Study protocol

Sealed Therapeutic Shoe vs. Total Contact Cast as Treatment of Diabetic Foot Ulcers: a Multicenter RCT

Clinical Trial Registration Number: Unique Protocol ID: 18RS6667

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Background

Approximately 19-34 % of all people with diabetes will at some time in life develop a diabetic foot ulcer (DFU).[1] People with diabetes are especially prone to develop foot ulcers because of different diabetic complications, especially angiopathy and peripheral neuropathy.

The DFUs are often hard to heal and the treatment is long-lasting. The DFUs result in lower physical and mental quality of life and affects social relationships.[2] The treatment is also very costly,[1, 3] it has been estimated that 25-50 % of diabetic inpatient care is related to DFUs.[4] Despite extensive treatment, all DFUs do not heal but some end in amputation. People with diabetes are at a 25-fold risk of amputation and every 20 second a person somewhere in the world has the foot amputated because of diabetes.[5] 85 % of these amputations are preceded by a foot ulcer[6] and many of these ulcers and amputation could have been prevented.[7]

Total contact cast (TCC) as gold standard treatment of DFUs

Plantar DFUs often are the result of a combination of foot deformities that increase plantar pressures when the person walks and that the person keeps walking despite high pressure and ulcers because he or she has lost sensation in the feet because of sensory neuropathy. Literature reviews and international guidelines[8, 9] recommend non-removable knee-high offloading devices, for example, a total contact cast (TCC) to treat plantar DFUs, as this offloads the ulcer from mechanical loading all day and night. Still, TCC is not accepted by all patients and is contraindicated in a number of cases because of negative side-effects. Most of these side-effects are the consequences of immobilizing the ankle joint, which impairs gait and results in lower ambulatory activity. For example, side-effects include reduction of joint flexibility, weight gain, muscle atrophy, sick leave from work and social isolation.[10] In addition, a TCC can give secondary ulcers why weekly visits to the hospital is necessary to change casts. For these reasons, TCC is only used for a minority of the patients for whom it could be beneficial, despite being the gold standard treatment.[11]

For working patients, casting often means sick leave from work, but casting can also be difficult for older patients with impairments of gait and balance. For patients where TCC is contraindicated or not tolerated, guidelines recommend removable offloading devices despite it is well known that these devices are not very effective.[8] In practice, this means that many patients do not receive effective treatment. Another problem is that many patients get new foot ulcers after treatment with TCC,[12] in part because adherence to using therapeutic footwear after healing is lower than desirable.[13]

Sealed therapeutic shoe as alternative treatment

The investigators have developed a new treatment concept, sealed therapeutic shoe, which potentially can fill the need for effective ulcer treatment without limiting ambulatory activity with its associated negative consequences for physical, mental and social health, and to a lower cost, resulting in fewer obstacles for clinical use.

The concepts include therapeutic shoes with custom-made insoles, where the new part is how the insole is optimized to offload the ulcer from mechanical loading and that the shoe is ”sealed” with a soft plastic strap and is used day and night, like a cast, and is only removed when changing the ulcer dressings. The ulcer is thereby offloaded but the person is free to ambulate and work as usual, and no cast changes are necessary. In addition to effective ulcer treatment and fewer side-effects the investigators hope that the positive experience of that high adherence to using therapeutic shoes results in healing will lead to higher adherence after healing, and thereby reduction of the risk of ulcer recurrences in the future.

The method to offload foot ulcers was first tested in a case-study, where it was found that the shoe and insole effectively offloaded the ulcer.[14] After this the investigators evaluated the whole sealed shoe concept in a feasibility study on seven people with DFU. All ulcers healed and complications were few.[17] The investigators are now going to evaluate the effects of sealed therapeutic shoes compared to gold standard treatment, that is, TCC.

Aims

The overarching aim is to evaluate whether sealed shoe can heal DFU at least as effectively as TCC, but with fewer adverse events during the treatment period, better long-term effects and to a lower cost.

Specific aims

Aim 1. To investigate whether a sealed shoe can heal DFUs at least as effectively as TCC.

Aim 2. To investigate whether there is a difference in adverse events during the treatment period with sealed shoe and TCC.

Aim 3. To investigate whether there is a difference in long-term effects (up to 12 months after end of treatment) with sealed shoe and TCC.

Aim 4. To investigate whether there is a difference in health economic outcomes between treatment with sealed shoe and TCC.

The null hypothesis is that a sealed therapeutic shoe does not heal DFUs at effectively as TCC, and that there are no differences between sealed shoe and TCC in adverse events, long-term effects and health economic outcomes.

Methods

The study is a non-inferiority multicenter randomized controlled trial (RCT).

