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Treatment of impending ulcers associated with hammer, mallet and claw toe deformities in the diabetic patient setting

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1. STUDY RATIONAL

Diabetes is one of the largest medical challenges facing the world today. 12% of the world's health budget is spent on diabetes, that is USD 673 billion (Euros 585 billion). It is estimated that a lower limb is amputated due to diabetes every 30 sec. on a global scale, and it is known that 85% of all amputations are performed due to a diabetic ulcer[1]. In Denmark 320.000 citizens has a diabetes diagnosis, an additional 200.000 are estimated to have diabetes unknowingly, and 750.000 to have the pre-stages of diabetes[2]. These numbers have doubled in the past ten years and are estimated to cost DKK 86 million a day (or Euros 11.6 million a day)[1]. One of the complications to diabetes is the "*diabetic foot syndrome*", which is a result of neurological abnormalities, vascular complications or a combination of the two. Knowledge about the causes of the disease has been gathered since the late nineteenth century[3]. In recent years, preventive therapy has been the focus of treatment, resulting in several national and international guidelines[4,5,6]. Focus has been on education in self-care and awareness of risk factors, combined with "Foot-at-Risk" evaluation[7], at least once a year and off-loading therapy crafted and applied by specialized personnel[3,4].

Steno Diabetes Center Copenhagen, University of Copenhagen, Denmark is a highly-specialized treatment facility focusing on the patient with diabetes. In spite of optimized treatment for patients with diabetes, and the fact that incidence of first time ulcers in patients with type 1 and 2 diabetes is declining, the incidence of first time ulcers is still 2.6 and 8.7 per. 1000 patient years for type 1 and 2, respectively[8]. Diabetic foot ulcers have a known association with increased mortality, morbidity and economic burden[9,10,11], at the same time most amputations in patients with diabetes are preceded by an ulcer[12].

Hammer, mallet and claw-toe deformities are some of the most common deformities associated with the *diabetic foot syndrome*. Prevalence has been reported between 32% and 46%[13,14]. These deformities are predictors of diabetic foot ulcers[15,16]. There are several theories on the etiology of hammer, mallet and claw toe deformities – the three classic deformities of the toes. In the diabetic patient setting, the classical theory is based on neuropathy (nerve damage associated with diabetes and other diseases), resulting in intrinsic muscle (muscles of the foot) dysfunction, changes that lead to imbalance between the flexor and extensor tendons, which in turn leads to hyperextension of the metatarsophalangeal (MTP) joint and/or flexion in the interphalangeal joints (IP), leading to the three classic deformities of the toes. The neuropathic theory is not sufficient to explain the full

scope of the problem, and other theories have been proposed[17]. In the non-diabetic patient, the neuropathic explanation is not viable, but the explanations still center on an imbalance between in- and extrinsic musculature, resulting from deformities in the foot either as flexor-substitution or stabilization deformities[18]. The deformities change the pressure on the plantar aspect of the foot[19]. These changes in pressure make specific contact points predilection sites for ulcers. The sites have been described as tip of the toe ulcers, cock-up ulcers, kissing ulcers and plantar metatarsal ulcers[20].

The treatment of hammer, mallet and claw toe deformities in diabetes has classically consisted of offloading in the form of shoes, insoles and/or orthosis (i.e. silicone spacers, felt pads etc.) or flexor tendon tenotomy (cutting tendons) done by scalpel. Several studies on flexor tenotomies performed with scalpel have been performed[21,22]; all have reported acceptable or positive results on ulcer healing and low complication rates, including one study from our own institute[23]. At Diabetic Foot Study Group 2018 we presented unpublished results from a study showing that tenotomy done by needle has comparable results to the classical scalpel. However, no study has, to our knowledge, been published comparing conservative treatment with surgical approach to these deformities, let alone randomized controlled trials (RCT).

2. WHAT DOES THIS TRIAL ADD TO CURRENT KNOWLEDGE?

This is to our knowledge the first RCT looking at flexor tenotomies as a preventive treatment, and/or compared to conservative treatment. At the same time this is the first study looking at needle flexor tenotomies, as opposed to the classic tenotomies done by scalpel.

