Cover page for protocol

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II. BACKGROUND AND SIGNIFICANCE

A. Background

Diabetes Mellitus (DM) is a growing healthcare problem worldwide[1] and currently affects more than 451 million people[2]. DM is associated with excess morbidity and mortality[3][4] with diabetic peripheral neuropathy (DPN) being the most common of the classic diabetic complications[5]. This means, that half the diabetic population will develop DPN during their lifetime[6]. Moreover, DPN is also the leading cause for disability in diabetic patients, mainly due to its complications including autonomic disturbances and events related to the diabetic foot. The most important being diabetic foot ulcers, foot amputations, and the Charcot neuroarthropathy (CN), while approximately 20-30% of patients will suffer from invalidating neuropathic pain at some point during their lifetime[7]. Furthermore, diabetic foot ulcers have been associated with ischemic heart disease (IHD), which is the leading cause of premature mortality in patients with DM[8]. At the same time, the five-year mortality after new-onset diabetic ulceration have been reported to be 43-55%, and 74 % in patients with diabetic foot amputation, which is significantly higher than the five-year mortalities for many forms of cancer[9].

Despite this, our knowledge is quite limited when it comes to risk stratification of the diabetic patients. It is clear that DPN is the single most important risk factor for development of complications regarding the diabetic foot whether talking about foot ulcers[10], amputations[11], or CN[12]. However, the current clinical tests to detect DPN are unspecific and with questionable sensitivity reported as low as 0.53[13]. Furthermore, the current clinical tests are solely assessing large fiber neuropathy and are not able to do a meaningful grading of the severity of the neuropathy, hence the need for new methods to provide efficient clinical outcome measures and useful clinical endpoints.

B. State-of-the-Art

Diabetic peripheral neuropathy (DPN) is the most common complication to advanced diabetes mellitus (DM)[14], and is strongly associated with invalidating and life-threatening complications like foot ulcers[15][16], CN [17][18], painful neuropathy[19], risk of fall and fracture[20], and lower foot amputations[11]. The incidence of DPN is reported with great variance, but several large studies have reported numbers around 20% for DM type I[21][22][23] and 50 % for DM type II[24]. Furthermore, patients with foot pathology attributable to DPN exhibit significantly higher mortality rates than those solely attributable to vascular diseases. This applies to both non-infectious neuropathic foot ulcers[25] and acute CN [26].

At this point no treatment for the underlying nerve damage of DPN is available[27], and the pathogenesis is still not fully understood[28][29][30]. Therefore, current strategies focus on prevention of the initial nerve damage using annual screening-tests targeting large nerve fibers. Available tests for large-fiber function include vibration perception, proprioception, 10-g monofilament, and ankle reflexes[31]. Tests for small-fiber function are not routinely used, but include pinprick and temperature sensation[31]. Most studies have reported that early stages of DPN mainly affect the small nerve fibers[32][33] raising the question of why these are not used in standard screening. However, mixed results do exist, as some studies have reported simultaneous development of DPN in small- and large nerve fibers[34][35]. The most common clinical tests (monofilament) have recently been reviewed, showing low sensitivity when trying to detect early neuropathy[13][36], but wielding fine results when detecting severe neuropathy[37].

