention Descriptive	Variation of plantar thermographic patterns in healthy persons and non-ulcer diabetic patients Diabetic patients: 87.2% variously allocated to 18 to 20 categories Healthy persons: 65% was allocated to 2 typical categories	C: Wider variation of plantar thermographic patterns in diabetic patients L: small number subjects control group and diabetic group was significant older L: unclear relevance clinical use (complicated method)

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Oe *et al.*, 2012[30]	Case report	Patients: 1 with diabetes mellitus type 2 and foot ulcer with osteomyelitis Study duration: 195 days	Dermal thermometry (Thermotracer TH7800N)	Infection assessment Descriptive	Skin temperature was elevated with osteomyelitis and normalised after resolving of osteomyelitis	C: thermography may be useful for screening osteomyelitis L: one case
Dermal thermography: *liquid-crystal thermography*						
Benbow *et al.*, 1994[31]	Cohort	Patients: 50 with neuropathic plantar foot ulcers with PVD (n=20) without PVD (n=30) Study duration: mean 3.6 years (range 30.0 – 4.1) Lost to study: 12 (7 in PVD group)	Liquid-crystal thermography at baseline (Novatherm)	Ulcer prevention Feasibility	Mean plantar foot temperature (MFT) ulceration vs. non-ulceration feet: PVD-: 7 plantar ulcers MFT 30.5°C vs. 27.8°C (P<0.01) PVD+: 1 plantar ulcer	C: liquid-crystal thermography may predict neuropathic plantar foot ulceration L: small number of events L: small size PVD group L: only thermography at baseline
Roback *et al.*, 2009[32]	Diagnostic	Patients: 65 foot related problems not reported Study duration: 69 examinations Lost to study: 0	Liquid-crystal thermography instrument (SpectraSole Pro1000)	Ulcer assessment Validity	Proportion identification of foot problems by liquid-crystal thermography compared with clinical assessment: 74% was identified which was clinically defined as several and / or large problem areas (n=27):	C: liquid-crystal thermography provides valuable diagnostic information in early stages of foot disease L: poor definition of categories / groups of foot problems L: according to the investigators the technique was easy and quick, but no data was reported regarding usability
Hyperspectral imaging						
Khaodhiar *et al.*, 2007[33]	Cohort	Patients: 37 1. 10 type 1 DM with 21 foot ulcers 2. 13 type 1 DM without ulcers 3. 14 nondiabetic control subjects Study duration: 6 months Lost to study: 0	Hyperspectral technology (HT); quantification of tissue oxy- (HT-oxy) and de-oxyhemoglobine (HT-deoxy)	Ulcer assessment Validity	Association between HT measurements (HT-oxy and HT-deoxy) and wound healing HT-oxy and HT-deoxy were lowest in nonhealing ulcers: Se = 93% (95%CI 66-100) Sp = 86% (95%CI 42-100) PPV = 93% (95%CI66-100) NPV = 78% (95%CI 56-93) P < 0.001	C: hyperspectral imaging can predict ulcer healing and can assist in the management of diabetic foot ulceration L: small size of subjects with ulcers L: multiple ulcers at same subjects, which may indicate ischemia L: treatment strategies not reported

Nouvong *et al*., 2009[35]	Longitudinal	Patients: 66 with 73 foot ulcers Study duration: 24 weeks Lost to study: 22	Hyperspectral imaging	Ulcer assessment Validity	Healing index to predict healing for healed and non-healed ulcers Se = 80% Sp = 74% PPV = 90%	C: hyperspectral imaging may predict diabetic foot ulcer healing L: type of ulcers (at inclusion) not reported L: treatment strategies not reported
Papazoglou *et al*., 2009[36]	Longitudinal	Patient: 11 with 11 foot ulcers Study duration: 10-61 weeks Lost to study: 0	Diffuse photon density wave (DPDW) methodology of near-infrared spectroscopy (NIRS) measurements of subsurface oxygenated haemoglobin concentration and total haemoglobin concentration in or around the wound	Ulcer assessment Validity	Change in optical absorption coefficient, oxygenated haemoglobin, and total haemoglobin: Healed ulcers: reduction Non-healed ulcers: change nearly zero $P < 0.05$	C: DPDW / NIRS can differentiate healing from non-healing L: small sample size L: type ulcers (at inclusion) not reported L: treatment strategies not reported
Neidrauer *et al*., 2010[34]	Longitudinal	Patients: 16 with 16 neuropathic foot ulcers, ABI > 0.75 Study duration: maximum of 20 visits (weekly), or healing / amputation Lost to study: 0	Diffuse photon density wave methodology of near-infrared spectroscopy (NIRS) measurements of subsurface oxyhemoglobin in or around the wound	Ulcer assessment Validity	Change in oxyhemoglobin in: Healed ulcers: reduction prior to closure Non-healed wounds: remained elevated	C: evaluation of diabetic foot ulcers using NIRS may provide an effective measurement of ulcer healing L: small sample size L: treatment strategies not reported
Weingarten *et al*., 2010[37]	Longitudinal	Patients: 16 with 16 neuropathic foot ulcers, ABI>0.75 Study duration: maximum of 20 visits (weekly), or healing / amputation Lost to study: 0	Diffuse photon density wave methodology of near-infrared spectroscopy (NIRS) measurements of subsurface oxyhemoglobin in or around the wound	Ulcer assessment Validity	7 ulcers healed, 6 limbs were amputated, 3 ulcers remained open Change in oxyhemoglobin in: Healed ulcers: reduction prior to closure Non-healed wounds: remained elevated	C: evaluation of diabetic foot ulcers using NIRS may provide an effective measurement of ulcer healing L: small sample size L: treatment strategies not reported

Yudovsky *et al*., 2011[39]	Retro	Patients: 66 Study duration: not reported Lost to study: 0	Hyperspectral imaging	Ulcer prevention Validity	21 sites ulcerated Prediction of the risk of diabetic foot ulcers formation Se = 95% Sp = 80% 58 days before tissue damage is apparent	C: hyperspectral imaging can assess the risk of diabetic foot ulcer development L: demographic information not reported. L: type ulcers (at inclusion) not reported L: treatment strategies not reported
Weingarten *et al*., 2012[38]	Longitudinal	Patients: 46 with 46 neuropathic foot ulcers, ABI>0.75 Study duration: maximum of 20 visits (weekly), or healing/amputation lost to study 0	Diffuse photon density wave methodology of near-infrared spectroscopy (NIRS) measurements of subsurface oxyhemoglobin and total hemoglobin in or around the wound	Ulcer assessment Validity	Prediction of wound healing: association between NIRS measurements of oxyhemoglobin and total hemoglobin and wound healing in 4 weeks: PPV = 82% Se = 0.90 Sp = 0.86 $P < 0.002$	C: possible to predict healing in 4 weeks using NIRS; can provide guidance toward the continuation of costly treatments L: treatment strategies not reported
			Photographic imaging			
Rajbhandari *et al*., 1999[42]	Diagnostic	Patients: 18 with 30 foot ulcers Study duration: 10 weeks	Foot ulcer area measurements using digital imaging technique, computer software compared with traditional tracing (1-mm2 graph paper) 3 observers	Ulcer assessment Validity	Inter-observer variation (mean coefficient of variation) Digital imaging: 16% Traditional tracing: 27% $P = 0.05$	C: reproducibility of digital method is superior to traditional tracing: usable for monitoring of wound healing L: no data reported regarding authors conclusion that digital imaging is also faster and easier to use
Bowling *et al*., 2009[40]	Diagnostic	Patients: 31 with 36 foot ulcers Study duration: multiple experiments	Foot ulcer area measurements using 3D digital imaging technique, compared with traditional elliptical measurement	Ulcer assessment Validity	Strong correlation between digital measurements and traditional hand-measured estimates of ulcers r: 0.961 $P < 0.001$	C: accurate digital ulcer area measurement in-depth analysis L: number of observers not reported

Bus *et al.*, 2010[17]	Diagnostic	Patients: 20 at high risk with variety of plantar foot problems Study duration: multiple experiments Lost to study: 0	Development of a photographic foot imaging device – two phase study to improve agreement between live and photographic assessment by optimizing illumination settings Phase 1 and 2: 4 observers	Ulcer assessment Descriptive	Agreement between live and photographic phase 1: 56-92% phase 2: 74-100%	C: important clinical signs of diabetic foot can be diagnosed from high quality photographs L: plantar surface only L: ulcer and abundant callus only, no inclusion of other pre-signs of ulceration or infection
Hazenberg *et al.*, 2010[20]	Diagnostic	Patients: 32 at high risk with variety of plantar foot problems Study duration: multiple experiments Lost to study: 0	Photographic imaging device (PFID) – photographic imaging 4 observers	Ulcer assessment Validity, reproducibility	Agreement between live vs. photographic assessment: ulcer very good (k =0.97) Absence of signs very good (k=0.83) Abundant callus good (0.61) between photographic assessments: good to excellent for all outcomes (k=0.70-1.00) between photographic assessments: ulcer good (k=0.72-0.88) absence of signs good (0.59-0.75) callus moderate to good (0.48-0.73)	C: ulcers and pre-ulcerative lesions diagnosed valid and reliable using PFID L: plantar surface only L: ulcer and abundant callus only, no inclusion of other pre-signs of ulceration or infection
Bowling *et al.*, 2011[41]	Diagnostic	Patients: phase 1: 3 foot ulcers phase 2: 20 ulcers Study duration: multiple experiments	3D digital optical imaging Phase 1: 5 observers Phase 2: one onsite observer, 3 remote observers answering clinical questions regarding the ulcer	Ulcer assessment Validity	Phase 1: agreement (variation) inter- and intra-observer variation of image wound area measurements inter-: 11.9% intra-: 3.3% Phase 2: agreement remote vs. onsite assessment: overall good	C: reliable assessment wound area L: one observer for onsite assessments of the ulcers as 'criterion standard' vs. 3 observers for 3D assessments L: small sample size for phase 1 – area measurements

Foltynski *et al.*, 2011[19]	Longitudinal	Patient: 10 with neuropathic foot ulcers Study duration: 3 months Lost to study: 0	Imaging system – TeleDiaFos / patient module (PM) – in the home environment: sends images of plantar foot, blood pressure, glucometer	Ulcer assessment Feasibility	Description imaging process mean (SD): nr. images transmitted: 27.1 (17.5) duration of use (days): 91 (21.1) average time (days) between image transfer: 4.5 (2.5) single case results of area measurements Usability on 4 domains – mean (range) on VAS: 6.33-8.22 (10 = excellent)	C: TeleDiaFos useful and accepted by patients a physicians L: small sample size L: method wound area measurements not reported L: missing data or transfer failures not reported L: no elderly (mean age (SD) 57.2 (6.7) L: limited to plantar surface
Foltynski *et al.*, 2011[18]	longitudinal	Patients: 10 with neuropathic ulcers Study duration: 3 months Lost to study: 0	Imaging system – TeleDiaFos / patient module (PM) – in the home environment: sends images of plantar foot, blood pressure, glucometer	Ulcer assessment Feasibility	Description imaging process (range) monitoring period (days): 54-131 nr. assessed wound pictures: 9-53 change in area after: 4 weeks: between -63,2% and 10.4% 12 weeks: between -98.2% and 83.8%	C: TeleDiaFos can be used at home C: TeleDiaFos enables assessment of wound healing L: no patient characteristics L: small sample size L: limited to plantar surface
Ladyzynski *et al.*, 2011[22]	Diagnostic	Patients: 23 with 33 plantar foot ulcers Study duration: multiple experiments Lost to study: 0	Imaging system – TeleDiaFos / patient module (PM) for ulcer area measurements, compared with 3 reference methods: (elliptical, Visitrak, Silhouette) 1 observer	Ulcer assessment Validity	Correlation Elliptical r: 0.949 Visitrak r: 0.985 Silhouette r: 0.987	C: effective wound monitoring using TeleDiaFos L: one observer only L: limited to plantar surface L: tracing of a ulcer area by the operator using the software only possible after debridement in case ulcer boundaries were not well-defined

Hazenberg *et al.*, 2012[21]	Longitudinal	Patients: 22 at high Study duration: 4 months Lost to study: 0	Photographic imaging device (PFID) in the home environment, sends photographs automatically of plantar surface to diabetic foot specialist	Ulcer prevention Feasibility	Description of imaging process: 12% missing data (122 of 1022 imaging sets) 34/35 referrals were justified Usability on 10 domains – mean (range) on VAS: 7-9 (10 = excellent) Quality of life (EQ-5D) on VAS: baseline: 7.5 end of follow-up: 7.9 P = 0.31	C: PFID is feasible in the home environment L: small number of events L: treatment regimens not reported L: limited to plantar surface
			Audio /video			
Wilbright *et al.*, 2004[43]	CC	Patients: I : 20, C : 120 with neuropathic foot ulcers Study duration: 12 weeks Lost to study: I : 3	I: real-time interactive video (Polycom ViewStation video conferencing) and handheld camera to link physician and wound care nurse using management algorithm. C: face-to-face treatment - regional diabetes foot program (DFP)	Ulcer treatment Effectiveness	I vs. C healing time: 43.2 vs. 29.3 days P = 0.828 wounds healed in 12 weeks: 75% vs. 81% P = 0.546 Healing time ratio: 1.4 vs. 1.0 P = 0.104 I : 10 patients required single visit to DFP for offloading device	C: no difference between telemedicine and DFP treatment; telemedicine is feasible L: small size telemedicine group L: treatment options (regarding offloading) not comparable in both groups, 50% of intervention group visited outpatient clinic once
Clemensen *et al.*, 2005[14]	Case series	Patients: 5 with foot ulcers Study duration: 3 consultations per patient Lost to study: 0	Teleconsultations using a videophone, supporting a visiting nurse Internet-based ulcer record	Ulcer treatment Feasibility	Experience based anecdotes: experts: had sufficient basis for coordinated treatment nurses: capable handling technology patients: satisfied with course of treatment	C: expert coordinated treatment in the home can be performed L: small sample size L: descriptive data only
Larsen *et al.*, 2006[16]	Case series	Patients: 5 with foot ulcers Study duration: 3 consultations per patient Lost to study: 0	Teleconsultations using a videophone, supporting a visiting nurse Internet-based ulcer record	Ulcer treatment Feasibility	Description consulting process: duration (range): 5 – 18 min Connection problems: minor 3/15, some 3/15, major 1/15 audio problems: major 3/15	C: treatment of diabetic foot ulcers may benefit from telemedicine L: small sample size L: descriptive data only L: no clear definition of connection problems which occurred

Clemensen *et al.*, 2008[15]	Case series	Patients: 5 with foot ulcers Study duration: 2 years Lost to study: 0	Teleconsultations using a videophone, supporting a visiting nurse Internet-based ulcer record	Ulcer treatment Feasibility	Experience based anecdotes: nurse: satisfied decision making and felt secure at a distance physician: satisfied and felt supported by visiting nurses patient satisfaction: felt secure, improvement because of autonomy	C: treatment of diabetic ulcers in the home effective by telemedicine L: small sample size L: descriptive data only

* Texas, University of Texas Classification of Diabetic Foot Wounds

Abbreviations per column:

Study design: RCT = randomised controlled study, Cohort = cohort study, CC = case-control study, Longitudinal = longitudinal study, Retrospective = retrospective study, Diagnostic = diagnostic study

Study population and characteristics: DM = Diabetes Mellitus, ABI = ankle-brachial index, PVD = peripheral vascular disease

Intervention and control conditions: DPDW = diffuse photon density wave, NIRS = near-infrared spectroscopy, PFID = photographic imaging device, 3D = three dimensional, PM = patient module

Results outcomes: OR = odds ratio, CI = confidence interval, Sp = specificity, Se = sensitivity, PPV = post predictive value, NPV = negative predictive value, k = kappa

Chapter 6

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Assessment of signs of foot infection in diabetic patients using photographic foot imaging and infrared thermography

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ABSTRACT

Background

Patients with diabetic foot disease require frequent screening to prevent complications and may be helped through telemedical home-monitoring. For this purpose, the goal of this study was to determine the validity and reliability of assessing the presence of diabetic foot infection using photographic foot imaging and infrared thermography.

Methods

In 38 diabetic patients, who presented with a foot infection or were admitted to hospital with a foot-related complication, photographs of the plantar foot surface using a photographic imaging device and temperature data from 6 plantar regions using infrared thermography were obtained. A temperature difference between feet >2.2°C defined a *hotspot*. Two independent observers assessed each foot for presence of foot infection, both live (using PEDIS classification) and from photographs 2 and 4 weeks later (presence of erythema and ulcers). Agreement between live assessment and (the combination of) photographic assessment and temperature recordings was calculated.

Results

Diagnosis of infection from photographs was specific (>85%), but not sensitive (<60%). Diagnosis based on *hotspots* was sensitive (>90%), but not specific (<25%). Diagnosis based on the combination of photographic assessment and thermography was both sensitive (>60%) and specific (>79%). Intra-observer agreement between photographic assessments was good (Cohen's κ 0.77 and 0.52 for both observers).

Conclusions

Diagnosis of foot infection in diabetic patients seems valid and reliable using photographic imaging in combination with infrared thermography. This supports the intended use of these modalities for the home monitoring of high-risk diabetic patients to facilitate early diagnosis of signs of foot infection.

Introduction

Diabetes mellitus is a common cause of lower extremity complications such as foot ulceration, infection and amputation.[1] The prevalence of diabetes and diabetic foot complications will increase rapidly in the following decades, further increasing the patient and economic burden of the disease.[2] To reduce this burden, effective screening and prevention is required.[2] Because foot ulcers are mostly of neurogenic origin, patients do not feel trauma occurring and therefore frequent assessment of foot status is important, both by the healthcare professional and the patient. However, frequent (e.g. weekly) screening by a healthcare professional would be too intrusive and costly. Self-assessment by patients is difficult or impossible, as many patients live alone, have cognitive, visual or physical impairments, or lack knowledge about the disease. Telemedical diagnostic support in the home environment can fulfil the need for frequent foot assessment and may prove to be a missing link in the screening of patients who are at risk for diabetic foot complications.

Several telemedical approaches have been developed to support medical practice, also for the prevention and management of diabetic foot disease. Treatment of diabetic foot ulcers can be supported in the patient's home through mobile phone and video interaction.[3-6] For ulcer monitoring, imaging devices such as optical scanners have been described.[7-9] Our group has developed a photographic foot imaging device (PFID) to use as home monitoring device for the early diagnosis of foot ulcers and pre-ulcerative lesions in diabetic patients.[10] The PFID provides high-quality digital photographs of the plantar foot surface that can be remotely assessed by a foot specialist.[10] Good validity and reliability of diagnosing foot ulcers and abundant callus from photographs produced by the PFID has been proven earlier, as well as good feasibility for using this device as a home-monitoring tool.[11,12]

Little is known about the value of photographic imaging to diagnose signs of foot infection. We have experienced in an earlier study that assessment of erythema, which is one of the cardinal signs of infection, can be difficult from digital photographs, but the validity and reliability have not yet been fully investigated.[10] Increased skin temperature is another important sign of infection and can be assessed using infrared thermography. The home-monitoring of foot temperatures using infrared thermometry has been shown to be effective for diagnosing signs of inflammation in diabetic patients, which, if adequately treated, has shown to prevent foot ulcers.[13-15] Also thermography has its limitations in reliable and valid assessment of foot infection, because it measures only one component of the spectrum of signs of infection, while other conditions related to diabetes such as autonomic neuropathy or vascular disease can also affect foot temperature. Furthermore, infrared thermography may be limited in predicting severity of infection or the outcome of treatment.[16]

Based on these limitations with either photography or thermography, we hypothesize that the combination of the two may improve the remote diagnosis of diabetic foot infection. If proven effective, such tools may be helpful to monitor patients in their home environment and contribute to adequate screening of patients who are at high risk of foot disease. The aim of this study was to determine the validity and reliability of diagnosing signs of diabetic foot infection based on assessments from digital photographs and infrared thermography, and the combination of these two.

Methods

Subjects

A convenience sample of 38 patients (31 men; mean (SD) age 65 (11) years) participated in this study. Patients were consecutive patients diagnosed with diabetes mellitus who presented at the outpatient clinic with a foot infection, or who were admitted to our multidisciplinary inpatient clinic with foot-related complications (i.e. foot ulcer, necrosis or Charcot foot, with or without suspicion of foot infection). All patients were recruited between May and December 2011. Each patient signed an informed consent form before the start of the study. The study protocol was approved by the medical ethics committee Twente.

Instrumentation

Digital photographs of the plantar surface of both feet were obtained under standardized lighting and foot positioning conditions using a previously described photographic foot imaging device (PFID).[10] In short, the PFID contains a camera module (featuring a charge-couple device image sensor, resolution 4 pixels/mm^2), light sources, mirror, glass plate, foot supports, and a computer, all contained in an ergonomically designed device.[10] The PFID produces three images under different lighting conditions (diffuse, medially and laterally oriented, to improve perception of 3D foot contours) that are automatically saved on a personal computer.
Foot skin temperatures were measured with an infrared thermometer (TempTouch®; Xilas Medical, San Antonio, TX), which is a probe designed for patients to measure sub-surface temperatures on their plantar foot surface. Foot temperature is measured with 0.1°C accuracy and is displayed on the probe.

Protocol

Live assessment of the feet of all patients was performed by two observers, who were certified wound care specialists trained for 13 and 17 years in diabetic foot care, and who assessed the foot independently from each other. The foot was assessed for presence of infection using PEDIS classification criteria.[17] Infection was defined as a PEDIS score grade 2 or higher. The feet were also assessed for presence of erythema, foot ulcers, abundant callus, blisters or fissures. The clinical sign and its location on the foot were entered in paper drawings of the foot surface boundaries. A foot ulcer was defined as a full-thickness lesion penetrating through the dermis. Abundant callus was defined as callus formation requiring treatment (i.e. sharp debridement), a blister as collection of fluid underneath the epidermis, and a fissure as a crack-like lesion of the skin.
After live assessment, the researcher instructed the patient to put their feet in the PFID for photographic imaging. The researcher subsequently measured foot temperature at six plantar regions on each foot using the TempTouch® thermometer: hallux, first, third and fifth metatarsal heads, metatarsocuneiform joint, and cuboid. Measured temperatures and foot location were entered in a clinical report form.

All assessments (live, photographic, and temperature) were carried out before any treatment of the infection (e.g. antibiotics, sharp debridement) was initiated.
Two weeks and again four weeks after inclusion of 10 subsequent patients, the same two observers that performed the live assessment assessed the photographs of the feet of these ten patients, again independently from each other. To reduce the chance of photographic memory and reporting bias, the photographs were randomly ordered and mixed with photographs of the feet of ten patients with a variety of (or absence of) foot problems that were assessed in a previous study. Photographs were assessed using IrfanView graphic viewer version 3.99. Observation of any clinical sign and its location on the foot were entered on paper drawings of the foot surface boundaries.

Data analysis
As reference for the diagnosis of erythema, observations during live assessment were used. As reference for the diagnosis of infection, the PEDIS score from the live assessment was used. A temperature difference >2.2°C measured between corresponding regions in the left and right foot, defined the warmer region as a *hotspot* (i.e. sign of infection). Intra-observer agreement between live and photographic assessment for the diagnosis of erythema and between PEDIS and a *hotspot* for presence of infection was determined based on calculated sensitivity, specificity, positive predictive value, and negative predictive value.
To explore the value of combining photographic and thermographic methods for the diagnosis of foot infection, agreement with PEDIS was computed using the algorithm shown in Figure 1. This algorithm uses three types of observations in a hierarchical order to define foot infection: *hotspot*, erythema, and foot ulcer. The hierarchy was based on a trial and error experiment to obtain the best balance in sensitivity and specificity.
Intra-observer agreement between the first and second photographic assessment for diagnosis of erythema was calculated using Cohen's κ. Inter-observer agreement for the diagnosis of infection based on PEDIS was also calculated using Cohen's κ.

Results

Twenty-one patients were recruited from our inpatient clinic and 17 from our outpatient clinic. A total of 75 feet in these 38 patients were assessed; one patient had unilateral amputation above the ankle. In one patient it was impossible to measure skin temperature because of technical problems. In the remaining 36 patients that were analysed for foot temperature, the mean maximum temperature difference measured between any pair of corresponding left and right foot regions was 4.4°C (range 1.3 – 9.2 °C, SD 2.0 °C). A *hotspot* was found in 30 patients.
Table 1 shows the number of observations per clinical sign of foot disease per observer for the live assessment and for both photographic assessments. In the 38 patients, infection (PEDIS) was scored 21 and 20 times, erythema 17 and 18 times, and ulcer

36 and 33 times by observer 1 and 2, respectively, during live assessment. Observer 1 missed two live assessments of two admitted patients, due to absence on one day. In the photographic assessment of these two patients, an ulcer and erythema was scored in one patient and absence of signs of foot disease in the other. Observer 2 missed seven live assessments (one inpatient and six outpatient clinic patients) due to absence on three days. In the photographic assessments of these seven patients, absence of signs of foot disease was scored in four patients, erythema in three.

Table 2 shows the agreement per observer for the diagnosis of infection between live assessment (PEDIS) and the combination of photographic and temperature assessments as determined by the algorithm. False-negative outcomes (6 for observer 1, 7 for observer 2) were mainly recording of a *hotspot* with thermography but lack of observation of erythema at a location where an ulcer was present. False-positive outcomes (3 for observer 1, 2 for observer 2) were recording of a *hotspot* and observation of erythema, at a location where a foot ulcer was present for observer 1, and observations of only a *hotspot* for observer 2. Choosing larger temperature differences than 2.2°C to define a *hotspot* (i.e. 3.2, 4.2, or 5.2°C) did not improve agreement with live assessment.

Sensitivity, specificity, positive and negative predictive values for the diagnosis of (signs of) foot infection through (the combination of) photographic and temperature assessment are shown in Table 3.