3. HYPOTHESIS

We hypothesize that treating hammer, mallet and claw toe deformities in patients with type 1 and 2 diabetes, and impending ulcers (defined as nail changes, and hypercallosities at the predilection sites for ulcers associated with hammer, mallet and claw toe deformities) with needle tenotomy is a safe and effective treatment, and superior compared to offloading (conservative) treatment done by silicon spacer, insoles, felt, and/or therapeutic sandals

4. AIM

The aim of the RCT is to evaluate the effect of needle tenotomy when treating impending ulcers associated with hammer, mallet and claw toe deformities.

The study is designed as a prospective RCT comparing needle tenotomy with conservative treatment, for patients with deformities and impending ulcers associated with the three deformities.
Primary endpoint will be number of new ulcers incurred, defined as ulcers associated with hammer, mallet and claw toe deformities, placed on treated foot.
Secondary endpoints will be complications: infections (defined as ailment associated with procedure or ulcer, that is diagnosed as infection by attending health professional), transfer lesions (defined as impending ulcers or actual ulcers at anatomical sites associated with hammer, mallet and claw toes in patients with diabetes, on non-treated hammer, mallet and claw toes after surgical treatment), minor amputations (defined as amputations below ankle level), major amputations (defined as amputations at or above ankle level).

5. STUDY I

5.1 Design

A prospective RCT involving patients with diabetes as well as one of the three deformities and an impending ulcer associated with the mentioned deformities. By randomization, patients will be allocated to either conservative treatment or tenotomy performed by needle.

5.2 Patients

Inclusion criteria

- Patients aged 18 years or above
- Type 1 or 2 diabetes
- Hammer, mallet or claw toe deformity
- Impending ulcer associated with above mentioned deformities
- Able to understand written and oral information
- Ability to follow planned visits and treatment
- Able to provide informed consent in Danish and/or English

Exclusion criteria

- Revascularization procedure in the affected limb planned, or undertaken within the 4 weeks prior to screening
- Hammer, mallet and claw toe that are rigid in both MTP, IP joints
- Ulcer associated with hammer, mallet and claw toe deformities
- Toe pressure < 30mmHg
- Prior major amputations on affected or ipsilateral leg
- Other corrective operation is indicated to treat patients foot deformities as deemed by investigator
- Current treatment with cytotoxic drugs or with systemically administered glucocorticoids
- Treatment of foot ulcers with growth factors, stem cells or equivalent preparations within the 8 weeks prior to screening
- Likely inability to comply with the need for planned visits because of planned activity
- Participation in another interventional clinical foot ulcer-healing trial within the 4 weeks prior to screening
- Prior enrolment in this trial
- Judgement by the investigator that the patient does not have the capacity to understand the study procedures or provide written informed consent

Discontinuation of patients

- Patient discontinues assigned treatment for any reason, while not fulfilling one of the studies accepted endpoints
- Participants who withdraw from treatment will be asked to remain in the trial for follow-up, and data will continue to be collected and analyzed.
- Patient incurs a serious adverse event (SAE), defined as death or sepsis related to the study procedure

- Investigator decides to discontinue patient due to health or compliance reasons
- Patient misses 3 consecutive visits
- Patient misses 5 or more visits during the full treatment period

Patients who discontinue the study early will be invited to have a clinical visit before being discontinued.

Patients that are discontinued will revert to their normal treatment plan, and continue in their respective clinics.

Endpoints

- New ulcer incurred
  - When/if new ulcer is incurred pictures will be send to two external evaluators to be confirmed as new ulcer
- Patient reaches 12 month visit without incurring a new ulcer
- Patient incurs minor or major amputation on either treated or non-treated limb
- Patient receives surgical intervention relevant for the study (other than planned in study)

5.3 Method

Patients that meet the inclusion and exclusion criteria will be randomized to either

A: Intervention

Needle-tenotomy

Off-loading Treatment

B: Conservative Treatment

Offloading treatment

Both groups will also be offered offloading treatment in the form of therapeutic sandals with individualized insoles.