In recent years several new tests for DPN has emerged. Most notably Neuropad[38][39], NeuroQuick[40], and Vibratip[41], alongside the NC-stat DPNCheck[42] for automated nerve conduction study(NCS), and SUDOSCAN[43] for a quantitative measurement of sweat function. Furthermore, more equipment-heavy diagnostic tools have been used in an increasing degree in settings of clinical research. These mainly include skin biopsies[44][45], corneal confocal microscopy (CCM)[46][45], and Quantitative Sensory Testing (QST)[47][48], which is combined test examining the sensory perception after application of different mechanical and thermal stimuli of controlled intensity evaluating the function of both large and small nerve fibers. Neuropad is an indicator test for measuring sweat production as an expression of small nerve-fiber function. The test is originally designed to detect neuropathy by changing color in accordance to sweat production. However, some groups have also measured absolute time to color change suggesting this as a measurement for severity of neuropathy[49]. The sensitivity and specificity of the test has been reported with great variance ranging from 65.1-100% and 32-78.5% respectively[50]. NeuroQuick is a small portable fan with ten different velocity settings testing thermal perception. It has been suggested as an early measure for neuropathy, but clinical trials are currently lacking. Vibratip and Ipswich Touch Test (IpTT)[51] both test peripheral vibration threshold and has proven consistent with established standards[41]. The NC-stat DPNCheck is an automated Nerve Conduction Study (NCS) aiming to increase the utilization of traditional NCS in a primary care setting. It has been reported to yield a sensitivity of 92% and a specificity of 82 % referenced against traditional NCS[52]. Tactile Circumferential Discriminator (TCD)[53] (cylindrical disc with metallic rods) and steel ball-bearing[54] both test for loss of protective sensation (LOPS). However, clinical use is limited due to lack of either sensitivity or specificity respectively. Like Neuropad, SUDOSCAN is designed to evaluate sweat secretion as a marker for small nerve-function and like Neuropad, SUDOCAN has been proposed as a tool for grading neuropathy[55]. In present studies, SUDOSCAN seems to correlate with vibration perception threshold as measured with a biothesiometer, while detecting DPN with a sensitivity of 78% and a specificity of 92%[56]. Axon reflex-mediated neurogenic vasodilation is another technique proposed as a method for early detection of DPN[59]. The method uses lacking vasodilatory response to cutaneous heating as a measurement of pre-clinical small fiber dysfunction, but currently remain on experimental ground[60][61]. In recent years, Magnetic Resonance Imaging (MRI)-scans with experimental sequences including blood oxygen level dependent signal (BOLD)-[57] and track-density imaging (TDI)-MRI[58] have also been of interest, as these might be able to detect early neuropathy. However, further studies are needed. Lastly, an experimental technique for tracking membrane potential and excitability called Perception Threshold Tracking (PTT)[62] has been suggested as a method for early detection of DPN, but the method needs clinical studies.

III. STUDY OBJECTIVES

To test Perception Threshold Tracking (PTT) and multi-level MRI as methods for early detection and grading of severity of neuropathy in patients with diabetes mellitus.

To use multi-level MRI for characterization of peripheral and central nervous system changes related to neuropathy in patients with diabetes mellitus.

To compare Perception Threshold Tracking (PTT) and MRI to methods of traditional clinical practice and established methods of clinical research like Corneal Confocal Microscopy (CCM) and Quantitative Sensory Testing (QST) as well as axon flair-mediated neurogenic vasodilation (AF).

To test reliability of different measurements of neuropathy.

A better understanding of the underlying neuropathy of diabetes and new methods for early, reliable detection of DPN could result in intensified treatment and prophylactic measures prolonging of the complication-free period of diabetes mellitus. Ultimately, this could potentially result in fewer complications related to the diabetic foot, and maybe even prolonged overall-survival and reduced healthcare cost.

IV. METHODS

A. Study Design

This study is a prospective, observational, cross-sector study starting March 1, 2019 running until December 1, 2021. The study will be conducted on patients from Aalborg University Hospital. Participants will be informed about the trial both written and vocally and no changed in antidiabetic medication will be performed. The instruments will include Corneal Confocal Microscopy (CCM), Quantitative Sensory Testing (QST), axon flair-mediated neurogenic vasodilation (AF), handheld heart rate measurement device (Vagus^{TM}), cuff, and MRI, which are all established methods of clinical research. Furthermore, participants will be tested using monofilament and Biothesiometry, which equals actual clinical practice, and with Perception Threshold Tracking (PTT), which is a new take on an older, well-known technology. Further tests will include a handheld pinprick device, measurements of peripheral arterial disease (PAD) and conventional NCS. The main endpoint of the study will be sensitivity/specificity of all examinations, as well as a comparison of the newer methods against more well-established modalities.

B. Study Population

The study population include four well-defined groups of subjects:

1. Patients with Type 1 diabetes and painful diabetic peripheral neuropathy (DPN).
2. Patients with Type 1 diabetes and non-painful diabetic peripheral neuropathy (DPN)
3. Patients with Type 1 diabetes and without diabetic peripheral neuropathy (DPN).
4. Healthy control subjects matched for age, BMI, and gender.

Diabetes duration, HbA1c, insulin use, ethnicity, and co-morbidities will be matched between group 1, 2 and 3 to best ability.