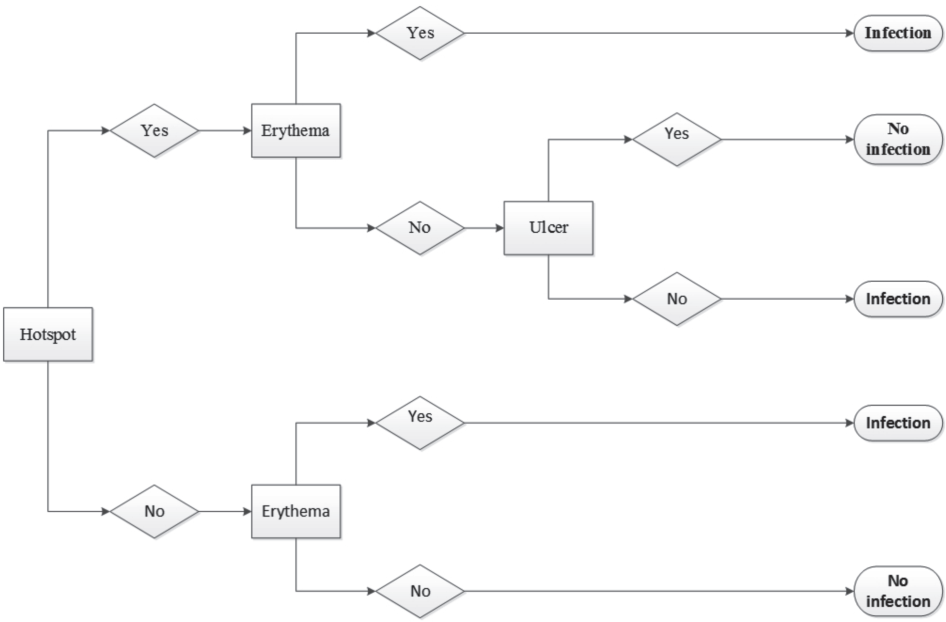

Figure 1. Algorithm used for the diagnosis of infection based on the combination of photographic and temperature assessments. In this algorithm, infection is defined based on a sequence of observations in a hierarchical order: presence (or absence) of a *hotspot* from temperature measurements, erythema on the photograph, and an ulcer on the photograph.

For assessment of erythema on photographs, sensitivity was <60% and specificity >85% in both observers. For diagnosis of infection through a *hotspot*, sensitivity was >90% and specificity <25% in both observers. The diagnosis of infection through the combination of photographic and temperature assessment (i.e. the algorithm as shown in Figure 1) resulted in sensitivity >60%, and specificity >79% for both observers. Intra-observer agreement between the two photographic assessments for diagnosis of erythema was good for observer 1 (κ = 0.77) and moderate for observer 2 (κ = 0.52). Inter-observer agreement for the diagnosis of infection (using PEDIS) in the live assessment was moderate (κ = 0.44).

Table 1. Number of observations per clinical signs of foot disease for the 75 feet of 38 patients assessed live and from photographs.

	Infection (PEDIS)	Erythema	Ulcer	Abundant callus	Blister	Fissure	Absence of signs*
Live assessment							
Observer 1	21	17	36	12	3	1	24
Observer 2	20	18	33	34	5	4	16
Photographic assessment 1							
Observer 1	-	14	35	15	2	1	24
Observer 2	-	11	37	24	5	3	21
Photographic assessment 2							
Observer 1	-	12	36	11	3	1	24
Observer 2	-	6	32	27	4	4	21

Each clinical sign could be observed more than once on the same foot.
* absence of any sign in the whole foot.

Table 2. Agreement between live assessment and the combination of photographic and thermography assessment for presence of diabetic foot infection.

			Combination of photographic and thermography* assessment	
			Present	**Absent**
Live assessment				
Observer 1†	PEDIS	Present	14	6
		Absent	*3*	11
Observer 2‡	PEDIS	Present	11	7
		Absent	*2*	8

False-positive observations are displayed in italic style; false-negative observations are underlined.
† observer 1 missed two live assessments
‡ observer 2 missed seven live assessments, and missed a PEDIS score on one occasion

Table 3. Sensitivity, specificity, positive and negative predictive values for the diagnosis of diabetic foot infection through (the combination of) photographic imaging and thermography

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Observer 1				
Live (erythema) vs. Photographic (erythema)	57	86	73	76
Live (PEDIS) vs. Thermography (*hotspot*)	90	21	62	60
Live (PEDIS) vs. Combination (algorithm)	70	79	83	65
Observer 2				
Live (redness) vs. Photographic (erythema)	50	87	80	62
Live (PEDIS) vs. Thermography (*hotspot*)	94	10	65	50
Live (PEDIS) vs. Combination (algorithm)	61	80	85	53

Discussion

The aim of this study was to determine the validity and reliability of diagnosing (signs of) diabetic foot infection from photographic imaging and infrared thermography. The findings show low sensitivity with high specificity, positive, and negative predictive values for the diagnosis of erythema as sign of infection using digital photographs. On the contrary, high sensitivity scores with low specificity and moderate positive and negative predictive values were found for the diagnosis of *hotspot*s as sign of infection using infrared thermography. Combining photographic and temperature assessment, and including information on ulceration obtained from photographs, greatly improved the balance of sensitivity and specificity and also improved the positive predictive value to diagnose diabetic foot infection.

These results show that photographic or temperature assessments alone are either not sensitive or not specific enough for diagnosis of diabetic foot infection, but the combination of modalities gives acceptable outcomes.

The results show that if photographic foot imaging or infrared thermography would be used separately as home-monitoring tool for the early diagnosis of signs of diabetic foot infection, diagnosis would be under-scored (in case of photographic imaging) or over-scored (in case of thermography). In both cases this is undesirable, because the first may result in lack of required treatment for what is a severe foot problem (i.e.

false negative cases), whereas the second would result in many unjustified and unnecessary referrals (i.e. false positive cases), which may lead to over-expenditure of clinical resources and an unnecessary burden for the patient. The false-negative observations found when combining the modalities were mainly observations of a *hotspot* without erythema at a location where a foot ulcer was present. In other words, these ulcers were considered infected during live assessment, but the absence of erythema observed from photographs resulted in a false-negative observation according to the algorithm. The wider range of possibilities to assess presence of infection during live assessment (e.g. smell and touch) may potentially explain these false-negative observations. The consequences are, however, acceptable for these cases because patients would still be referred for treatment based on the ulcer seen on the photographs. This emphasizes the advantage of combining the two modalities for the diagnosis of infection. Another advantage compared to using only thermography is that photographic imaging allows the diagnosis of other pre-ulcerative lesions such as abundant callus or blisters in addition to signs of foot infection.

No earlier published data was found for the use of digital photography to diagnose diabetic foot infection. In studies on non-diabetic patients, agreement scores between photographic and live assessments for presence of infection (i.e. cellulitis, erythema, or infection) vary widely, with reported sensitivity ranging from 32% to 71%, specificity from 27% to 91%[18-20], and κ from 0.12 to 0.92[20-23]. Skin temperature monitoring of the diabetic foot was previously shown to be an effective tool for early diagnosis of inflammation, which resulted in a significant reduction in the incidence of ulceration in high-risk patients[13-15]. Additionally, it has been used to monitor neuropathic ulcer healing[24] and the acute Charcot foot[25]. To our best knowledge, this is the first study that examined the validity and reliability of the combined use of photographic imaging and thermography for the diagnosis of diabetic foot infection.

An interesting and important finding from the study was that the inter-observer agreement for the live diagnosis of infection using PEDIS was only moderate (κ 0.44). These outcomes are not unprecedented since a previous telemedicine study in vascular surgery showed that onsite surgeons disagreed about the presence of erythema or cellulitis in approximately one third of inpatients who had undergone peripheral bypass surgery or amputation, or who were admitted for wound healing problems.[20] This may question the use of the PEDIS system as "gold standard" reference for the live assessment of diabetic foot infection, and it may question the skills of clinicians to accurately use this classification system. Apparently, the diagnosis of infection is difficult to reach agreement on, which limits its use as suitable reference for studies. Other authors have confirmed this for the diagnosis of signs of infection in diabetic foot ulcers[26], and two systematic reviews on the clinical examination and diagnostic testing of infected diabetic foot ulcers concluded that infection in diabetic foot ulcers cannot be reliably identified using clinical assessment.[27,28]

The implications for clinical practice are that an usable set of tools is available in a semi-automated setup for the early diagnosis of (signs of) diabetic foot infection on a remote basis. Assessment of other signs than infection using photographic imaging

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has previously been shown to be valid and reliable, and implementing a system like the PFID as home-monitoring tool has shown to be feasible.[11] Therefore, these tools allow a complete remote assessment of the most important (pre-) signs of diabetic foot disease. The next step would be to assess the (cost-)effectiveness of this setup in comparison to usual care for early diagnosis and prevention of foot complications in high-risk diabetic patients. If the system proves to be effective in these studies and implementation in the daily care of the high-risk diabetic patient is feasible for the given health care setting, a major decrease in patients' burden and healthcare costs can be expected as well as improvements in patient autonomy and quality of life.