5.3.1 Needle Tenotomy Procedure

Patient is placed in seated posture with feet elevated. The toe(s) with hammer, mallet or claw toe deformity is anesthetized by a digital toe block with 1-5 ml of 1% lidocaine administered for each toe. The toe digital block is administered through a plantar approach, at the web level of the deformed toe(s), with a 0,6 mm diameter and 30mm long needle.

After anesthetizing the toe(s) the plantar aspect of the toe at web level is disinfected with an alcohol based disinfectant twice.

Both the long and short flexors are then severed with a 1.2mm diameter and 40mm long needle through a plantar approach, immediately proximal to the web level of the toe.

After the procedure a dry gauze bandage is applied and the patients treated foot/feet is/are elevated for 20 minutes to achieve haemostasis, and the bandage is checked for bleeding before discharge.

5.3.2 Offloading Treatment

Offloading Treatment: The patient's ulcer and deformity are offloaded by treatment with one or a combination of the following treatments:

- Therapeutic sandals with rocker-bottom and individual insoles
- Silicone device
- Handmade shoes with rocker-bottom and individual insoles
- Air-cast Walker
- Felt pad
- Capsule
- Own shoes and individual insoles

5.4 Visit-plan

Patients in both the intervention and conservative groups will be expected to adhere to a specified visit-plan

Visit-plan Study IV	Inclusion	Day 0	Day 7	Day 14	End[1]	Follow-up[2]
Duration	3 hours	30 min	30 min	30 min	30 min	30 min
In/exclusion criteria	+					
Baseline blood samples and physical exam	+					
Patient history	+					
Foot Examination	+	+	+	+	+	+
Changes in Medicine/ new ailments			+	+	+	+
Toe systolic blood pressure (TSB) Ankle/brachial pressure index (ABPI)	+					
Neurological assessment	+					
Randomization	+					
Tenotomy/silicone spacer application[3]		+				
Standard Care & offloading	+	+	+	+	+	+
Footwear assessment		+[4]	+	+	+	+

1: This visit only happens if patient incurs on of the named endpoints

2: Follow-up visits are performed at 3, 6 and 12 months

3: Depending on allocated treatment

4: All Patients receive therapeutic sandals with individualized insole

5.5 Detailed description of visits

The following section describes all visits in the study. All visits will be conducted by trained scientific staff, under responsibility of site investigator, and according to the delegation log. Procedures included in the visits will be conducted according to standard operating protocol (SOP) and manual of operations (MOP). It is the responsibility of principal investigator to train scientific staff in SOP and MOP. And to ensure that relevant SOP and MOP are available for the study personnel before procedures are performed.

5.5.1 Inclusion

Inclusion visit can only take place when written consent form is signed by patient, and filed in patient log.

The following procedures will be performed:

- In/exclusion criteria (see section 5.2)
- Baseline blood samples including:
    - Hemoglobin A_1C
    - Creatinine
    - Estimated glomerular filtration rate
    - Hemoglobin
    - Albumin
    - International normalized ratio
    - Low-density lipoproteins
    - Leucocytes
    - C-reactive protein
    - *All blood samples are analyzed immediately, and nothing is preserved in biobank. The total amount of blood is evaluated to be less than 50ml pr. patient.*

- Baseline physical examination including measurements of:
    - Blood pressure
    - Heart rate
    - Oxygen Saturation
    - Heart and pulmonary auscultation
    - Electro Cardiogram

- Height
- Weight

- Patient history including information on:
  - Gender
    - male or female
  - Diabetes type
    - 1 or 2
  - Duration of diabetes
    - measured in years with no decimal
  - Duration of foot ulcer
    - measured in days
  - Competing diseases/comorbidity (ASA group is also registered)
    - By diagnosis and year of debut
  - Current medicine
    - quantity and type
  - Smoking
    - quantity and nature, present or past
  - Alcohol intake
    - quantity
  - Height, weight and BMI
    - In m(two decimals), kg(one decimal) and kg/m^2(one decimal)
  - Prior surgery on feet
    - Type and year
  - Prior ulcers of feet/legs
    - Location and year
  - Prior amputations
    - Location, type and year
  - Prior/current history of Charcot's ailment
    - Debut year
    - Activity
  - Retinopathy
    - Simplex, proliferative and/or laser treated

    - Urinary albumin excretion rate
        - Normal, micro-, macro- or prior albuminuria
    - Peripheral neuropathy
        - Yes/no
        - Pain associated with?
    - Prior offloading therapy
        - Type
    - Relationship status
        - Married yes/no and/or living with partner yes/no
- Foot examination
    - Inspection of pressure point, and deformities
    - Pulses
    - Deformities
- TSBP and ABPI
    - TSBP and ABPI are performed by educated staff and results evaluated
    - Patients with TSB under 30 mmHg are referred to department of vascular surgery where deemed necessary
- Neurological assessment
    - Biothesiometry tests are performed by educated staff
    - Monofilament testing is performed by educated staff
    - Neuropathy symptoms are examined and registered
- Randomization
    - Randomization is performed in RedCAP
- Impending ulcer evaluation
    - Anatomical placement

5.5.2 Visit Day 0

- Foot examination
    - Inspection of pressure point, and deformities
    - Pulses
    - Deformities
    - New Ulcers

- Standard care & offloading
    - See section 5.3.2
- Tenotomy/conservative treatment application
    - The allocated treatment is performed
    - For details on tenotomy see section 5.3.1
    - For details on conservative treatment see section 5.3.2
- Impending ulcer evaluation
    - Anatomical placement
- Ulcer evaluation (if ulcer incurred)
    - Assessment of ulcer surroundings
    - Assessment of infection
    - Assessment of healing
- Measurement of longest length, width and depth in mm
- Measurement of area in mm^3(length*width*depth)
    - Assessment of incision site (where applicable)
    - Measurement of length, width and depth of ulcer(s) after debridement
- Categorizing by Texas Grading System
- Footwear assessment
    - Footwear and/or current offloading is evaluated
    - All patients in conservative and treatment group will be offered therapeutic sandals with customized insole at this visit
- Changes in medicine/new ailments
    - Changes to the patient's medicine, and/or new diagnosis are registered

5.5.3 Visit Day 7, 14

The following is a specification of the above mentioned visits. If at any visit, before week 10, the impending ulcer has been deemed as progressed to active ulcer, patient is planned for end visit. If Patient incurs ulcer between visit day 14 and 3 month visit, patient contacts study personal to arrange end visit as soon as possible.

- Foot examination

    - Inspection of pressure point, and deformities
    - Pulses
    - Deformities
    - New Ulcers (not associated to registered impending ulcers)
- Changes in medicine/new ailments
    - Changes to the patient's medicine, and/or new diagnosis are registered
- Standard care & offloading
    - See section 5.3.2
- Impending ulcer
    - Has impending ulcer progressed to active ulcer
- Ulcer evaluation (if relevant)
    - Assessment of ulcer surroundings
    - Assessment of infection
    - Assessment of healing
    - Ulcer photo
    - Measurement of longest length, width and depth in mm
    - Measurement of area in mm^3(length*width*depth)
    - Assessment of incision site (where applicable)
    - Measurement of length, width and depth of ulcer(s) after debridement
    - Categorizing by Texas Grading System
- Footwear assessment
    - Footwear and/or current offloading is evaluated
- Complications
    - Complications associated with tenotomy is registered (if relevant)
    - SAE is registered (if relevant)

5.5.4 End

End visit is only performed if patients impending ulcer(s) has progressed to active ulcer(s), or impending ulcer has not progressed to active ulcer at 12 month visit.

- Foot examination
    - Inspection of pressure point, and deformities
    - Pulses

    - Deformities
    - New Ulcers (not associated with registered impending ulcers at visit day 0
- Changes in medicine/new ailments
    - Changes to the patient's medicine, and/or new diagnosis are registered
- Standard care & offloading
    - See section 5.3.2
- Impending ulcer
    - Has impending ulcer progressed to active ulcer
- Ulcer evaluation (if relevant)
    - Assessment of ulcer surroundings
    - Assessment of infection
    - Assessment of healing
    - Ulcer photo
    - Measurement of longest length, width and depth in mm
    - Measurement of area in mm^3(length*width*depth)
    - Assessment of incision site (where applicable)
    - Measurement of length, width and depth of ulcer(s) after debridement
    - Categorizing by Texas Grading System
- Footwear assessment
    - Footwear and/or current offloading is evaluated
- Complications
    - Complications associated with tenotomy is registered (if relevant)
    - SAE is registered (if relevant)

