ISRCTN16238274 https://doi.org/10.1186/ISRCTN16238274

Influence of cutaneous pain insensitivity on the incidence of new foot ulcers in patients with diabetic polyneuropathy

Submission date	Recruitment status	[ ] Prospectively registered
22/05/2023	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
30/05/2023	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
30/05/2023	Nutritional, Metabolic, Endocrine	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
People with diabetes have a high risk of foot wounds (ulceration) and amputation. If people at risk for an ulcer could be identified, the incidence could be reduced. The risk of first ulceration is increased in people with loss of protective sensation (LOPS) measured using a tuning fork (vibration perception) a touch test and a monofilament (pressure perception). Another important marker of neuropathy at the foot is the loss of protective pain perception (LOPP), which is not often documented in clinical practice and the predictive value for the development of a first ulcer is unknown. The aim of this study is to evaluate the effect of LOPP on the development of a first-ever ulcer (FEU) of the foot in people with diabetes.

Who can participate?
Adults aged over 18 years old with diabetes mellitus type 1 and 2 and LOPS

What does the study involve?
Participants will be evaluated at a routine foot check in a specialised diabetes practice in Essen, Germany, using a vibration sensation of the feet with the tuning fork test. They will also potentially be examined for sensitivity to touch with a monofilament, during their yearly foot check in the diabetes program. A pointed, flexible glass fibre (pinprick) is now also used to check whether a "prick" can be felt as an indication of pain sensitivity. A follow-up examination is performed yearly in person, by telephone or by letter until the first ulcer, death or end of the observation period has occurred.

What are the possible benefits and risks of participating?
There is no benefit to participating in the study, and there is no disadvantage to not participating.

Where is the study run from?
Contilia GmbH (Germany)

When is the study starting and how long is it expected to run for?
September 2016 to December 2022

Who is funding the study?
1. Heinrich Heine University (Germany)
2. Investigator initiated and funded (Germany)

Who is the main contact?
Dr Anna Katharina Trocha, a.trocha@contilia.de (Germany)

Contact information

Type(s)
Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
The value of loss of protective pain sensation in predicting a first ulceration of the foot in people with diabetes

Acronym
FIRST UP

Study objectives
The aim of this study is to document the predictive value of either preservation of or loss of protective pain (LOPP) on first-ever ulcer (FEU) onset and/or time to FEU in a diabetic population also known to have a loss of protective sensation (LOPS).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/10/2017, Ethics Commission of the North Rhine Medical Association ([Ärztekammer Nordrhein], Teerstegenstraße 9, 40474 Düsseldorf, Germany; +49 211 4302 2273; addressethik@aekno.de), ref: 2017308

Study design

Prospective observational single-centre follow-up study

Primary study design
Observational

Study type(s)
Prevention, Screening

Health condition(s) or problem(s) studied
First-ever foot ulcer in people with diabetes

Interventions
This study is an examination of the pain sensitivity of the skin on the feet and its influence on the incidence of first-time foot ulceration in patients with diabetic polyneuropathy.

Foot ulcerations in diabetes mellitus are pathognomonic for diabetic foot syndrome. They result from chronic repetitive submaximal mechanical stress, especially pressure and friction over bony prominences during walking and occur predominantly in cases of reduced sensitivity due to diabetic neuropathy. According to German Disease Management Program (DMP), diabetic neuropathy of the feet is diagnosed by testing 64 Hz vibration sensation (using Rydel-Seiffer tuning fork) and/or 10g pressure sensation (using Semmes-Weinstein monofilament). However, neither of these sensory modalities is causally involved in ulcer development. Testing especially neuropathically impaired pain perception could provide prognostic information about the risk for plantar ulceration in diabetic patients and is also independent of the patient's language and cognitive ability. Cutaneous pain sensation can be tested using established methods of "quantitative sensory testing"(QST). Heat or cold or mechanical pain stimuli can be applied. Previous studies with mechanical pain stimuli had shown that patients with diabetic foot ulcers do not perceive a pointed pressure stimulus of 512 mN(= 51.2 g) on the foot as painful.

Loss of protective pain perception (LOPP) is diagnosed by a handheld pinprick-pain simulator device (Optistim Stimulator, Firma MRC-Systems GmbH, Hans-Bunte-Straße 10 in 69123 Heidelberg (info@mrc-systems.de) consisting of an optical glass fibre exerting a force of 512 mN to the plantar aspect of the proximal interphalangeal joint of the second toe three times, each for 1 second. Pain perception is judged to be preserved if a sharp sting-like cutaneous discomfort or pain was felt at least once. If none of the three pinprick simulations is felt, loss of protective pain is diagnosed on that foot.

The examination is carried out by a specialized diabetes nurse experienced in routine foot checks at the disease management program.

The examination will be carried out face-to-face during the baseline foot check. The test result is recorded with the date. Yearly after the baseline examination will determine which participant developed a foot ulcer (by personal follow-up/interview/letter/record evaluation).

A single examination for pain perception during a routine foot check at baseline will be undertaken at a Specialist Care Center for Diabetology.

Intervention Type
Other

Primary outcome(s)

1. First-ever ulcer occurrence measured using patient medical notes at a follow-up of 12, 24, 38, and 48 months
2. Death measured using patient medical notes by the end of the observation period

Key secondary outcome(s))
Time to first-ever ulcer measured using patient medical notes calculated using acceleration failure time (AFT) regression at one timepoint

Completion date
01/12/2022

Eligibility

Key inclusion criteria
1. Diabetes Type 1 or 2
2. Neuropathy
3. No history of a first-ever foot ulcer

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Total final enrolment
132

Key exclusion criteria
1. No diabetes
2. No neuropathy
3. History of first-ever ulcer

Date of first enrolment
15/01/2017

Date of final enrolment
01/10/2018

Locations

Countries of recruitment
Germany

Study participating centre
Medical Care Center for Diabetology
Herwarthstraße 102
Essen
Germany
45138

Sponsor information

Organisation
Heinrich Heine University Düsseldorf

ROR
https://ror.org/024z2rq82

Funder(s)

Funder type
University/education

Funder Name
Heinrich-Heine-Universität Düsseldorf

Alternative Name(s)
Heinrich Heine University Düsseldorf, HHU

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Germany

Funder Name
Investigator initiated and funded

Results and Publications

Individual participant data (IPD) sharing plan
The dataset generated during the study is not expected to be made available to maintain patient data security for the small number of type 1 diabetic patients who participated from a single center.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet		23/10/2017	25/05/2023	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes