Living with painful diabetic neuropathy

physical activity and quality of life

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Chapter 1

General Introduction

General Introduction

Diabetes mellitus and diabetic neuropathy

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both (1). Insulin deficiency invariably leads to chronic hyperglycaemia (i.e. elevated levels of plasma glucose) causing disturbances in carbohydrate, fat and protein metabolism (2). The most common types of DM are type 1 (T1DM) and type 2 (T2DM). As a result of suboptimal control of blood glucose, blood pressure and lipids, patients with DM suffer from complications such as cardiovascular disease, nephropathy, retinopathy and neuropathy (2).

In 2016, there were an estimated 1.1 million DM patients in the Netherlands, of whom approximately 10% had T1DM and 90% T2DM (3). The estimated total economic burden of DM in 2016 was € 6.79 billion (3). Healthcare costs (excluding costs of complications) were €1.57 billion, while direct costs of complications were €1.27 billion and indirect costs due to productivity losses, welfare payments and complications were €3.95 billion (3). In 2018, the International Diabetes Federation estimated that worldwide 425 million people have DM (4), making it the largest global epidemic of the 21st century (5). In that year, approximately 12% of global health expenditure ($727 billion), was directed towards DM and its complications, and similar to the number of individuals with DM, this number continues to increase at an unsustainable rate (4).

Diabetic neuropathy is characterized by diffuse and focal nervous system damage that occurs in up to half of all individuals with DM (6) and is a major cause of morbidity and mortality (7). It is a highly prevalent condition that substantially affects patients in their daily lives (8). Diabetic neuropathy is a neurodegenerative disorder of the peripheral nervous system that preferentially targets sensory axons, autonomic axons and later, to a lesser extent, motor axons (9). Progressive diabetic neuropathy involves retraction and dying back of terminal sensory axons in the periphery, with relative preservation of the cell bodies. Its stocking and glove pattern of involvement reflects damage to the longest sensory axons first with, for example, loss of distal leg epidermal axons preceding loss in more proximal limbs. For this reason, diabetic neuropathy is considered a length-dependent neuropathy (9). The current approaches to management of diabetic neuropathy focus on improving glycaemic control, lifestyle modifications and the management of concomitant neuropathic pain.

Painful Diabetic Neuropathy (PDN)

Approximately 25-50% of the patients with DM experiences neuropathic pain (10-12). PDN is a complex and disabling condition that can have far-reaching consequences in daily life (13, 14), due to pain, sensory loss, the development of pressure ulcers (PU's),

balance impairments and an altered gait with increasing falls (15-17). These complaints can result in a more sedentary lifestyle (13) with impaired levels of physical activity (16), less engagement in social activities, dependency on others, social isolation, depression and as a final result decreased quality of life (QoL) (11, 18-20). Patients with PDN report a sharp, stinging, electrical, burning sensation that aggravates at night with numbness or loss of sensation of the involved area (21). Patients can also report other positive sensory symptoms, such as brush-evoked allodynia (when a normally non-noxious stimulus evokes pain) and paraesthesia (9).

Reported risk factors for the development of PDN include female sex, poor glycaemic control (22), impaired renal function (23) and high body mass index (BMI) (24). Also, a higher prevalence of pain has been consistently reported in patients with more severe neuropathy as defined by clinical scoring scales and sensory loss upon quantitative sensory testing (22-24).

Up to date, there is no cure for PDN and treatment of the pain is based upon symptom relief. Unfortunately, current pharmacological treatment of the pain often does not provide sufficient pain relief and can present with many side effects (25, 26).

Diabetes mellitus and physical activity
Being physically active can reduce the prevalence and severity of complications of DM, while on the other hand, sedentary behaviour can lead to a higher risk of negative health outcomes such as vascular and neurological complications (27, 28). The favourable effects of increased physical activity in patients with DM include improved blood sugar control, decreased body fat, and an improved body reaction to insulin therapy (28, 29). Furthermore, aerobic exercise has shown to improve the QoL in patients with PDN (30).

Despite the beneficial effects of physical activity, patients with DM are known to be less engaged in moderate or vigorous physical activity compared to individuals without DM (16, 31). In addition, physical activity interventions have shown inconsistent effects on increasing and maintaining levels of physical activity in patients with DM. Dropout rates in physical exercise programmes are high (up to 45%), possibly due to the occurrence of PU's, overuse injuries, lack of motivation and/or a combination of factors associated to the complexity of the diabetic problems (low levels of knowledge about managing diabetes and its complications around exercise (32)), neuropathic pain and/or PDN related fears (27, 33, 34).