5.5.5 Follow up

The following is a specification follow up visits. Performed at 3, 6 and 12 months post day 0 visit

- Foot examination
    - Inspection of pressure point, and deformities
    - Pulses
    - Deformities
    - New Ulcers
- Changes in medicine/new ailments

    - Changes to the patient's medicine, and/or new diagnosis are registered
  - Standard care & offloading
    - See section 5.3.2
- Impending ulcer
    - Has impending ulcer progressed to active ulcer
- Ulcer evaluation (if relevant)
    - Assessment of ulcer surroundings
    - Assessment of infection
    - Assessment of healing
    - Ulcer photo
    - Measurement of longest length, width and depth in mm
    - Measurement of area in mm^3(length*width*depth)
    - Assessment of incision site (where applicable)
    - Measurement of length, width and depth of ulcer(s) after debridement
    - Categorizing by Texas Grading System
  - Footwear assessment
    - Footwear and/or current offloading is evaluated
  - Complications
    - Complications associated with tenotomy is registered (if relevant)
    - SAE is registered (if relevant

5.6 Randomization

- Will be done in an open source electronic data capturing system (REDCaP), using the REDCaP Randomization module. This is based on an allocation table which will be generated by a statistician at our institute, with no other connection to the study.
- Patients will be block randomized, and stratified by treatment facility. Blocks will be of 5 patients each, stratified by study site.

5.8 Statistics

All statistical analysis will be performed using the version of SAS currently used at our institute. All data will be analyzed on the intention to treat basis. All baseline data will be presented using appropriate summarizing statistics. Appropriate comparable statistical analysis will be applied to

- Incidence of new ulcer(s) in treated limb
- Mean time (in days) to healing of incision sites
- Incidence of minor amputations
- Incidence of major amputations

Odds-ratio will be applied to

- The incidence of secondary infection
- Pain in treated limb, associated with tenotomy
- Transfer lesion

Sample-size

The calculation is done with a Type 1 error rate (α) at 5%, and a power (1-β) at 80%. The primary endpoint is number of new ulcers incurred.

In the general diabetic population life time prevalence of diabetic ulcers has been reported at 15-25%[24], the yearly incidence in the same group is 6%. This study focuses on patients with a deformity reported to have a 1.5 hazard ratio[25], and signs of an impending ulcer like callus formation, which has been reported with a relative risk of 11[26]. The incidence of new diabetic foot ulcers incurred by the study population is set at 10%, according to the above mentioned considerations.

The incidence in the intervention group (μ_A) is set at 6%, so the anticipated reduction in incidence is 4% compared to the incidence in the control group (μ_B) which as above mentioned is set at 10%.

However, the numbers for incidence of new diabetic foot ulcers is an uncertain size, especially when looking at the specific group we are looking at, therefore the standard deviation (σ) is set at 10.

The calculator used is a 2 means, 2 sample, 2-sided equality calculator. The formula is

$$nB=(1+1/\kappa)\ ((\sigma\ z1-\alpha/2+z1-\beta)/(\mu A-\mu B))2$$

nB= Sample size

κ= The matching ratio

With the above described parameters, the sample size is 98 patients, which due to an expected dropout of 10% will be extended to 110 patients.

6. PERSPECTIVE

The results of these studies will allow us to evaluate if there's a clinical advantage to performing preventive tenotomies. Several studies have shown that tenotomies done by scalpel are safe, and that most patients go on to heal their ulcers, but none have compared tenotomies to standard care, and no studies have looked at tenotomies as a preventive treatment against new ulcers. Our hypothesis is that patients with impending ulcers associated with hammer, mallet and claw toe deformities will have a lower incidence of new ulcers associated with hammer, mallet and claw toe deformities. At the same time, unpublished data from our institute show that tenotomies done by needle has comparable results to tenotomies done by scalpel. The economic perspectives are vast if a preventive minimal invasive procedure, that can be performed in everyday clinical work, with a minimal surgical technique requirement, can lead to significant reductions in incidence of new ulcers.

7. QUALITY CONTROL AND MONITORING

The studies will be performed in accordance with the Helsinki Declaration, International Council for Harmonization of technical requirements for pharmaceuticals for human use (ICH) Guidelines for good Clinical Practice (GCP)[27]. and after approval by the The National Committee on Health Research Ethics and the Data Monitoring Board in Denmark. The study will be registered on http://www.clinicaltrials.gov/.

Permission for a third person to have access to patient data will be obtained at screening visit. Investigators will provide access to source data and relevant documents in connection with monitoring, inspections, and audits to all relevant authorities.

8. ETHICAL CONSIDERATIONS AND DATA SAFETY

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki 1996 and the principles of GCP[28]

7.1 Ethical committee approval

The appropriate approval from a local Danish ethical committee will be obtained before start of trial, and their guidelines will be followed throughout the process. Patients will receive oral and written information on the study, before being required to sign an informed consent paper.

7.2 Personal data usage and protection

The appropriate approval from the Danish data protection agency will be obtained before the study commences, and their guidelines will be followed throughout the process. All patient data will be stored and treated in accordance with regulation 2016/679 from the European parliament on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, dated 27 April 2016[29], and the Danish amendment to regulation 2016/679[30].

7.3

Patient Perspective and Conclusion

Patients enrolled in this study will receive a treatment that is already implemented in our and several other clinics, and the unpublished data from our retrospective study and the formerly published data on tenotomies, points towards tenotomies being a safe and effective treatment of hammer, mallet and claw toes. Patients who don't receive intervention in the form of tenotomies in the study, will receive standard offloading and ulcer treatment, and be offered to undergo tenotomy if an ulcer occurs and tenotomi is found relevant. In conclusion the patients enrolled in the study will receive a treatment with potential benefits for them, and a low risk of complications making the study ethically sound.

9. BUDGET/ECONOMY

10.1 Budget

Category	Description	Expenses Covered
Salary	Monthly salary for chief investigator (64,171.75 monthly) for 36 months	1.155.092
Salary	Salary for podiatrist 16 hours a week (208 DKK/hour) for 3 years (156 weeks)	259.584
Publication	Publication Fee	15.000
Total		1.429.676

All figures refer to DKK

Consumables are not included, because they are present in clinic, and would be used regardless of patients' participation in the study

10.2 Economy

The study is funded by Steno Diabetes Center Copenhagen, and two private funds namely Jascha and Ejnar og Aase Danielsens Fond.

- Aase og Ejnar Danielsens Fond-50,000 dkk
- Jascha Fonden – 250,000
- Steno Diabetes Center Copenhagen – 1,129,676

There are no economic incentives for patients, but they will be offered refunding of travel expenses, in correlation with kilometers traveled. As an alternative to travel expense reimbursement, patients who participate in this study, will be offered transport to and from the treatment facilities in accordance with planned visit.

There are no economic incentives or potential winnings for treating health professionals.

10. RECRUITMENT

Patients will be recruited and treated at the three study sites, Bispebjerg Hospital, Hillerød Hospital and Steno Diabetes Center Copenhagen. Healthcare professionals (doctors, nurses and podiatrists) with daily care of patients with diabetes will be encouraged to look for potential study candidates in the outpatient clinics. If any potential candidates are found, patients will receive written information on the project, asked if we can contact them regarding the study and referred to one of the investigators for further screening. When referred to investigator, eligibility criteria will be confirmed based on information from the patients' electronic record (sundhedsplatformen). Patients will hereafter be contacted by telephone. If patients do not respond to contact by telephone, they will be contacted by letter.

In addition to the above mentioned method, primary investigator will conduct a screening of patients that are currently treated at the three institutes for eligible candidates. This screening will be conducted through the patient electronic record (sundhedsplatformen). The data that is screened in patient electronic record, includes all data relevant for in/exclusion criteria, namely prior diagnosis, operations, medicine use and visit information.

Identified candidates will be contacted by letter. If patients do not respond to letter, they will be contacted by phone.

Before written consent is given, patients will be informed orally and in writing by the educated study personnel, including information on procedures, visits, goal of the study, and their rights as participants.