Inclusion criteria:

1. Men and women minimum 18 years of age and maximum 70 years of age
2. Signed informed consent form
3. Diagnosed with diabetes type I (for group 1-3)
4. Diagnosed with DPN defined as a threshold above 25-volt biothesiometry or absent feeling on the big toe using 10g-monofilament. (for group 1-2)
5. Answered questionnaire: PainDETECT
6. Nothing abnormal on initial tests (group 4)
7. Accepted initial screening blood samples
8. MRI-compatible participant

Exclusion criteria:

1. Current or previous alcohol- or drug abuse

2. Abnormal screening blood samples
3. Not being able to understand Danish written and/or verbally
4. Not being able to corporate to examination (e.g. not being able to speak, suffering from senile dementia etc.)
5. Previous chemotherapy or intake of experimental medicine
6. Active HSV- or VZV-infection or known HIV
7. Known severe skin disease
8. Known neural damage or disease in the neural system (e.g. MS, Guillain-Barre etc.)
9. Critical limb ischemia defined as in current clinical consensus[63]
10. Allergy or intolerance to histamine or inability to make do without for one day
11. Pregnancy
12. Active cancer-disease

C. Assessment of Resources

The study will be conducted in collaboration with Steno Diabetes Center Northern Denmark (SDCN) and Department of Radiology, Aalborg University Hospital. SDCN has access to patients with diabetes and can provide the necessary premises.

The study will be conducted in collaboration with Center for Neuroplasticity and Pain (CNAP), Aalborg University and SDCN, who have the technical and financial resources needed to establish the setup and conduct the examinations. Furthermore, an experienced research Bio. Med. Lab. Technologist is signed for the project thereby, alongside the Ph.D.-students, ensuring trained personnel. The study is set for a long inclusion, but additional time is available if required, as the Ph.D.-students are employed until 31st of October 2022.

The project is initiated by Professor Niels Ejskjær, Aalborg University and SDCN, and is supported economically by Steno Diabetes Center North Denmark and Aalborg University. The support is however limited to staff salary and purchase of smaller equipment.

D. Study Procedures

Diabetic patients will be recruited during their scheduled visit to the outpatient clinic of SDCN, Aalborg University Hospital. Healthy controls will be recruited based on the included diabetic population using relatives of diabetic patients, medical students, and people known by participating staff.

After the informed consent is obtained the screening of the participant will be executed. Afterwards the participant have to attend three different sessions as shown in appended flowchart. Each session includes different tests and the sessions will be ordered randomly, since they have no influence on each other. Moreover, a conventional nerve conduction test will be performed, however this test will be performed as per usual by the department of neurophysiology, as this is a standard examination for patients with neuropathy.

PainDETECT

PainDETECT is an English questionnaire validated for detecting neuropathic pain[64]. It has later been translated and validated in Danish[65], and will be given each participant alongside instructions after form of consent has been signed. The patients will answer the questionnaire individually and will need to complete this before any other examinations can be conducted, as this will help placing the patients in the correct group.

Estimated time: 5-15 min.

Clinical examination

This mainly include biothesiometry and 10g-monofilamnent as these simple measures equals current clinical standard when screening for neuropathy. In biothesiometry, the detection limit of vibration is determined with slow rising strength until the patient perceives the vibration. In 10g-monofilament testing the physician uses a thin nylon fiber, which bends at a pressure of 10 grams. The filament is applied to four specific spots at the bottom of the foot. The tests are usually conducted during the scheduled visit to the outpatient clinic. If not, these tests will be performed just after inclusion before other experimental tests. This point also includes measurements of blood pressure measured at the arm, leg and toe as well as oxygen pressure in the blood vessels of the toe (TPO_2). This allows a good assessment of potential PAD. Results from the clinical examination might be collected as a Neuropath Disability Score (NDS). Above mentioned examinations might be conducted at any of the later mentioned sessions (see appended flowchart).

Estimated time: 15-20 min (possibly partly conducted during already scheduled appointment).

512 mN pinprick

This is a small custom-made pinprick device based on standardized QST (see below) principles. The device functions much like the monofilament described above but differs since it has a sharp finish thereby activating not large- but small nerve fibers. This test is conducted either during the scheduled visit or just after inclusion in the study alongside clinical examination.

Estimated time: 5 min.

Conventional nerve conduction

Will be conducted by the department of Neurophysiology, Aalborg University Hospital, as “golden standard” for assessment of large nerve fiber function. The test is a standard clinical test and might already be conducted at the time of inclusion.

Estimated time: 30 min.