Diabetes mellitus and pain; psychological aspects in PDN
DM is a multidimensional condition and daily management is burdensome and long-term complications occur frequently. It is known that people with DM are at high risk of having a poor psychological well-being (35-37). Sources of psychosocial problems could

arise from strained coping with changed life routines (36) and worries about disturbed glucose regulation (hypo- or hyperglycaemia) and complications of DM (35, 37). People with DM often show negative coping strategies (36), and they frequently expect that DM will negatively affect their future, resulting in increased diabetes fatalism (perceptions of despair, hopelessness and powerlessness), decreased medication adherence, and decreased levels of self-care behaviours (diet, exercise and blood sugar testing) (38). Also, anxiety is common in patients with DM, with a prevalence of 20%-32% (39, 40). Fear of hypoglycaemia has proven to be a strong barrier to physical activity (41), leading to the aggravation of the consequences of DM (42-44). Studies indicate that untreated psychological well-being may can lead to cardiovascular complications and depression(45), and depression might be associated with cognitive decline, further impairing self-care abilities (2, 46).

While PDN has been associated with important psychological changes and comorbidities, including increased anxiety, depression and impaired sleep (42-44), only little is known about the exact mechanisms and the effects of these changes on daily life functioning in patients with PDN. It is plausible that mood disorders, anxiety and fears contribute to the reasons why patients with PDN are less capable to cope with their DM related problems and to maintain an active lifestyle.

Pain itself is also known to highly affect psychological wellbeing. To do justice to the complex experience of pain, the International Association for the Study of Pain (IASP) defined pain as "*an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage* (47). The interpretation of pain and its consequences in daily life is known to be influenced by behavioural and cognitive efforts used in the attempt of dealing with pain. Within the field of chronic pain research, a lot of work has been done on the relationships between pain, coping and fears (48-50).

Fear avoidance model

The Fear-Avoidance-Model (FAM) has been designed to identify and explain how chronic pain problems, and associated disability, can develop in persons with various chronic pain conditions (48, 50-52). In this model, chronic pain is approached from a biopsychosocial perspective (48) and it explains how pain-related fear may lead to avoidance behaviour and selective attention to pain-related stimuli (hypervigilance) (48, 50-52). The FAM proved to be a strong predictor for disability and depression in the long run (49, 52).

Definition of pain (IASP):
An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage

Key Notes and the etymology of the word pain for further valuable context:

1. Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
2. Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
3. Through their life experiences, individuals learn the concept of pain.
4. A person's report of an experience as pain should be respected.
5. Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
6. Verbal description is only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

Research on the FAM succeeded to identify specific fears such as fear of movement, fear of pain or fear of (re)injury which proved to have a disabling role in chronic pain (48). When fearful patients expect that certain movements/activities/situations may be harmful to their body by causing (re)injury and as a result, negative exaggerated or irrational thoughts about the pain arise (pain catastrophizing) (53). This fear stimulates avoidance behaviour, which can have enormous health consequences such as disability, depression and disuse related physical deconditioning (52, 54), further fuelling the vicious circle of chronic disabling pain. On the other hand, when pain is perceived as non-threatening, patients are likely to maintain engagement in daily activities, through which functional recovery is promoted (Figure 1) (52, 55, 56). Since patients with PDN seem to share the comorbidities of depression and fear (and as a consequence disability) with other chronic pain populations, it seems apparent to integrate the knowledge obtained from the FAM into the field of PDN.

How to measure PDN related fear?

When assessing a certain outcome measure, one can use a ruler with a fixed unit; e.g. kilograms for measuring weight. However in medical or psychological sciences, we often measure qualities for which no measure with a fixed unit exists; e.g. pain, disability or QoL. For this reason, these qualities are measured using constructed surrogate outcome measures that are composed by a set of items or questions, to which numbers are assigned. Most pain- and diabetes-related fear scales are ordinal (e.g. as numeric rating scales and visual analogue scales), which are based on the classic test theory (CTT) (57). Ordinal scales can be ordered, but the difference between the categories is unknown or unequal (e.g. level of QoL).