General practitioners will be contacted by mail and asked to refer likely candidates to relevant study site (i.e. Hillerød, Bispebjerg or Steno). The general practitioners and licensed podiatrists in the region will be informed by standard text.
To increase potential candidates found, adds in relevant locale newspaper and in national magazines. The ads will be in the following standard texts.

Written consent will be acquired at inclusion visit by study related personnel. Patients will be required to fill out written consent form, after they have received oral and written information and been allowed up to 24 hours consideration and the possibility of bringing a personal assessor to participate at information and screening visits. If the patient needs additional time to consider, a follow-up meeting will be arranged minimum 24 hours after the first visit. Patients are informed that they can always withdraw their commitment to participate in the study, without consequences for their further treatment. No study related procedures are done until informed consent is signed by the patient.

11. DISSEMINATION OF RESULTS

The study is initiated by Peter Rossing. Data is owned by the investigators. Positive, inconclusive as well as negative study results will be published in both national and international oral and written presentations as well as peer-reviewed international scientific journals. If data against expectations are not published in international journals, positive as well as negative study results will be published on a public website, for example www.clinicaltrials.gov.

12. PATIENT INFORMATION

13.1 Written Information

All patients will receive information detailing the project, written information on their rights as Participants in research projects from the Danish ethics committee[31], and written information on the procedure, potential unintended side effects, and what to expect after the operation.

13.2 Verbal Information

All patients will be informed in layman's terms on the details of the operations, potential unintended side effects, and what to expect after the operation.

[1] Diabetic Foot International (http://www.d-foot.org/d-footinternational/)
[2] The Danish diabetes society (http://www.diabetes.dk/presse/diabetes-i-tal/diabetes-i-danmark.aspx)
[3] Some historical aspects of diabetic foot disease. (Connor 2008)
[4] NICE Guidelines on Diabetic Foot Problems prevention and management (2015)
[5] Prevention and management of foot problems in diabetes - IWGDF (2015)
[6] Increased healing in diabetic toe ulcers in a multidisciplinary foot clinic- An observational cohort study (Almdal 2015)
[7] Diabetic foot disease: From the evaluation of the "foot at risk" to the novel diabetic ulcer treatment modalities (Amin 2016)
[8] Decreasing incidence of foot ulcer among patients with type 1 and type 2 diabetes in the period between 2001-2014 (Rasmussen 2017)
[9] High prevalence of ischemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study (Prompers 2006)
[10] Cost of treating diabetic foot ulcers in five different countries (Cavanagh 2012)
[11] Reoperation and Reamputation After Transmetatarsal Amputation A Systematic Review and Meta-Analysis (Thorud 2016)
[12] Peripheral vascular disease and diabetes. In: Diabetes in America: diabetes data compiled 1984. (Palumbo 1985)
[13] Prevalence of Radiographic Foot Abnormalities in Patients with Diabetes (Smith 1997)
[14] Prevalence of foot pathology and lower extremity complications in a diabetic outpatient clinic (Holewski 1989)
[15] Foot ulcer risk and location in relation to prospective clinical assessment of foot shape and mobility among persons with diabetes (Cowley 2008)
[16] A prospective study of risk factors for diabetic foot ulcer (Boyko 1999)
[17] Role of intrinsic muscle atrophy in the etiology of claw toe deformity in diabetic neuropathy may not be as straightforward as widely believed. (Bus 2009)
[18] McGlamrys comprehensive textbook of foot and ankle surgery
[19] Elevated plantar pressures in neuropathic diabetic patients with claw hammer toe deformity. (Bus 2005)
[20] Percutaneous Tenotomy for the Treatment of Diabetic Toe Ulcers (Tamir 2014)
[21] Percutaneous flexor tenotomy for treatment of neuropathic toe ulceration secondary to toe contracture in persons with diabetes- a systematic review. (Roukis 2009)
[22] Effectiveness of percutaneous flexor tenotomies for the management and prevention of recurrence of diabetic toe ulcers a systematic review (Scott 2016)
[23] Percutaneous flexor tenotomy for preventing and treating toe ulcers in people with diabetes mellitus (Rasmussen 2013)
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