This study has some limitations. First, imaging using the PFID is limited to the plantar surface of the foot, whereas approximately 50% of all ulcers seen in specialized centres occur on the dorsal or lateral foot surface or in-between toes.[29] In addition, for the temperature measurements we also chose to assess only the plantar foot surface following an earlier protocol.[14] Because in all cases the infection was present on the plantar side of the foot (and in some cases also on the dorsal side), this limitation to assessing only the plantar foot sufficed. However, we cannot draw conclusions from the results for infection that occurs on the dorsal side of the foot. Photographic systems that also image the dorsal and lateral side of the foot and temperature assessments of the dorsal side of the foot are needed to obtain a more complete analysis of the diabetic foot. Second, the results may be specific to the two observers, both certified and experienced wound consultants, who performed all assessments. Both observers have a long-standing experience in daily foot care of diabetic foot patients and both have experience in assessing digital photographs of diabetic feet. In our clinical setting, these wound consultants would be the specialists of choice to perform remote assessments when these tools would be implemented in clinical practice, which supports their involvement in the current study. Nevertheless, generalizability of the results to other health care professionals may be limited.

In conclusion, the present study demonstrates the validity and reliability, and with that the potential value, of using photographic imaging in combination with infrared thermography for the diagnosis of foot infection in diabetic patients. As a result, this combination of modalities may hold promise as home-monitoring system, with the opportunity for remote assessment of high-risk diabetic feet. This can facilitate the early diagnosis of (signs of) foot infection and also other important (pre-) signs of diabetic foot disease, which may prove in future studies to be effective in preventing more devastating consequences.

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Chapter 7

General discussion

Diabetes mellitus is a common cause of lower extremity pathology such as ulceration, infection and amputation[1], causing a major socioeconomic burden[2]. In diabetes, self-care is an essential element of disease management and prevention of ulceration.[3] Diabetes related complications, like neuropathy, retinopathy, limited joint mobility, or cognitive impairments impede self-care in daily life. And problems such as ulcers most often arise in between visits to the foot clinic or local health care professionals. Telemedicine tools can support self-care, and may be a missing aspect in the screening of patients who are at high risk for foot complications.

Diabetic foot in the era of telemedicine

Telemedicine in general means "any medical activity involving an element of distance".[4] Synchronous to the digital revolution (the shift to digital communication technologies) in the early 1990s, telemedicine services are being increasingly used. However, its implementation in routine health-care services is impeded by the lack of evidence for its (cost-) effectiveness. Telemedical services have been developed for diagnostic, therapeutic, or educational purposes in many different medical specialties, like dermatology, radiology, cardiology, orthopaedics, pathology and surgery. In diabetes care, telemedical developments and services mainly focus on self-monitoring of glucose levels and is proven feasible.[5] For the remote monitoring and support for treatment of the diabetic foot, several attempts have been made to develop telemedical tools or approaches to support in the prevention, monitoring and/or treatment of diabetic foot ulcers. For this purpose, we have developed a photographic foot imaging device as a non-interactive diagnostic approach for at-home monitoring of the foot status of high risk patients.

The general aim of this thesis is to expand the knowledge base on the use of telemedical tools in the management of foot disease in patients with diabetes mellitus. A more specific aim of the studies described in this thesis was to evaluate the value of photographic foot imaging for the assessment and early diagnosis of foot ulcers and pre-signs of ulceration, and, in combination with dermal thermography, the diagnosis of foot infection in diabetic patients. Supportive aims were to develop and improve the telemedical system for optimal foot imaging and data transfer, to evaluate validity and reliability of assessing signs of foot disease from photographs, to evaluate the feasibility of the system in the home environment, and to explore and review the currently existing telemedical approaches for the management of diabetic foot disease. The main findings of the studies in this thesis will be discussed here. Furthermore, in this general discussion, methodological issues in the studies performed will be considered as well as the implications of the findings for clinical practise. Finally, future perspectives will be discussed.

Main findings

A variety of partners contributed to the development of the concept to monitor high-risk patients in the home environment using digital photographic imaging. Diabetic foot care professionals from two hospitals (Ziekenhuisgroep Twente, the Netherlands and Mathias Spital Rheine, Germany) provided clinical input. Several industrial partners and the University of Twente provided engineering and technical input. As a result, we developed a new photographic foot imaging device (PFID) that provided high quality digital photographs of the plantar surface of both feet under standardized lighting and foot position conditions. **Chapter 2** describes the imaging device, and the process of trial and error, in which we optimized illumination settings (from prototype to a definitive version), to enhance the agreement between live and photographic assessments of (pre-)clinical signs of diabetic foot disease. Subsequent studies, presented in this thesis, were carried out with the definitive version of the PFID.

Any tool can only be useful when clinical signs of foot disease can be diagnosed in a valid and reliable manner. No other studies could be identified providing insight into the accuracy and reliability of using digital photography to diagnose important signs of diabetic foot disease. In **Chapter 3**, results on the validity and reliability of diagnosing foot ulcers and pre-ulcerative lesions using the PFID were presented. Agreement scores between live and photographic assessments were very good for diagnosing ulcers and absence of any sign, and good for diagnosing abundant callus. Intra-observer agreement between repeated photographic assessments was good to excellent for all outcomes and all four observers that were involved. Inter-observer agreement for the photographic assessment was good for ulcer and absence of signs, and moderate to good for callus. Inter-observer agreement scores for the live assessment of the same signs were slightly higher. The data showed that trained professionals could assess foot ulcers and pre-ulcerative lesions in a valid and reliable manner from digital photographs produced by the PFID.

Next to providing assessments that are valid and reliable, the tool has to be feasible and safe as a home-monitoring tool to enhance acceptance and adherence to using the system, by both patients and physicians. To assess the feasibility of using the PFID, the system was installed in the home-environment of 22 high-risk patients for a period of four months. The results were presented in **Chapter 4**. Within the follow-up period, an acceptable percentage of image sets was missing (12%, mainly due to modem or server failure), nearly all referrals for treatment based on remote assessments of the foot were justified and resulted in treatment, and usability scores were high. Health-related quality of life improved after monitoring with the PFID, but not to a significant level. The results from this study demonstrate the feasibility of using the PFID in the home environment for the diagnosis of important clinical signs of diabetic foot disease.

Several other initiatives with respect to the use of telemedicine application for prevention, monitoring and treatment of diabetic foot disease have been described in the scientific literature. At-home treatment of diabetic foot ulcers by a visiting nurse could be well supported through mobile phone and video interaction.[6-9] Other studies showed the use of specially designed imaging devices for ulcer monitoring.[10-12] Furthermore, several studies have shown the value of dermal thermography in the diabetic foot.[13-18] The refereed literature on this topic was reviewed and results were presented in **Chapter 5**. This systematic review shows that the use of and knowledge on telemedicine for the diabetic foot is still in its infancy, but several promising approaches exist that have been shown to be effective in the prevention, monitoring or treatment of diabetic foot disease. Dermal infrared thermography of the plantar foot surface showed to be the only tool to date that was effective in reducing the risk for ulceration in diabetic patients. The use of hyperspectral imaging showed to predict diabetic foot ulcer healing and development. Photographic foot imaging can accurately assess pre-signs of ulceration, ulcers and ulcer area and is feasible to use in the home-environment. Finally, video /audio supported treatment of diabetic foot ulcers was also shown to be feasible in the home-environment, but data are preliminary. For some of these approaches, feasibility and effectiveness are not known yet, while for all approaches it is important that their cost-effectiveness in managing the diabetic foot is demonstrated to achieve wide acceptance and use in diabetic foot care.

Our systematic review did not show any studies on the use of telemedical tools to remotely assess diabetic foot infection. Furthermore, in our validity and reliability study (**Chapter 3**) the total number of patients with erythema (rubor) was too small to draw relevant conclusions from. Another cardinal sign of infection is increased skin temperature (calor). Dermal temperature can be assessed using infrared thermography. Although three randomized trials have shown the effectiveness of at-home monitoring of foot temperatures[16-18], the applied tools have their limitations, for example due to the presence of vascular disease or autonomic neuropathy, in diagnosing diabetic foot infection. To evaluate the hypothesis that a combination of photographic imaging and thermography may improve the diagnosis of signs of diabetic foot infection, we conducted a study to assess the validity and reliability of this combination. The results were presented in **Chapter 6** and showed that diagnosis of signs of foot infection from photographs was specific but not very sensitive. On the other hand, diagnosis from temperature recordings was sensitive, but not very specific. Diagnosis based on the combination of photographic assessment and thermography was both sensitive and specific. The data illustrate that for the remote diagnosis of (signs of) foot infection in diabetic patients, the most valid and reliable method is to combine photographic imaging with infrared thermography.

Methodological considerations

In this section, the methodological aspects, strengths and limitations of the studies in this thesis will be discussed.

Photographic foot imaging device

Photographic imaging with the PFID was limited to the plantar foot surface, while 50% of ulcers seen in specialized diabetic foot clinics in Europe appear on the dorsum of the foot or in-between toes.[19] Nevertheless, the plantar surface remains the primary target surface because (a) many pre-signs of ulceration such as callus and blisters are more common on the plantar than dorsal foot surface due to biomechanical influences[20]; (b) the plantar surface is not directly visible to the patient; and (c) plantar foot ulcers are generally less predictable than dorsal ulcers because of their more complex aetiology. In addition, other telemedicine approaches have also mainly focussed on the plantar foot surface while some have proven efficacious in preventing diabetic foot disease, like the at-home use of infrared dermal thermography.[16-18] Ideally, the possibility of imaging the foot dorsum should be implemented in future designs of the device.

Study population

The population studied in this thesis concerned patients with type 1 or 2 diabetes mellitus who were a representative sample of patients at high risk of ulceration. Patients were recruited from the out- or inpatient units of two specialized diabetic foot clinics, were diagnosed with peripheral neuropathy and had (pre-) signs of plantar foot ulceration or recent history of plantar foot ulceration. For these patients, the recommended frequency of foot screening is highest among all diabetic patients (at least once every 1-6 months).[3] For the feasibility study on the use of the PFID (**Chapter 4**) the system was installed at patients' homes located both in urban and rural regions and in different types of housing, like mobile homes and farms. Such high-risk patients and such settings are typical for the patients that would be targeted with the support of home-monitoring devices. This increases the external validity of the study results.

Observers and reference methods

All four observers that performed the live and photographic assessments in the studies conducted within this thesis, have a long-standing experience in foot care of diabetic foot patients and also have experience in assessing digital photographs of diabetic feet. Observers were two (vascular) surgeons and two certified wound consultants. Although generalizability of the assessment outcomes to other health care professionals such as podiatrists or nurses may not be straightforward, in our and many other clinical settings, wound consultants and surgeons would be the specialists of choice to perform the remote assessments when these tools would be implemented in clinical practice. This supports their involvement in this study.

For the diagnosis of foot ulcers, pre-signs of ulceration (e.g. abundant callus), and the absence of any sign, live assessment of the patient was chosen as the most useful 'gold standard' reference condition, and inter-observer agreement for these outcomes showed to be good. For the diagnosis of diabetic foot infection, however, the inter-observer agreement scores for the live assessment using the PEDIS classification[21], was only moderate. This may off course be the result of the difficulty with which the observers were able to classify the outcomes, but it may also show the inherent difficult in assessing diabetic foot infection (using the PEDIS system). In support of this, other authors also stated that diagnosis of infection is difficult to reach agreement on between observers.[22-25] Nevertheless, live assessment using a system like PEDIS is currently still the best available reference, and therefore chosen in studies on diagnosis of infection.

Clinical implications

Demonstrating that the PFID is a valid, reliable and feasible approach for the home-monitoring of the feet of high-risk diabetic patients is an important step towards implementing such a system into diabetic foot practice. Due to the additional value of combining digital photography and infrared thermography in the screening and monitoring of high-risk patients, future designs of the device should combine digital imaging and dermal thermography. If proven (cost-) effective over regular treatment in preventing severe complications in high-risk patients, and if the organisation of health care allows the integration of such a home-monitoring system, implementation will be improved. Implementation can then show to improve outcomes of diabetic foot disease, increase patient autonomy and health-related quality of life, reduce patient burden of the disease, reduce clinical visits for foot care, and substantially reduce health care expenditures on foot care.

Future research perspectives

Research in the field of telemedicine is complex and challenging, and still in its infancy with respect to the management of diabetic foot disease. Newly developed telemedicine devices or applications have the risk of being outdated at the moment of implementing such a device when cost-effectiveness has been shown, simply because of the fast developments in (information) technology. Nevertheless, the more widely available broad band internet in patient's homes does facilitate implementation of telemedical approaches. Before any telemedical tool for the management of diabetic foot disease will be widely implemented in daily foot care, the patient, health care professional, as well as the insurance company must be convinced of its value and accept it as a useful additional tool. The next important step in the development of digital photography and dermal thermography as telemedical tools for diabetic foot management is to prove the (cost-) effectiveness of these methods. High-quality randomized controlled trials are needed to assess cost-effectiveness of the approach in comparison with usual care to prevent foot disease in diabetic patients.

Future technical developments

Future telemedicine devices will probably be smaller, easier to use, and more intelligent. The PFID was developed to evaluate the foot in a home-environment, was ergonomically designed, small enough to be placed in the patient's bedroom or bathroom, and found to be easy to use. In future designs, physical aspects of the device will have to be improved. The device should preferably include dorsal photography. In this perspective, upcoming three-dimensional (3D) imaging (i.e. stereo- scopic) or tomographic techniques may play a role in the near future. Three-dimensional imaging is possible using infrared, ultrasound, or near-infrared technologies for example, and enables evaluation of the whole foot and depth measurements of foot ulcers or other lesions. These techniques may be applicable in the home environment in the future. Results presented in **Chapter 6** also suggest that future designs of a home-monitoring device for diabetic foot patients should include dermal thermography. The challenge will be to design a system that incorporates both photographic imaging and thermography and that is applicable to the diabetic foot. Infrared scanners seems to have both features (physical principles of image formation and thermography) and is therefore probably most suitable. It can produce 3D thermograms by detecting irregularities and visualizes temperature distributions. Medical applications of 3D thermography system have been described in a few experimental settings only.[26,27]

Importance for diabetic patients and diabetic foot care professionals

For successful implementation of the PFID or any further improved version of the device in the future, adherence to using the system should be optimal. Diabetic foot patients are known to have low adherence in different aspects of care.[28] A home-monitoring device should be designed in such a way that it becomes part of a patient's daily routine. It therefore needs to fulfil ergonomic and aesthetic requirements so that is can be placed at any location inside the patient's home and will be very easy to use. Beside the intended use of the PFID in the patient's home, it may also be used in other remote settings, such as general practitioners office, another health care centre, or as part of ambulant diabetes screenings unit. Although this will jeopardize to some extent the ease of use and the daily routines with having a system in the home, it can improve cost-effectiveness when multiple patients can use the same telemedical system at a central location within the neighbourhood. These deviations from the home-monitoring approach should be explored and tested.

In addition to proving the cost-effectiveness of the telemedical approach, future technical and research initiatives should explore the feasibility of automated screening and diagnosis of foot disease. Such an automated diagnosis can significantly relieve the work of health care professionals who would normally assess photographs and data from each assessment, which may provide a great advantage to health-care expenditure. In such a setting, patients will only consult the physician in case the system detects a problem. Future studies should evaluate the accuracy and value of automated diagnosis. In a first attempt to evaluate the feasibility of automated screening of the foot, the Ziekenhuisgroep Twente collaborated with the Signals and Systems group of the University of Twente, to evaluate whether signs of foot disease could be classified through pixel classification of digital photographs.[29] This could be considered an intermediate step towards automatically assessing diabetic foot disease. Kloeze *et al*. described that RGB (red, green, blue) colours data in the photograph is informative with respect to the detection of foot ulcers. However, pre-signs of ulceration (e.g. abundant callus, blisters or fissure) require more sophisticated routines in pixel classification for automated diagnosis. Future research should further explore the use and value of automated diagnosis form digital photographs, but also from other imaging modalities like infrared thermography, hyperspectral imaging, photometric stereo imaging, and 3D surface imaging. Currently, a project called 'Early detection of ulceration in diabetic feet, an intelligent telemedicine-monitoring system', granted by public funding from ZonMw (the Netherlands Organisation for Health Research and Development), is conducted by the University of Twente and the Ziekenhuisgroep Twente. The goal of this project is to develop an intelligent telemedicine monitoring system that combines promising imaging modalities for an automated assessment of the foot of the patient.

Conclusion

This thesis showed the value of a photographic foot imaging device as a non-interactive diagnostic approach for the at-home monitoring of the foot status in high risk diabetic patients. The approach was found to be valid and reliable for diagnosing (pre-) signs of diabetic foot ulceration, feasible in the home environment, and valid and reliable for diagnosing signs of infection in case it is combined with dermal infrared thermography. The data from this thesis expand the knowledge base on the use of telemedical approaches for the management of the diabetic foot and provide useful insight for future directions in research and care for the high-risk diabetic foot patient.