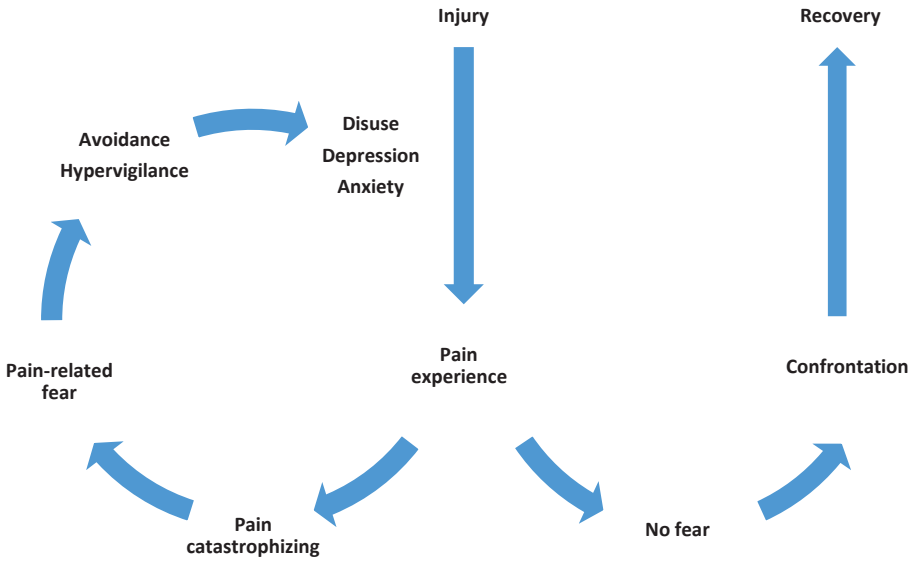

Figure 1: FAM, Vlaeyen, 2000

In practice, subjects are asked to complete all items of the scales, even though some may be irrelevant for their level of fears and/or disability (58). Also, often a sum of item scores is calculated, hereby assuming equal relevance and weighting of each item (57, 59). A reason why physicians continue to use ordinal measures in clinical trials despite the known constraints (58), can be the fact that using ordinal scales is a very practical way of presumed quantification of observations in a clinical setting, hereby providing a seemingly good indication of the clinical question of interest. However, physicians may often be unaware that quantitative observations are based on counting observed events, while meaningful measurements are based on the arithmetical properties of interval or ratio scales (58, 60).

Rasch analysis is a statistical approach that was developed to the measure of human performance, attitudes and perceptions, which makes it very suitable for the field of rehabilitation medicine (61). It is named after its inventor, the Danish mathematician Georg Rasch, who published his theory in 1960 (62). Rasch models have the possibility to transform ordinal scores to interval data (63). The Rasch model is based on the theory that people can be arranged in such a manner that if a person is able to perform a particular task, this individual should also have the ability to complete tasks with a lower rank order (62). In other words, patients with a higher ability (less ill), should have a greater chance of obtaining a higher score on any item of interest. Therefore, the probability of confirming

an item depends on the difference between the persons' ability and the difficulty of the item (62, 64, 65). In the same way, items can be ranked from the most easy to most difficult. Thereafter, both the *person ability* and the *item difficulty* can be placed on the same mutual interval ruler.

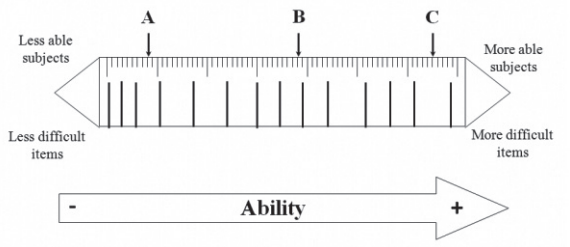

Figure 2: Representation of the ability continuum. Thick lines indicate, from left to right, the location of items of increasing difficulty. Arrows indicate the location of subjects A, B, and C on the ability continuum.

For the measurement of PDN related fear, several questionnaires are available that try to capture various fear qualities, each assumingly measuring one specific element of DM related fears (66, 67) or pain-related fears (68-73). In daily clinical practice it is not feasible to use all of these questionnaires, as this would be a high burden for patients. In addition, all these measures are ordinal-based constructed and have never been subjected to modern clinimetric evaluation like Rasch analyses (59, 62, 74, 75). For this reason, it is unknown whether all of these fear forms may be related or not, or, in other words, whether there could be an overlap between the questions presented to patients assessing the assumingly different constructs. One of the aims of this thesis was to develop single, simple to apply, questionnaire that assesses all the various qualities of PDN related fear, while also fulfilling Rasch requirements.

Exposure in vivo

Based on the FAM, a cognitive behavioural therapy was developed which appeared to be successful in breaking the vicious circle, resulting in a decrease in fears, a higher level of physical activity, better QoL and also in the long term a decrease in the level of disability. This Exposure in Vivo treatment (EXP) is a second-generation cognitive-behavioural intervention that is characterized by systematic and repeated exposure to feared movements, activities and/or sensations in order to activate fear. In EXP, catastrophic interpretations regarding potentially threatening stimuli are challenged and corrected, resulting in a lowered threat-value of these stimuli. Through reduction of the perceived harmfulness of activities, EXP aims to improve functional ability and QoL in chronic pain patients with pain related fear specifically.

The EXP that was developed for patients with chronic pain who report substantial pain-related fear, and fear of movement/(re)injury in particular, is individually tailored to target personal fears in a highly structured manner and aims to restore a normal pattern of daily function (76-81). In this interdisciplinary treatment, physicians in rehabilitation medicine, physiotherapists, occupational therapists and behavioural therapists are involved. EXP has shown to be effective in patients with various chronic pain problems who experience pain related fear, including chronic low back, post-traumatic neck pain, complex regional pain syndrome type 1 (CRPS-1) and work-related upper extremity pain (77-79, 81-87).

Patients with PDN frequently share the comorbidities of depression and anxiety (and as a consequence disability) with other chronic pain populations. However, the knowledge obtained from the treatment of populations with other pain syndromes has not yet been integrated into the field of PDN. One could hypothesize that a physical intervention or psychological treatment alone will not suffice to restore QoL and participation in in these patients, as these treatments address only one of the components of the FAM ('bio' or 'psycho'). Possibly, EXP could be of added value to increase physical activity in patients with PDN. However, the current EXP treatments were designed for chronic pain conditions for which increase of activity or involvement/use of the painful body part is not putting them at additional risk for inflicting damage/injury. PDN, on the other hand, can present with potential risks for injury, such as PU's and/or hypoglycaemia, which can make EXP unsuitable for patients with PDN. There seems to be a need for a customised EXP treatment that is specifically adapted to the fears, needs and in addition the risks of patients with PDN. At the start of this dissertation, there was no literature on EXP for PDN.

Aims and outline of this dissertation

The main aim of this dissertation was to gain more knowledge and understanding in the underlying biopsychosocial processes that are involved in coping with PDN, to design a diagnostic tool to measure these underlying biopsychosocial concepts such as fears (Part I), and from this, to develop a rehabilitation treatment that was specifically adapted to the risks and needs of patients with PDN (Part II).

The dissertation aims to answer the following research questions:

Part I: insights into psychosocial factors that affect well-being in patients with PDN.

1. How do patients cope with PDN and can we gain a better understanding of PDN related fears and coping?
2. Is pain catastrophizing associated with disability and QoL in patients PDN?
3. Do fears affect disability and QoL in patients with PDN and which fears contribute most to this association?

4. Can we develop a new questionnaire that captures PDN related fears and anxiety based on interval outcome measures?

Part II: rehabilitation treatment modalities for patients with PDN.

5. What is the current evidence on the effectiveness of biopsychosocial rehabilitation treatments on physical activity and QoL in patients with PDN?
6. Development of a treatment protocol; which PDN specific elements should EXP treatment contain for patients with PDN?
7. What is the effectiveness of a specifically designed EXP treatment on disability and QoL in patients with PDN ?

In Part I of this dissertation, we investigated whether the known mechanisms for pain related disability, as presented in the FAM, and confirmed within various populations with chronic pain, are applicable in patients with PDN. In order to gain more insights into the perceptions, fears and consequences of PDN in daily life, our project started with a qualitative study in which three focus groups with each four patients with PDN were performed (Chapter 2). To further quantify these fears, we identified available validated questionnaires that matched these self-reported fears, each measuring one specific element of DM related fear or pain related fear (Chapter 3 and 4). From these data a new questionnaire was developed; the Painful diabetic neuropathy Anxiety Rasch Transformed Questionnaire (PART-Q30©) (Chapter 5).

Part II of this dissertation focusses on rehabilitation treatment modalities that may help patients with PDN cope with their pain and/or restore physicial activity levels and QoL. A systematic review was performed to provide an overview of the current evidence on the effects of biopsychosocial rehabilitation treatments that combine exercise therapies with psychological therapies (Chapter 6). Next, we designed a new, customised EXP treatment that was that was specifically adapted to the needs and risks of patients with PDN. Chapter 7 describes the EXP rehabilitation treatment protocol. In Chapter 8, we elaborate on the effectiveness of this newly developed EXP treatment for PDN (ActiFeeT Study).

Finally, a general discussion on the main findings, conclusions and recommendations is presented in Chapter 9.

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Part 1

Insights in fears and coping styles in patients with painful diabetic neuropathy

Chapter 2

Living with painful diabetic neuropathy: insights from focus groups into fears and coping strategies

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Abstract

Objective: Painful Diabetic Neuropathy (PDN) is known to negatively affect quality of life. Being physically active is a crucial part of successful diabetes self-management, but regimen adherence is often low. Coping strategies and fears have shown to be related to less physical activity. The aim of the present study was to obtain more in-depth information on psychological risk factors leading to less physical activity in persons with PDN.

Design: Three semi-structured focus group interviews were conducted with a representative sample of persons with PDN (N=12). Data were transcribed verbatim and analysed using a hybrid method of thematic analyses and a grounded theory approach.

Main Outcome Measures: fears and coping strategies related to physical activity in persons with PDN.

Results: Several specific fears were identified; fear of hypoglycaemia, fear of pain increase, fear of total exhaustion, fear of physical injury, fear of falling, fear of loss of identity, and fear of negative evaluation by others. To cope with these fears, avoidance, remaining active, cognitive distraction, and acceptance strategies were described.

Conclusion: In persons with PDN, diabetes-related fears and pain-related fears play a role in less engagement in physical activity, indicating the need for new methods for improving self-management in persons with PDN.

Introduction

Painful Diabetic Neuropathy (PDN) affects at least 25% of all persons with diabetes (1, 2). Unfortunately, current pharmacological treatment does not provide sufficient pain relief and can have side effects in many persons with PDN (3, 4). In conjunction with diabetes, neuropathic pain (NP) can lead to a myriad of symptoms such as insomnia, high levels of anxiety, depression, and social and physical limitations, which have a considerable impact on quality of life (QoL) (5-7). Insights into the complexity of living with these problems and personalized treatment seem to be needed to support persons with PDN in improving their daily life functioning.

An important part of diabetes self-management is engaging in physical activity. Being physically active can reduce the prevalence and severity of complications, while sedentary behaviour can lead to a higher risk of negative health outcomes such as vascular and neurological complications (8, 9). Despite the beneficial effects of physical activity, persons with type 2 diabetes mellitus (DMII) are less engaged in moderate or vigorous physical activity compared to individuals without DMII (10, 11). Also, physical activity interventions show inconsistent effects on increasing and maintaining physical activity in persons with DMII, which might be due to the complexity of the diabetic problems, neuropathic pain, and/or fears (8, 12, 13).

It has been suggested that persons with PDN could perceive fears such as agoraphobia, fear of complications, self-management in public, and anxiety after diabetes diagnosis; all of which may affect physical activity (13-15). For example, fear of hypoglycaemia might lead to dysfunctional self-management behaviour such as avoiding physical activity and overeating in certain subgroups (16, 17). Next to these possible diabetes-related fears, fears specifically related to the neuropathic pain may also contribute to heightened anxiety levels and that may lead to additional behavioural consequences in persons with PDN (13). It is known from studies in persons with PDN and other chronic pain conditions that catastrophic thinking about pain could be an important determinant of disability and diminished QoL (18-21). Therefore, it is plausible that persons who feel anxious about their neuropathic pain and its consequences may also tend to avoid physical activity because of these fears.

The aim of the present study was to gain more in-depth information on the personal experiences of potential fears and PDN related coping strategies, in order to obtain a better understanding of the complexity of PDN. The findings of this study could enable us to design a personalized treatment strategy that aims to improve physical and psychological wellbeing in persons with PDN.

Methods

Participants

Potential participants were selected by a specialized outpatient clinic for persons with PDN in the Netherlands (Maastricht University Medical Centre). Medical staff assessed eligibility (diabetes type 2, peripheral neuropathy, NP) during medical consultations, or by reviewing patient files. Participants were included if they were over 18 years of age, Dutch-speaking, diagnosed with type 2 diabetes and peripheral neuropathy (physical examination and by neurophysiological testing such as electromyography), with moderate to severe NP, and who were moderately to severely disabled due to pain. Furthermore, participants were selected by purposeful sampling, based on stringent criteria to reflect the appropriate population as closely as possible. Homogeneity was required since the research topics (pain, fears) might be only relevant to certain segments of the PDN-population. We intentionally chose to select this specific population with severe complaints, in order to be able to obtain sufficient in-depth information about psychosocial factors that may play a role in PDN related pain and fears. Final inclusion of participants was performed according to a predefined set of assessment instruments, all definitions and cut-off values are described further on (Eligibility assessment). Participants with severe psychiatric problems and chronic pain syndromes due to other causes were excluded.

Eligible persons with PDN were asked whether they were interested in more information. Those who were interested were sent a hardcopy information package by mail that included a detailed study description, along with an informed consent form. Persons with PDN who were willing to participate were asked to send the signed informed consent form to the researchers in an enclosed, pre-paid envelope and for non-respondents one follow-up phone call was done two weeks later. Self-report questionnaires were sent to the consenting participants to collect baseline data and assess eligibility criteria such as level of disability, NP and psychiatric problems. Participants were asked to return completed questionnaires in an enclosed, pre-paid envelope. When eligible, the respondents were invited to participate in a focus group interview (FG). The present study was approved by the Medical Research Ethics Committee University Hospital Maastricht, Maastricht University (METC 11-4-045). Informed consent was obtained from all individual participants included in the study.

Measures

Eligibility assessment

To measure pain intensity the Numeric Rating Scale (NRS) (22), ranging from 0 (no pain) to 10 (maximum pain) was verbally applied, and a score ≥5 was used as selection criterion for participation.

Furthermore, the subscale Pain Severity Index of the self-report modified Brief Pain Inventory for diabetic peripheral neuropathy (BPI-DPN) was utilized (23, 24), which included four items (worst pain, least pain, average pain, and pain now) using 0 (no pain) to 10 (maximum pain) numeric rating scales. In previous studies, the Cronbach's alpha has shown to be high (0.94) for this scale (24). In our study with a small sample size, Crohnbach's alpha over the 4 items was 0.75. The mean of all scores was expressed as a Pain Severity Index (PSI) and classified into mild (0-3), moderate (4-6), and severe (7-10), and a score of ≥5 was used as an additional inclusion criterion.

To confirm PDN, the validated Diabetic Neuropathy Symptom Score (DNS) (25) was used, comprising four-items (unsteadiness, NP, paraesthesia, numbness), ranging from 0-4 with a score of ≥ 1 indicating the presence of PDN. Correlations between the DNS and Neuropathy Symptom Score (NSS) has shown to be high (Spearman r= 0.88)(25).

The degree of NP was assessed using seven self-report questions of the Douleur Neuropathique 4 questionnaire (DN4) (26, 27), measuring symptoms such as pain characteristics and abnormal sensations (tingling, pins and needles, numbness, itching). The total score range was 0-7 with a diagnostic cut-off score of ≥ 3. The DN4 has shown to be significantly related to neurological and electrophysiological measurements and to the Short-Form McGill Pain Questionnaire in persons with PDN. Furthermore, the DN4 and DN4-interview scores showed a high diagnostic accuracy for PDN with areas under the receiver operating characteristic curve of 0.94 and 0.93, respectively (28).

Pain disability was measured using the validated Pain Disability Index – Dutch Version (PDI-Dutch) (29, 30), comprising seven items that asses the degree of pain interference during daily living activities, work, leisure time, and sports. Items were scored on a NRS from 0 (no disability) to 10 (maximum disability) with a total score range of 0-70, and a score ≥ 29 used as inclusion criterion. The internal consistency of the PDI-Dutch has shown to be good in persons with back pain (Cronbach α 0.83-0.86)(29). In our population the Cronbach α was 0.75.

Demographic and psychological characteristics
Baseline information was collected using standard questions on age (years), gender (male/female), marital status (with partner yes/no), education level (low/medium/high), employment status (retired/sick leave/voluntary work/no employment/self-employed), medication use and comorbidities.

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) (31). The questionnaire consists of 14 items, 7 evaluating cognitive and emotional aspects of anxiety (HADS-A) and seven representing the cognitive and emotional aspects of depression (HADS-D). Each question is scored on a 4-point Likert scale, ranging from 0 to 3, where a higher score represents more severe depression or anxiety. In a group of persons with chronic pain (fibromyalgia), the Cronbach's α of HADS-D and HADS-A were 0.82 and 0.81, respectively (32). In our population, the Cronbach's α of HADS-D and HADS-A were 0.84 and 0.79, respectively.

Fear avoidance beliefs were measured using the Dutch version of the Tampa Scale for Kinesiophobia (TSK-DV) (33, 34). Test–retest reliability has shown to range from r=0.64-0.80 (35). The internal consistency of the TSK has shown to be good (Cronbach's α = 0.81) (36). In this study, the Cronbach's α was 0.71.

Pain catastrophizing was assessed using the Pain Catastrophizing Scale (PCS) – Dutch Version by Crombez and Vlaeyen (The Pain Catastrophizing Scale, Unpublished authorized translation, 1996). Van Damme and colleagues have shown the Dutch PCS demonstrated good reliability and validity (37). In our sample, the Cronbach's α was 0.88. This questionnaire measures negative thoughts and beliefs during actual or anticipated painful experiences. The items are scored on a five-point Likert scale with scoring possibilities ranging from 'not at all' (score = 0) to 'always' (score = 4). The PCS scores can range from 0 to 52. High scores indicate that more catastrophic thoughts or feelings are experienced. The PCS has shown to have adequate to excellent internal consistency (38).

The Short Form Health Survey (SF–36) was used to measure QoL (39, 40). The SF-36 is a 36-item health survey comprised of eight subscales measuring functional health and well-being (41). The psychometric properties have been evaluated across populations with various conditions. Previous studies in chronic pain patients have shown a Cronbach's α ranging from 0.79-0.91(42). In our sample, the Crohnbach α for the total score was 0.71. Crohnbach α's for the subscales were: physical functioning α = 0.78; role limitation due to physical health α = 0.78; role limitations due to emotional problems α = 0.87; energy/fatigue α = 0.67; emotional well-being α = 0.77; social functioning α = 0.65; pain α = 0.96 and general health α = 0.84, respectively.

Design

In the present study, semi-structured focus group interviews (FG) were conducted to explore in-depth information about potential fears and cognitions, in order to understand and interpret behaviours and the underlying motives within the situational context of persons with PDN. The consolidated criteria for reporting qualitative research (COREQ) were used to aggregate and report information on data collection and analysis (43).

The interviews were guided by two researchers and lasted 120 minutes each and were moderated by one of the authors (IK) and facilitated by a research assistant (medical student). The interviewer was an experienced physiotherapist in the field of pain-/ fear rehabilitation experienced and trained in conducting FG interviews, which was beneficial to ask specific questions to obtain in-depth information. The participants did not know the interviewer and facilitator in advance. The FG's were conducted in a recording studio, videotaped, and field notes were taken. In addition, participants were encouraged to answer moderators' questions, and to talk and interact with each other. Probe questions, such as 'Would you explain further?' were asked to elicit additional information. Interview questions are provided in Table 1. These questions were discussed and adapted by a rehabilitation physician, a physician of internal medicine, and a psychologist. Three interviews were performed.

In line with the grounded theory approach, prior clinical knowledge on possible problem areas of persons with PDN were used as a starting point for topics and probes in the preliminary discussion guide (44-46). Also, in accordance with the grounded theory approach, the research process was not pre-determined, but evolved by a process of systematic data analysis (47, 48). The moderator led the discussion based on a semi-structured interview guide. The FG questions were categorized into different types (opening, introductory, transition, key, ending) on the basis of Krueger's method (48). Initially, unbiased open questions were asked, such as 'Tell me about your experience about how to live with pain', and probes were changed based on respondents' statements for further clarification (Table 1) (44). The participants were encouraged to share and compare their experiences and emotions, and to comment on each other (48). Experiences and thoughts were prompted by comments of other group members and certain ideas were accepted or rejected by individuals. This interaction between the participants provided insights and in-depth understanding. Theoretical understanding was developed as the data were gathered and analysed and the research process stopped when no new understanding emerged (49). The point at which theoretical saturation was achieved was the indicator of sample size as well as the required number of FG in qualitative research (45). Typically, one FG is composed of less than ten participants who share a common experience (46).

Table 1. Examples of the questions used in the focus groups

· Would you please describe how you occupy yourself every day?
· Tell me about your experience about how to live with pain?
· What is changed in your life through the pain?
· Due to which complaints do you feel restricted?
· Are you more cautious than other fellow diabetes patients who do not have pain?
· In what situations do you feel uncertain?
· What makes you cautious?
· When you think about the future with diabetes, is there anything where you are worried about?
· Do these thoughts or feelings affect your daily activities?
· Is there anything else I have forgotten to ask you about the impact of the pain on your daily life?

Data collection and analysis

Data collection and analysis were interrelated and started when the first data were collected (45). The FG's were video-recorded and the conversations were fully transcribed in NVivo 8 directly after FG completion (50). According to the grounded theory approach, open codes were assigned to all relevant phenomena through line-by-line coding by two researchers who worked independently (IK; physiotherapist/health scientist and NS; medical and psychology student). The derived codes of the two researchers were compared and discussed and merged into one codebook. All potentially relevant issues were incorporated into the next interview guide. After completing the subsequent FG, relevant phenomena from the corresponding FG were coded either by using existing matching codes from the previous interview, or by creating new codes. Accordingly, two researchers coded each interview independently. Prior to the study, we defined that when the codes differed, they were to be discussed by the two researchers until agreement was reached on the new codebook. In practice, this situation occurred rarely. This process was conducted systematically, until no new topics appeared and theoretical saturation was reached. The created codes of the final code book after completion of all interviews were categorized into higher order themes. In this process of categorization, a group of clinical experts consisting of 3 experts in the field of health psychology and 3 experts in rehabilitation medicine were involved by discussing and consenting on the higher order themes.

Results

Participant characteristics

In total, three FG took place until theoretical saturation was achieved. Of the 13 invited participants with PDN, 12 attended one of the three FG with four participants each. The reason for one dropout was admission to a hospital. Table 2 shows the baseline characteristics of all participants.