Corneal Confocal Microscopy

Corneal Confocal Microscopy (CCM) is a noninvasive method for studying of the human cornea in vivo. It is used in an increasing fashion for assessment of corneal small nerve fiber pathology as an expression of peripheral neuropathy[46]. Before examination, the eye of the participant will be anaesthetized using 0.4% benoxinate hydrochloride and Viscotears for front eye lubrication. The examination will be conducted by personnel trained by seasoned international operators.

Estimated time: 60 min.

Quantitative Sensory Testing

Quantitative Sensory Testing (QST) is a way of assessing large and small sensory nerve fiber function using several different stimuli. The method has been verified using different protocols, and will be conducted in

accordance to the original protocol by German Research Network on Neuropathic Pain (DFNS)[66]. All measurements are made on the dorsum of the foot. The test will be conducted by either PhD-students or research bio. med. lab. Technologist. The protocol consists of seven tests measuring 13 parameters including:

1) **Thermal detection, thermal pain thresholds and paradoxical heat sensations:**
   The tests for thermal sensation will be performed using a thermal sensory testing device. Cold detection threshold (CDT) and warm detection threshold (WDT) are measured initially and the number of paradoxical heat sensations (PHS) are counted. Cold pain threshold (CPT) and heat pain threshold (HPT) are then calculated as a mean threshold temperature of three consecutive measurements. All thresholds are to be obtained with ramped stimuli increasing by 1 degree Celsius per second, terminated as the patient presses a button. Cut-off temperatures are set at zero and 50 degree Celsius and the baseline temperature is set at 32 degree Celsius, as this represents the mean value of skin temperature.

2) **Mechanical detection threshold for modified von Frey filaments**
   Mechanical detection threshold (MDT) is to be measured using a standardized set of modified von Frey hairs that exert forces between 0.25 and 512 mN. The final threshold will be the geometric mean of five series of ascending and descending stimulus intensities.

3) **Mechanical pain threshold for pinprick stimuli**
   Mechanical pain threshold (MPT) is to be measured using thin, blunt, weighted pinprick stimulators that exert forces between 8 and 512 mN. The set will consist of seven different stimulators and the MPT will be the mean of five series.

4) **Mechanical pain sensitivity and dynamic mechanical allodynia**
   Mechanical pain sensitivity (MPS) is to be tested using the same weighted pinprick stimuli as for MPT (see above). To obtain a stimulus–response-function, the seven pinprick stimuli is applied in a balanced order, five times each, and the subject is asked to give a pain rating for each stimulus on a 0–100 numerical rating scale with 0 being no pain and 100 being worst pain imaginal.
   Stimulus–response-functions for dynamic mechanical allodynia (ALL) are determined using a set of three light tactile stimulators: a cotton wisp (force: 3 mN), a cotton wool tip fixed to an elastic (force: 100 mN), and a standardized brush (force: 200–400 mN). The three tactile stimuli are applied five times each with a single stroke of approximately 1–2 cm in length over the skin. They are intermingled with the pinprick stimuli in randomized order and subjects are asked to give a rating on a scale equal to the one used for MPS (see above).

5) **Wind-up ratio: the perceptual correlate of temporal pain summation for repetitive pinprick stimuli**
   In this test of temporal summation, the perceived magnitude of a single pinprick stimulus is compared with that of a train of 10 pinprick stimuli of a force of 256 mN repeated at a rate of one prick per second. Subjects are asked to give a pain rating representing the pain at the end of the train using the same scale as for MPS and ALL (see above). Single pinprick stimuli are alternated with a train of 10 stimuli until both are done five times at five different skin sites on the same foot. The mean pain rating of trains divided by the mean pain rating to single stimuli is calculated as wind-up ratio (WUR)

6) **Vibration detection threshold**
   Vibration detection threshold (VDT) is tested using a tuning fork (64 Hz) placed over the medial malleolus. Vibration threshold is determined by the mean of three series of descending stimulus intensities.

7) **Pressure pain threshold**
   This test is performed using a pressure gauge device able to deliver a pressure up to 200 N/cm^2. The pressure pain threshold (PPT) is determined with three series of ascending stimulus intensities on m. tibialis ant., each applied as a slowly increasing ramp of 50 kPa/s.

Estimated time: 60-90 min.

Axon flair-mediated neurogenic vasodilation

Axon flair-mediated neurogenic vasodilation (AF) uses Laser Doppler flowmetry (LDF) [66] or laser Doppler imaging (LDI) [67] to analyze vasomotor small fiber function by quantifying the integrity of the vasomotor-mediated axon reflex. While LDF assesses the flare response following acetylcholine iontophoresis with temporal resolution at a single defined skin point, LDI records flare responses with spatial and temporal resolution, generating a two-dimensional map of superficial blood flow [61]. In this study, the participants' surface skin temperature of the dorsum of the foot will be standardized to 32 degree Celsius using a warm blanket or warming pad. Either histamine or Acetylcholine will then be applied to a small area and vasodilation will be measured in accordance to earlier studies[67].

Estimated time: 15-20 min

Perception Threshold Tracking

Perception Threshold Tracking (PTT) is a potential new method for early detection of neuropathy. It is a further development of conventional threshold tracking[68] that excels in describing membrane potential of not only large, but also small nerve fibers[62]. The trial is conducted using two types of surface electrodes placed on the dorsum of the foot: patch and pin electrodes for stimulation of large and small nerve fibers respectively. The perception threshold is then estimated by slowly increasing the intensity of stimuli until the patient presses a button indicating that the stimuli is perceived. As this happens, the intensity is initially heighted by 20 % and then lowered until the patient relieves the button indicating that the stimulus is no longer felt. The intensity is then lowered by 20% and then increased until perception is indicated by pressing the button. This is repeated three to five times to increase precision. The perception threshold is taken as the average of the six to ten times the patient pressed the button. This procedure will be repeated a number of times using different electrodes. The patient will feel no significant pain, as the stimuli given is just around the individual perception threshold, which is a huge benefit of this method compared to other available neural tests.

Estimated time: 35-45 min

Multi-Level Magnetic Resonance Imaging

The multi-level MRI will be used to assess brain structure, function and metabolism and the peripheral nerve structure and function. The MRI session will consist of 1) an anatomical 3D scanning of the brain, 2) functional

MRI scan, 3) whole brain diffusion tensor imaging (DTI) for assessment of microstructure and fiber tracts, 4) MR spectroscopy assessment of metabolite, 5) BOLD signal for microvascular function in central level and peripheral level, and 6) MRI neurography of the peripheral nerve fibers. Additionally, cuff occlusion procedure will be performed in the MRI scanner (cf. next section). Heart rate, respiration rate, will be recorded throughout the MRI scan.

Estimated time: 90 min

Cuff occlusion

During the BOLD-MRI a cuff occlusion procedure will be performed to investigate the microvascular function. A cuff will be mounted around the leg, proximal to the knee, and inflated (240 mmHg) for 5 minutes to reduce or blockage the blood flow in the lower leg.

Estimated time: 15 min

Cognitive Tests

A validated cognitive questionnaire will be performed to test the mild cognitive impairment and possible affected cognitive domains in the participants. Moreover, a cognitive task will be performed in the scanner in order to test the participants' cognitive psychomotor speed and memory.

Estimated time: 15-20 min

Vagus Test Procedure

A commercial available handheld device (Vagus™, Medicus Engineering Aps, Aarhus N, Denmark) will be used to test the autonomic nervous system and hereby the autonomic neuropathy. The participant will hold the device during four steps, where the device will 1) measure the heart rate at rest, 2) measure the heart rate response from laying position to standing position, 3) measure the relationship between heart rate during expiration and inspiration, and 4) measure the heart rate conditions during exhalation with a resistance of 40mmHg and at rest.

Estimated time: 10-15 min

Blood samples

Blood samples will be taken after informed consent has been signed. Blood taken is estimated not to exceed 15 ml and will include:

Hgb, leukocytes and diff. counting, blood platelets, cobalamin, folate, sodium, potassium, creatinine, bicarbonate, CRP, ALAT, alkaline phosphatase, LDH, bilirubin, albumin, coagulation factors, vitamin D 1.25, Calcium-ion, TSH, HbA1c and M-component.

The blood samples will be taken and handled as usual by the biochemical department and will be destroyed after usage. No biobank will be made. All samples will start being analyzed immediately (within 2h), however, some samples (like vitamin D) will take some time to analyze. All results will be available within 10-12 days but samples will always be destroyed as soon as the analysis has been initialized.

V. DATA COLLECTION

Patient data will be collected using the electronic patient journal (EPJ) after consent of the participant. Only patients with an active continuity of care at SDCN will be included (as well as healthy controls). The principle investigator is employed at SDCN as a medical doctor alongside one of the Ph.D.-students.