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Chapter 8

Samenvatting in het Nederlands

Achtergrond

Wereldwijd hebben 366 miljoen mensen diabetes mellitus (suikerziekte) en dit aantal zal naar verwachting stijgen tot 552 miljoen (1 op de 10 volwassenen) rond het jaar 2030. Nederland telt ruim 1,2 miljoen diabetes patiënten. Een diabetische voet is een combinatie van voetafwijkingen die ontstaan als gevolg van de ziekte diabetes mellitus. Veel diabetes patiënten krijgen complicaties, waarvan problemen aan de voeten tot de meest ernstige en kostbare complicaties behoren, omdat ze kunnen leiden tot ernstige infecties en amputatie. Elke 30 seconden wordt in de wereld een been afgezet ten gevolge van diabetes. De kwaliteit van leven bij deze patiënten is sterk verlaagd en de kosten voor de gezondheidzorg voor behandeling zijn erg hoog (wereldwijd 471 miljard dollar). Bijna alle amputaties worden voorafgegaan door een ulcus (wond) aan de voet. Daarom is snelle, adequate behandeling en bij voorkeur preventie van deze voetulcera van groot belang.
Internationale richtlijnen schrijven voor dat diabetes patiënten met een hoog risico op voetulcera minstens elke 1 tot 6 maanden professionele voetzorg moeten krijgen. De vraag is echter of deze richtlijnen ook overal worden gevolgd. Daarnaast ontstaan voetproblemen vaak tussen opeenvolgende bezoeken aan de therapeut, verpleegkundige of arts. Bijkomend probleem is dat veel diabetes patiënten beperkt zijn in de controle en verzorging van hun eigen voeten. Dit komt doordat ze bijvoorbeeld alleen wonen, slecht kunnen zien, last hebben van stijve gewrichten, cognitieve problemen hebben, weinig kennis over de ziekte hebben, of doordat door de aanwezige neuropathie (verminderd gevoel) niet wordt gesignaleerd dat er problemen zijn.
Om deze redenen zouden patiënten baat kunnen hebben bij wekelijkse of zelfs dagelijkse inspectie van de voet door een specialist teneinde problemen vroegtijdig te herkennen en snel te behandelen, zodat verdere complicaties worden voorkomen.

De rol van Telemedicine

Frequente controle ten behoeve van vroege herkenning van problemen vindt bij voorkeur plaats in de thuissituatie door middel van een telemedische aanpak waarbij kenmerken van voetproblemen in beeld worden gebracht. Telemedicine verwijst naar “iedere op afstand geleverde medische activiteit”. Synchroon aan de digitale revolutie in de jaren ’90 worden telemedische technieken steeds meer gebruikt. Telemedische methodes zijn ontwikkeld voor diagnostische, therapeutische en onderwijskundige doeleinden in verschillende specialistische vakgebieden, zoals de dermatologie, radiologie, cardiologie, orthopedie, pathologie en chirurgie. Voor de diagnose en ondersteuning van de behandeling van de diabetische voet zijn diverse initiatieven ontplooid om telemedische systemen te ontwikkelen.
Wij hebben een geavanceerde fotografische voetscanner ontwikkeld die moet bijdragen aan de vroege diagnostiek van voetproblemen in de thuissituatie bij

patiënten met diabetes mellitus. Conventionele digitale camera's zijn ontoereikend, omdat iemand anders de foto's moet maken, en omdat omgevingsfactoren en onjuiste camera-instellingen kunnen leiden tot foto's van slechte kwaliteit. Om deze nadelen te overwinnen hebben we, in samenwerking met diverse technische partners, de voetscanner ontwikkeld. Met dit systeem worden meerdere keren per week onder gestandaardiseerde omstandigheden (belichting, voetpositie) foto's gemaakt van de zool van de voet, die via internet automatisch worden gestuurd naar een database server, waarvan ze worden gedownload en beoordeeld door een specialist op het gebied van de diabetische voet. De patiënt kan het apparaat volledig zelfstandig bedienen.
Het beoogde doel van de fotografische voetscanner is om voetproblemen bij diabetes patiënten, zoals ulcera en voorstadia van ulcera (eeltvorming, roodheid, blaren), vroegtijdig te herkennen en te behandelen. Als het apparaat bewezen succesvol blijkt in de vroege herkenning van problemen en adequate verwijzing van patiënten, kunnen dramatische complicaties zoals infectie en amputatie voorkomen worden.
Een succesvolle implementatie van deze methode kan de mobiliteit en de kwaliteit van leven van patiënten verbeteren. Daarnaast verbetert de autonomie van patiënten, vooral bij patiënten die in afgelegen gebieden wonen en waar de afstanden tot de gezondheidscentra groot zijn.
Deze techniek kan een goede aanvulling zijn op al bestaande, thermografische, methoden, zoals infrarood thermometers, waarvan gebruik in de thuissituatie bij het ontstaan van voetulcera een aangetoonde preventieve werking heeft. De laatstgenoemde techniek heeft echter de beperking dat het slechts één element meet van het spectrum van voorsignalen van voetwonden en infectie, namelijk temperatuursverhoging, terwijl andere complicaties van diabetes mellitus zoals autonome neuropathie (zenuwschade) of problemen met de bloedvoorziening in de voeten, ook van invloed kunnen zijn op de temperatuur van de voet.
Het algemene doel van dit proefschrift is om de kennis te vergroten over het gebruik van telemedische technieken, die ontwikkeld zijn voor de behandeling van de diabetische voet. De studies in dit proefschrift beschrijven de waarde van de fotografische voetscanner voor vroegtijdige diagnose van voetulcera en voorstadia van ulcera, in combinatie met huid thermografie. Subdoelstellingen bestonden uit het ontwikkelen en verbeteren van de fotografische voetscanner, het evalueren van de validiteit en betrouwbaarheid van de beoordelingen van de foto's voor de diagnose van ulcera en voorstadia van ulcera, het evalueren van de bruikbaarheid van het systeem in de thuissituatie; ook werd in een literatuurstudie onderzocht welke telemedische technieken voor de behandeling van de diabetische voet in de thuissituatie reeds bestaan en hoe effectief deze zijn.

Verschillende partners hebben bijgedragen aan de ontwikkeling van de fotografische voetscanner. **Hoofdstuk 2** beschrijft de voetscanner en het proces van optimalisatie van de belichtingsinstellingen, bedoeld om de overeenkomst tussen de klinische en fotografische beoordeling van symptomen van de diabetische voet ziekte te verbeteren.

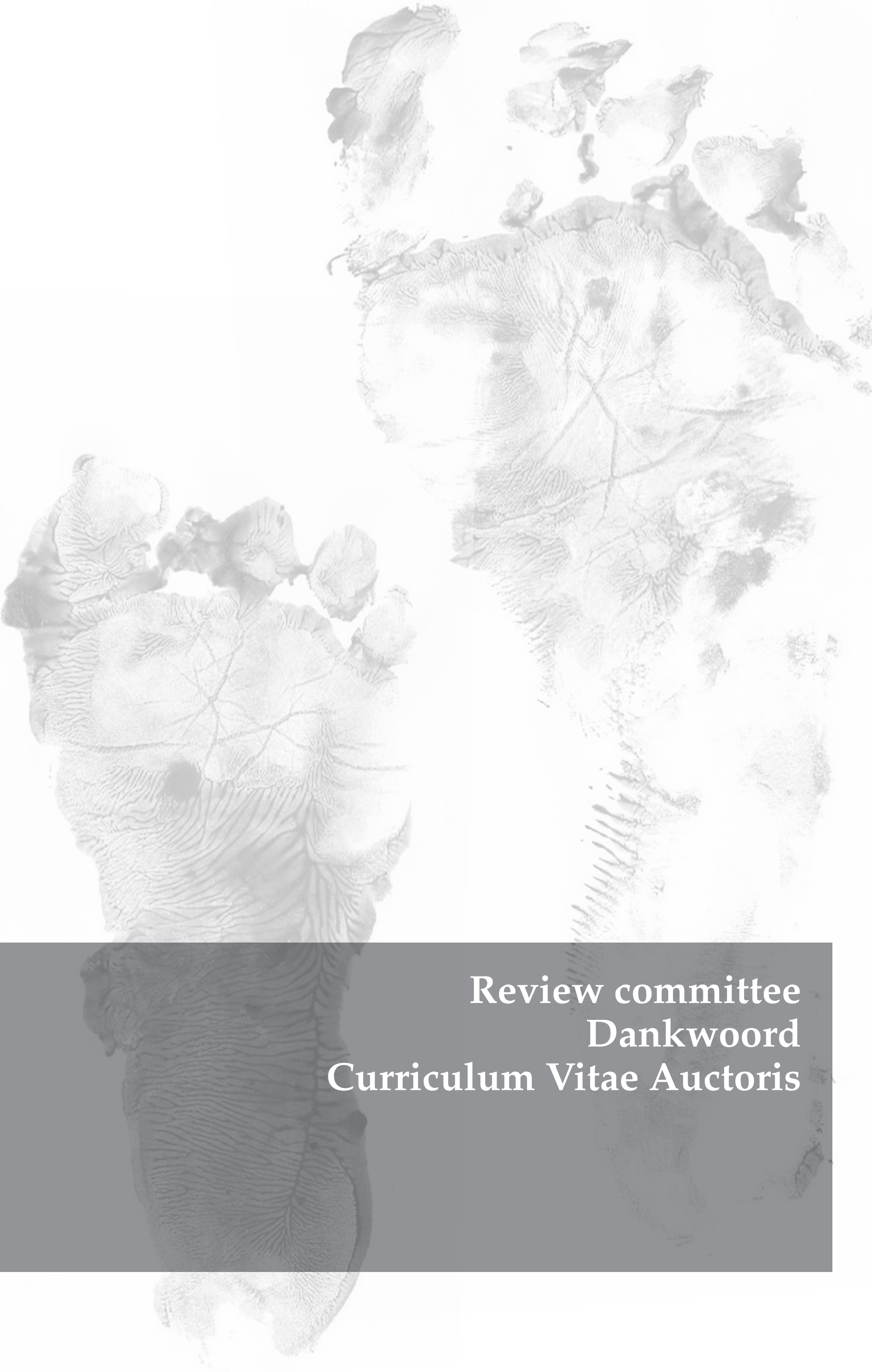
De andere hier beschreven studies werden uitgevoerd met de definitieve versie van de fotografische voetscanner.
Een apparaat is alleen nuttig als klinische symptomen van de ziekte op een valide en betrouwbare wijze kunnen worden gediagnosticeerd. In de literatuur kon geen enkele andere studie worden kon gevonden, die inzicht gaf in de nauwkeurigheid en betrouwbaarheid van het gebruik van digitale fotografie voor de diagnose van symptomen van de diabetische voet. Uit de resultaten die in **hoofdstuk 3** beschreven zijn, is gebleken dat de voetscanner foto's genereert waarvan de beoordelingen valide en betrouwbaar zijn voor de diagnose van ulcera, overmatige eeltvorming en de afwezigheid van symptomen. In dit onderzoek werden beoordelingen van foto's van voeten van patiënten, die met de voetscanner zijn gemaakt vergeleken met live (klinische) beoordelingen van de voet door een viertal specialisten (wondverpleegkundigen en chirurgen).
Om de acceptatie en het gebruik van de fotografische voetscanner door zowel diabetische voet specialisten als patiënten te optimaliseren, moet het systeem bruikbaar zijn in de thuissituatie. Voor evaluatie van de bruikbaarheid van de voetscanner werd het systeem voor een periode van vier maanden in de thuissituatie van 22 hoog-risico diabetes patiënten geïnstalleerd. De resultaten van deze studie werden gepresenteerd in **hoofdstuk 4**. Gedurende de follow-up periode werd een aanvaardbare hoeveelheid foto's niet ontvangen (12 %, voornamelijk als gevolg van falen van de modem of het netwerk), waren bijna alle verwijzingen terecht (met behandeling als gevolg), en bleek het systeem bruikbaar voor de patiënt. De kwaliteit van leven van de patiënt verbeterde na de periode waarin de scanner thuis geïnstalleerd was, echter niet significant. De resultaten van deze studie tonen evenwel aan dat de fotografische voetscanner bruikbaar is in de thuissituatie voor de diagnose van klinische symptomen van de diabetische voet.
In de wetenschappelijke literatuur worden verschillende andere telemedische initiatieven beschreven voor het behandelen van de diabetische voet. De literatuur die tot op heden over dit onderwerp is gepubliceerd werd op systematische wijze verzameld, beoordeeld en beschreven in **hoofdstuk 5**. Uit de resultaten blijkt dat het gebruik van en de kennis over de telemedische aanpak van de diabetische voet nog in de kinderschoenen staat, maar dat er een aantal veelbelovende technieken bestaat die effectief zijn gebleken bij de preventie, monitoring of de behandeling van de diabetische voet. Tot op heden blijkt infrarood temperatuur metingen van de voetzool de enige effectieve methode voor de risicoreductie van het ontstaan van ulcera bij diabetes patiënten. Daarnaast werd beschreven dat hyperspectrale technologie de genezing en het ontstaan van een ulcus kan voorspellen. Beoordelingen van digitale fotografische beeldvorming bleek betrouwbaar te zijn voor de diagnose van (voorstadia) van ulcera en het bepalen van de oppervlakte van een ulcus. Daarnaast bleek deze techniek goed bruikbaar in de thuissituatie. Ten slotte werd aangetoond dat ondersteunende behandeling met video of audio apparatuur (bv. mobiele telefonie) van diabetische voetulcera ook haalbaar is in de thuissituatie. Voor het merendeel van de hier beschreven technieken is de effectiviteit nog niet aangetoond; daarnaast bleek

kosteneffectiviteit van alle technieken voor de behandeling van de diabetische voet nog niet te zijn bewezen. Dit laatste is cruciaal ten aanzien van het geaccepteerd en geïmplementeerd krijgen van een dergelijke techniek voor de behandeling van de diabetische voet in de thuissituatie.

In het literatuuroverzicht zijn geen studies beschreven die een telemedische aanpak voor de diagnose van een diabetische voet gerelateerde infectie vermelden. Daarnaast bleek in onze validiteits- en betrouwbaarheid studie (**hoofdstuk 3**) het totaal aantal patiënten met erythema (roodheid) te klein om relevante conclusies te kunnen trekken. Een ander belangrijk symptoom van infectie is warmte (toegenomen huidtemperatuur). Temperatuurmetingen van de huid kunnen worden gedaan met behulp van infrarood thermografie. Hoewel uit drie goed uitgevoerde (gerandomiseerde) onderzoeken blijkt dat (infrarood) metingen in de thuissituatie van temperaturen van voetzolen effectief is, heeft deze techniek ook zijn beperkingen. De aanwezigheid van andere factoren, zoals perifeer vaatlijden en/of perifere neuropathie kan invloed hebben op temperatuurmetingen, waardoor thermografie mogelijk van minder waarde is voor de diagnose van infectie. Om te evalueren of de combinatie van digitale fotografie en thermografie tot een meer accurate methode leidt voor de diagnose van diabetische voetinfectie, hebben we een studie uitgevoerd om de validiteit en betrouwbaarheid van deze combinatie te bepalen. De resultaten daarvan werden gepresenteerd in **hoofdstuk 6** en tonen aan dat de diagnose van infectie op basis van een foto specifiek was, maar niet erg sensitief. Dit zou in de werkelijkheid betekenen dat de diagnose van een voetinfectie vaak gemist zou worden bij diabetes patiënten in de thuissituatie, hetgeen ernstige gevolgen kan hebben. Voor temperatuurmetingen bleek juist het omgekeerde (sensitief, maar niet specifiek). Een diagnose gebaseerd op de combinatie van beide modaliteiten was zowel sensitief als specifiek. De resultaten illustreren derhalve dat voor een diagnose van (symptomen van) diabetische voetinfectie in de thuissituatie, digitale fotografische beeldvorming het beste kan worden gecombineerd met (infrarood) thermografie.

In **hoofdstuk 8** werden de voorafgaande hoofdstukken samengevat en bediscussieerd.

Chapter 9



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Curriculum Vitae Auctoris

Stijn (Constantijn) E.V.B. Hazenberg was born on of February 25, 1977 in Oss, the Netherlands. In 1996 he graduated from the Titus Brandsma College in Oss and started his study Biomedical Sciences in Nijmegen, at the Radboud University. After one year he switched to Medical school, spend his internship in Surinam, and obtained his Medical Degree in 2003. He then worked as a clinical house officer for one year in the Jeroen Bosch Ziekenhuis in ʻs Hertogenbosch (dr. K. Bosscha) and started his surgical residency in 2005. During the first four years of his training in the Ziekenhuisgroep Twente (dr. J.G. van Baal), he started scientific research in the field of the diabetic foot and telemedicine. The final 2 years of his surgical residency were completed at the University Medical Center in Utrecht (Prof.dr. I.H.M. Borel Rinkes and Prof.dr. F.L. Moll), including one year differentiation in vascular surgery. After he finished his residency in 2011, he continued his training as a fellow (CHIVO) in vascular surgery at the University Medical Center in Utrecht (Prof.dr. F.L. Moll) until July 2013. Since then he works as a vascular surgeon at the vascular surgery department of the University Medical Center in Utrecht and Diakonessenhuis in Utrecht. He lives in Utrecht with his wife Sanne and their two children, Friso and Aimée.