Participants

Inclusion criteria: at least 18 years old, diagnosed diabetes mellitus (all types) and foot ulcer under metatarsal heads. A foot ulcer is here defined as “a break of the skin of the foot that includes minimally the epidermis and part of the dermis.”[15]

Exclusion criteria: large ulcers (covering 3-5 metatarsal heads), toe pressure or TcPO2 <30 mmHg, infection of IWGDF grade 3 (if uncontrolled or treatment has not been administered) or IWGDF grade 4, life expectancy <1 year, active Charcot foot, need of custom-made shoe,

and inability to read or write Swedish. In addition, people will be excluded where dementia, language- or other communication difficulties, active alcohol or substance abuse, or other factors increase the risk that adverse events will not be noted or reported, if the person does not have adequate social support.

The study is a randomized controlled non-inferiority trial where it will be investigated whether a new intervention (sealed shoe) is at least as effective as the established intervention (TCC).

Primary outcome is proportion of healed ulcers after 12 weeks of treatment. Based on the literature and our feasibility study the proportion of healed ulcers after 12 weeks treatment is estimated to 90% with sealed shoe or cast.[16, 17] If accepting p=0.05, a statistical power of 80% and a non-inferiority limit of 10%, 112 participants are needed. To compensate for attrition of participants, the aim is to recruite 150 participants. However, if it turns out that it is too difficult to recruit 150 participants, the recruitment of participant will end when the primary end point (healing at 12 weeks) has been observed for 56 participants per group, giving a total of 112 which fulfills the sample size calculation.

The participants will be randomized to treatment with sealed therapeutic shoe or TCC. The randomization will be stratified for ulcer size (smaller or bigger than 1 cm^2, ulcer size calculated as longest diameter*longest perpendicular diameter) and study center, and use random permuted blocks of randomly varying size.

Recruitment of participants

People who fulfill the inclusion criteria and not the exclusion criteria will be given oral and written study information and asked about whether they are interested in participating in the study. Those who agree will sign an informed constant to participate.

Intervention group, sealed therapeutic shoe: A prosthetist/orthotist will try out new therapeutic shoes to the participants and make individual insoles after casts of the feet. There will a limited number of shoe types to choose between and the procedure and material for the insole production will be standardized. The ulcer will be offloaded by adjusting the insoles with the help of plantar pressure measurement using the F-scan system (Tekscan, Boston, MA, USA). The "seal" of the shoe consists of a soft plastic strip (Bracelok, DJO Nordic, Malmö) that have to be broken to remove the shoe.

Control group, TCC: The participants will be treated with TCC, applied in a standardized manner. Participants in this group will also receive shoes and insoles, according to the same protocol as above, before TCC treatment is initiated to be comparable to the other group in the long-term follow-up after healing, when both groups will use shoes and insoles to prevent reulceration.

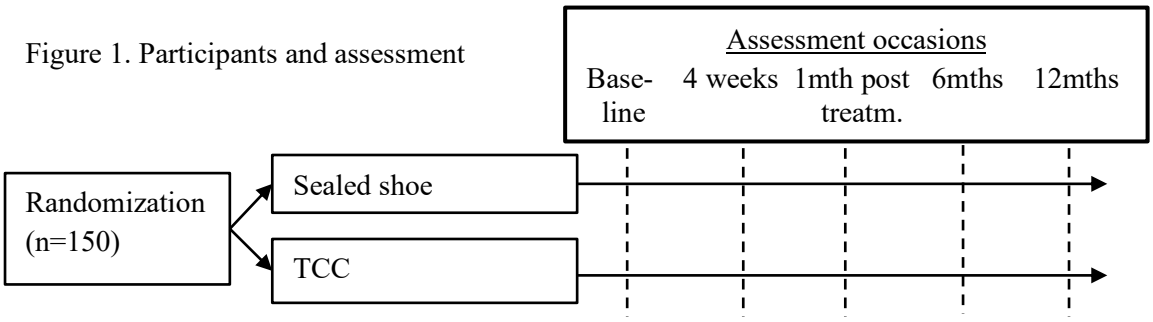
Both groups will visit the cast technician 1-2 times/per week depending on the status of the ulcer. The cast technician will change dressings, note whether the seal has been broken (for the intervention group), change casts (for the control group), photograph and document ulcers and complications, and ask participants if they have experienced any issues with the treatment. After this, a new dressing is applied, and the shoe is sealed (intervention group) or

a new cast is applied (control group). Participants will use a cover on the shoe or cast while taking a shower, and for the intervention group a cover will also be used when sleeping. Both groups will receive written information about potential complications and contact information to the clinics.

Data collection

Participants in both groups will be assessed by a physiotherapist on five occasions (Figure 1): at base-line, four weeks into the treatment period, and then 1, 6 and 12 months after healing (when treatment is ended). For the 4 week into treatment and 1 month post-treatment assessments, a visit window of ±1 week will be used. For the 6 and 12 months post-treatment assessments, a visit window of ±1 month will be used. Standardized and validated instruments and assessment methods will be used for the data collection (Table 1).

Figure 1. Participants and assessment



Aim 1: Ulcer healing (primary end point)

Primary outcome measure is ulcer healing after 12 weeks of treatment, defined by the Food and Drug Administration (FDA) as full skin epithelization of the ulcer, confirmed by a second observation 14 days later.[18] The cast technicians will assess ulcer healing in both the intervention group and control group. They will also photograph the ulcer and healed skin so a person blinded to group allocation can assess ulcer healing afterwards.

Aim 2: Adverse events during treatment (secondary end points)

Adverse events that are judged to be related to the offloading devices (shoe or TCC) will be classified as adverse device effects (ADE) and serious adverse device effects (SADE).[32] ADE include, but are not limited to, skin abrasions, blisters, sleep disturbances, issues with gait and balance, etc. SADE include, but are not limited to, new foot ulcers that result in amputation (major amputation = above ankle, minor amputation = below ankle), sepsis, etc.

Averse events that are not related to the offloading devices are classified as adverse events (AE) and serious adverse events (SAE).[32] AE include, but are not limited to, skin abrasions, new foot ulcers on the contralateral foot and not related to the device, etc. SAE include, but are not limited to, death, amputation, onset of acute Charcot foot, sepsis, etc. (not related to the offloading device). However, in accordance with previous studies on this patient population, the investiagators choose not to include all AE and SAE as the patient population suffers from multiple co-morbidities and therefore a high incidence of illness and hospital admissions unrelated to the DFU and offloading devices can be expected.[33] Therefore, all

ADE and SADE will be assessed, but only certain types of AE and SAE that are of particular interest, such as, amputation, death and onset of acute Charcot foot.

ADE, SADE, AE and SAE will be assessed with the aid of questionnaires, case report form (CRF), photographs of ulcer and skin, and patient files.

Aim 3: Long-term effects (secondary end points)

The secondary endpoints are time to healing and measures listed in Table 1. Each secondary endpoint is measured between one and five occasions during the study. For example, incidence of new foot ulcers, amputation, onset of acute Charcot-foot, death, adherence to using therapeutic shoes and locus of control will be assessed. Our hope is that the positive experience in the intervention group of that using therapeutic shoes can heal ulcers will result in a stronger internal locus of control and higher adherence to using therapeutic shoes after healing, so that fewer people will reulcerate or be affected by foot complications in the long term.

Data from patient files, questionnaires and the physiotherapists' assessments will be used for the analysis.

Aim 4: Health-economic outcomes (secondary end points)

The questionnaires RAND-36 and EQ-5D-5L will be used to assess general quality of life. Data from patient journals, Swedish Social Insurance Agency's system, and self-report questionnaires will be used to assess health care consumption and other costs.

Statistical analysis

See separate document for statistical analysis plan.

Research ethics

The participants will be informed about risks of the interventions in the written information that also will include contact information for the clinics. Risks will be minimized by excluding certain patient groups with heightened risks of side-effects not being noted or reported, and by a frequent follow-up during the intervention period. The study has been approved by the region ethics review board in Uppsala, Sweden (documents 2018/387 and 2019-03512).

Table 1. Overview of variables and assessment methods.

Variable	**Assessment method**	**Assessment occasion**					**Specific aim**
		Treatment period		*Follow-up after treatment end*			
		Base-line	4 weeks	1 month	6 months	12 months	
Ulcer healing	Clinical observation + blinded photo assessment	X	X	X			1
Skin complications	Clinical observation + blinded photo assessment	X	X	X			2
Glycemic control	Blood sample (HbA1c) [a]	X	X	X	X	X	2,3
BMI	Measurement of weight and height	X	X	X	X	X	2,3
Gait function	10 meter walk test[b] [19]	X	X	X	X	X	2,3
Gait function	Timed up and go[b] [20]	X	X	X	X	X	2,3
Balance	Berg balance scale[b] [21]	X	X	X	X	X	2,3
Muscle atrophy	Calf circumference[a] [22]	X	X	X	X	X	2,3
General quality of life	RAND-36[c] [23],EQ-5D-5L[c] [24]	X	X	X	X	X	2,3,4
Disease-specific quality of life	DFS-SF[c] [25]	X	X	X	X	X	2
Physical activity	ActivPAL[d] [26]	X	X	X	X	X	2,3
Physical activity	National Board of Health and Welfare's indicator questions[27]	X	X	X	X	X	2,3
Bone mass density	DXA[e] (heel bone)	X		X	X	X	2,3
Locus of control	Questions from MHLC-C[c] [28]	X		X	X	X	2,3
Ankle range of motion	Goniometer [a] [29]	X		X	X	X	2,3
Ankle strength	Dynamometer [a] [30]	X		X	X	X	2,3
Adherence to therapeutic shoes	Questions from Q-TFA [c] [31]	X		X	X	X	3
Treatment satisfaction	Visual analogue scale[c]		X	X			2
New ulcers, amputations, death, Charcot foot	Patient file and self-report [c]				X	X	3
Health care consumption	Patient administration systems and self-report[c]			X	X	X	4
Sick leave from work	Self-report,[c] Swedish Social Insurance Agency's system			X	X	X	4

[a]Standardized method, [b]function test, [c]questionnaire, [d]activity monitor, [e]Dual-energy X-ray absorptiometry

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