Data collected will include demographic data such as name, age, sex, weight, and height, and clinical information related to diabetes, such as type, duration, medication, complicating peripheral arterial disease, and status of complications. This to ensure correct grouping of the patients and to make sure that they meet the inclusion criteria.

VI. DATA ANALYSIS

A. Sample Size Considerations

The following sample size estimation is made on the ability to separate a group of diabetic patients without neuropathy from a group of diabetes patients with 'moderate' neuropathy. The calculations are based on published measurement of the sensory nerve action potential amplitude in nerve fiber conduction assessments[45]. Setting the significance level to 0.05 and the power to 0.8 results in a sample size estimation of 16 persons in each group. $n = \frac{15.7*\sigma^2}{d^2} = \frac{15.7*(4.7^2+7.5^2)}{(14.4-5.7)^2} = 16$. The study involves several experiment measures, but we expect that max 20% of the measures will be dropouts. The number of participants needed to be recruited in each group will therefore be $N = \frac{n}{1-dropout} = \frac{16}{0.8} = 20$. We want to compare four groups as defined in section IV.B. Study Population. The total number of participants will therefore be 80.

B. Statistical Methodology

The data will initially be analyzed by a series ANOVA test to compare each measurement between the four groups.

To avoid 'mass significance' a combined analysis of all measurements will be performed by logistic regression models (LRM) in three steps. This will allow an estimate of the odds ratio and accuracy of each of the measurements and the measurements in combination. First, a series of univariate LRM will be performed for each measurement to investigate the odds ratio and accuracy of the individual. Second, a multiple factor LRM with all measurements as factors will be performed to estimate the odds ratio and accuracy for all measures in combination. Thirdly, factor reduction will be performed to assess the accuracy and odds ratio of a set of independent measures.

Simple bivariate correlation will be performed to further investigate the relation between measurements. Due to the complexity of the measurements a further analysis of the interdependency of the measures using factor analysis will be performed.

VII. DATA AND SAFETY MONITORING PLAN

The project will be reported to the Data protection Agency (DPA), and all sensitive data will be stored in either Red-CAP or on the protected server of Aalborg University Hospital, "*Elektronisk system adgang*" (ESA).

Data are stored in accordance with the stipulations in The Danish Personal Data Protection Act (Persondataloven) and other relevant Danish legislation. If any data processing would occur in foreign countries, the data will be anonymized and handled according to the Danish Data Protection Act.

The data can only be used for the interpretation of this project and will therefore not be of interest to third party.

The project is included in "Region Nordjyllands fællesfortegnelse".

VIII. STUDY LIMITATIONS

Both PTT and QST require corporation from the patients and include subjective measures of pain. As the measured thresholds are not purely objective, psychosocial factors might influence test results.

The study includes diabetic patients exclusively and might not be applicable on populations with different causes of neuropathy.

The expected number of participants are set at 80, thus maybe require additional larger studies to confirm findings.

IX. ETHICAL CONSIDERATIONS

A. Informed Consent

The initial enquiry about participating will be made by the patients' doctor during the scheduled visit at the outpatient clinic. The participants will then receive information regarding the project both written and verbally and information for participants ("deltagerinformation") will be handed out. Further information will later be given by a person fully informed about the study and with comprehensive knowledge of the different tests involved. Desirably either by the affiliated research bio. Med. lab. Technologist, the principle investigator, or one of the Ph.D.-students.
Healthy control subjects will be approached verbally or in writing and will later receive information equal to the diabetic population. In other words, the healthy control subjects will first receive brief information alongside information for participants ("deltagerinformation"). At least 24h after receiving written information, the healthy control subjects will be invited to participate in an informational meeting. If they chose to participate, they will need to sign informed consent and proceed in the study like the other groups.

The given information will include:

- That this is a scientific project testing a potential future method to detect diabetic peripheral neuropathy.
- Information regarding the different tests involved incl. the risk of minimal to moderate pain associated with especially QST and cuff occlusion.
- That withdrawal from the project is possible at any time.
- That data collected will be published in an anonymized form, without any traces of personal data
- That data collected will be safely stored in accordance with the rules in force.

Potential participants are allowed at least 24 hours for reflection and additional, informational meetings might be scheduled. During the scheduling of the informational meeting the participant will be informed about the right to an assessor or relatives both for the meetings and sessions. Participants are informed about their right and the possibility for an additional meeting before signing informed consent. No external

funding has been given. Neither of the core members have any conflicts of interest to declare. The project will be prospectively registered to www.clinicaltrials.gov.

B. Risks and Side Effects

As the project is mainly observational and contains no interventions the overall risk for the patient is extremely limited. No changed/adjustments in medication will be made and there will be no risk for hypo/hyperglycemia. The main issue for the participants is the fact that some time is needed for the conduction of the examinations, and the fact that patients might be required to take additional trips to the hospital. Furthermore, a small amount of transient pain might be felt during some of the examinations; however, no lasting side effects are reported regarding any of the examinations. Listed below are the potential risks and side effects of the different examinations included in the protocol:

1. Blood samples: Almost negligible risk of infection, small bleeding or pain around syringe insertion.
2. QST/PTT: Participants might feel a small amount of transient pain during some parts of the examinations. No lasting pain will occur.
3. CCM: Pupil-dilation might result in impair vision and increased sensitivity to light for a short period of time. Driving is not permitted while vision is impaired.
4. AF: A transient warm sensation might be felt in relation to the area of medicine application.
5. Cuff occlusion: There may be discomfort and mild to moderate pain may occur for less than 5 minutes when inflating the cuff. However, no lasting pain will occur after deflation of the cuff.
6. MRI scanning: There are no known harmful side-effects associated with MRI. However, being in the MRI scanner can cause discomfort and claustrophobia. The participant can at any time use the emergency squeeze ball to stop the investigation.

C. Benefits to Subjects

The subjects will not directly benefit from participation. However, the trial might shed some light on a condition, which they either already have or are bound to develop. Furthermore, the findings might help them later due to a better understand and prevention/delay of mentioned condition. In addition, the study might help their fellow diabetics, as this is a potential new test for early detection and grading of neuropathy, which both patients and the scientific community sorely needs.

D. Costs to Subject

Participants might need to travel to the hospital two additional time(s). No further cost for the participants is associated with this project.

E. Compensation to Subject

No economical compensation will be payed. However, patients may be entitled to a driving allowance in accordance to the Danish Health Act. However, neither healthy controls or subjects with diabetes can receive driving allowance for visits that are not a part of the standard care (session 1, 2, and 3). In case of unforeseen side effects, the patients will be compensated in accordance to the Danish Health Act and "*patienterstatningsordningen"*.

F. Provisions for vulnerable subjects

The participants are not expected to be any more vulnerable than the average patient is, and the trial does not contain any particularly distressing examinations.

X. PLANS FOR DISSEMINATION OF FINDINGS

The study is to be published as several articles in an internationally acknowledged scientific magazine. The results will be published regardless of the outcome of the project and is publish whether accepted in scientific journals or not in accordance to "komitelovens §20". Further dissemination might include conferences like Diabetes Foot Study Groups (DFSG) annual meeting.

XI. REFERENCES

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XII. APPENDICES

PainDETECT

painDETECT

SPØRGESKEMA OM SMERTER

Dato: Patient: Efternavn: Fornavn:

Hvordan vil du vurdere styrken af dine smerter nu, i dette øjeblik?

0 1 2 3 4 5 6 7 8 9 10

ingen værst mulige

Hvor stærke har dine stærkeste smerter været inden for de seneste 2 uger?

0 1 2 3 4 5 6 7 8 9 10

ingen værst mulige

Hvor stærke har smerterne i gennemsnit været inden for de seneste 2 uger?

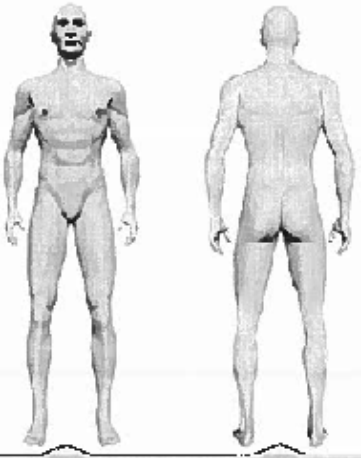
0 1 2 3 4 5 6 7 8 9 10

ingen værst mulige

Sæt kryds ved det billede, der bedst beskriver forløbet af dine smerter:

- Konstante smerter med lette udsving ☐
- Konstante smerter med smerteanfald ☐
- Smerteanfald, ingen smerter mellem anfaldene ☐
- Hyppige smerteanfald, med smerter mellem anfaldene ☐

Marker det område, hvor du primært har smerter



Forplanter dine smerter sig til andre områder af din krop? ja ☐ nej ☐

Hvis ja: marker med en pil, i hvilken retning dine smerter forplanter sig.

Lider du af en brændende fornemmelse i det område, hvor du primært har smerter (f.eks. som brændenælder)?

slet ikke ☐ meget lidt ☐ lidt ☐ moderat ☐ meget ☐ rigtig meget ☐

Har du en kriblende eller prikkende fornemmelse i det område, hvor du primært har smerter (f.eks. som myrekryb eller elektrisk snurren)?

slet ikke ☐ meget lidt ☐ lidt ☐ moderat ☐ meget ☐ rigtig meget ☐

Er let berøring f.eks. af tøj eller en dyne i det område, hvor du primært har smerter, smertefuld?

slet ikke ☐ meget lidt ☐ lidt ☐ moderat ☐ meget ☐ rigtig meget ☐

Har du pludselige smerteanfald i det område, hvor du primært har smerter, som elektriske stød?

slet ikke ☐ meget lidt ☐ lidt ☐ moderat ☐ meget ☐ rigtig meget ☐

Fremkalder kulde eller varme f.eks. af vand i et badekar, af og til smerter i det område, hvor du primært har smerter?

slet ikke ☐ meget lidt ☐ lidt ☐ moderat ☐ meget ☐ rigtig meget ☐

Har du nedsat følesans i det område, hvor du primært har smerter?

slet ikke ☐ meget lidt ☐ lidt ☐ moderat ☐ meget ☐ rigtig meget ☐

Fremkalder et let tryk i det område, hvor du primært har smerter, f.eks. med en finger, smerter?

slet ikke ☐ meget lidt ☐ lidt ☐ moderat ☐ meget ☐ rigtig meget ☐

(Udfyldes af lægen)

slet ikke	meget lidt	lidt	moderat	meget	rigtig meget
x 0 = 0	x 1 =	x 2 =	x 3 =	x 4 =	x 5 =

Samlet antal point ud af 35

PD-Q - Denmark/Dansk - Final version - 25 Jun 07 - Mapi Research Institute.

painDETECT

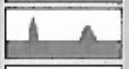
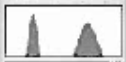
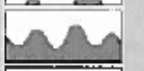
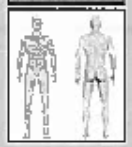
Spørgeskema om smerter – pointgivning

Dato: Patient: Efternavn: Fornavn:

Angiv antal point for spørgeskemaet om smerter:

Antal point ☐☐

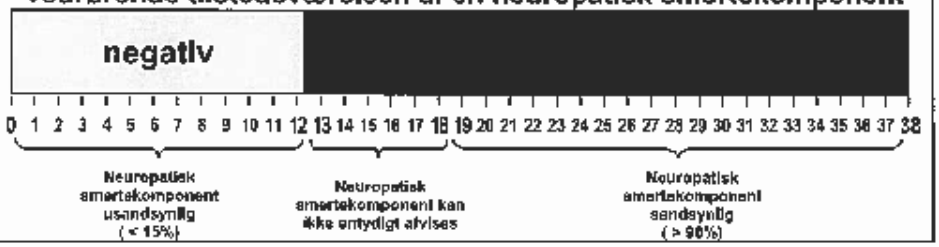
Læg følgende tal sammen i henhold til afkrydsningerne vedrørende smerteforløb og hvordan smerterne forplanter sig. Beregn herefter det endelige antal point:

	Konstante smerter med lette udsving	0
	Konstante smerter med smerteanfald	-1 hvis markeret, eller
	Smerteanfald, ingen smerter mellem anfaldene	+1 hvis markeret, eller
	Hyppige smerteanfald, med smerter mellem anfaldene	+1 hvis markeret
	Forplanter smerterne sig?	+2 hvis ja

Samlet antal point ☐☐

Screeningresultat

vedrørende tilstedeværelsen af en neuropatisk smertekomponent



Dette spørgeskema kan ikke erstatte en lægelig diagnostik.
Det bruges til at screene for forekomst af en neuropatisk smertekomponent.

DFNS

pain

R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle, CurrMed ResOpin Vol 22, 2006, 1911-1920 © 2005 Pfizer Pharma GmbH, Pfizerstr.1, 76139 Karlsruhe, Germany

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Consent form

See separate document.

Flowchart

Sessions mentioned below can be conducted in any order as long as the sessions are completed with 3 months.