Table 2. Demographic, medical, and psychological characteristics of the participants (N=12)

	N (%) / Mean ± SD
Male gender	8 (66.7)
Age, Mean (SD)	65.3 ± 10.26
Marital status	
With partner	11 (91.7)
Education[1]	
Low	7 (58.3)
Medium	3 (25)
High	2 (16.7)
Employment status	
Retired	4 (33.3)
Sick leave	3 (25)
Voluntary work	1 (8.3)
No employment	2 (16.7)
Self-employed	2 (16.7)
Number of years DMII	17.9 ± 9.1
Number of years PDN	11.3 ± 6.5
Depending on electric wheelchair	5 (41.7)
Administering of insulin	
Oral	3 (25)
Injection	8 (66.7)
Pump	1 (8.3)
Pain Severity Index (0-10)[2]	6.5 ± 1.2
Douleur Neuropathique 4 questionnaire (DN4) (0-4)	3.6 ± 0.6
Pain Disability Index (0-70)[2]	45.3 ± 8.7
Fear avoidance (TSK-DV) (17-68)[2]	40.6 ± 8.0
Pain Catastrophizing Scale, (0-52)[2]	23.3 ± 9.7
HADS	
Anxiety (0-21)[2]	7.8 ± 3.4
Depression (0-21)[2]	9.4 ± 4.3

Table 2. Continued

	N (%) / Mean ± SD
Quality of Life (SF-36), (0-100)[3]	
Physical functioning	23.3 ± 15.1
Role functioning physical	6.3 ± 15.5
Role functioning emotional	50 ± 46.1
Social functioning	58.3 ± 20.9
Bodily Pain	51 ± 8.9
Mental health	27.1 ± 16.7
Vitality	41.7 ± 16.4
General health	31.3 ± 19.6

PDN: Painful Diabetic Neuropathy; DM: diabetes mellitus type 2; TSK_DV: Tampa Scale for Kinesiophobia, Dutch Version (higher scores predict higher disability); HADS: Hospital Anxiety and Depression Scale; SF-36: Short Form Health Survey.

[1] 'Low education': lower vocational education; 'medium education': medium general secondary education; 'high education': higher vocational education. [2] total score range (higher scores indicate more problems) [3] total score range of all subscales (higher scores indicate better health).

Data coding

During data analysis, 68 codes were discovered during the first interview. According to the grounded theory approach, the emerged codes were wide ranging and included topics such as pain and physical complaints (e.g. hypoglycaemia, sores, insomnia, and fatigue), limitations concerning walking, unsteadiness, standing still, and walking stairs, falling, cycling, and commuting. Furthermore, risks with regard to excessive physical exertion in different situations and the expected negative consequences (e.g. pain, complete exhaustion, dependency on others) were mentioned, and the way of dealing with physical demands and social situations (e.g. avoidance, using aids). Moreover, topics concerning emotional problems emerged (e.g. pain, depressive symptoms, end-of-life topics). In the second FG, most of these topics were confirmed and further elaborated upon. In addition, 12 new codes were added to the codebook (e.g. embarrassment, distraction, (non-) acceptance, physical training, not been taken seriously, employment issues, relational problems, travelling, custom-made shoes, further physically decline, frustrations). During the third interview, again, most of the topics were in line with the topics from the two prior FG; however, no new themes emerged. All relevant phenomena from data of the third interview could be categorized into the 80 existing codes, which indicated that the point of theoretical saturation was achieved and no further FG were necessary. Subsequently, the 80 codes were categorized into higher order themes. The higher order themes were seven types of fears and four types of coping strategies. The final code book is provided as supplemental data.

Fears

Fear of hypoglycaemia

The majority of insulin-dependent participants were afraid to (re-)experience hypoglycaemia, and therefore inject insulin, stick to their diet, and perform physical activity very carefully. Notably, some participants mentioned that they maintained a slightly higher blood glucose level than recommended, in order to prevent hypoglycaemia.

> *Quote (male, 56 years, insulin treatment, 22 years of PDN, living together, sick leave, no walking aid): I had a period of hypoglycaemia when I was driving and I caused an accident. I never dare to step into the car again.*

Fear of an increase in pain

After many years suffering from DMII, most of the respondents were used to diabetes-related complaints and could cope with it. However, the additional occurrence and presence of pain such as NP had a substantial debilitating effect on their functioning in daily life. In certain situations, the level of pain increased, which was described as a horrible experience. From respondents' perspective, the increase in pain was probably caused by performing physical activity that was too exhausting. When perceived severe pain, some of the participants were not able to cope with this high level of pain and experienced feelings of helplessness and loss of control. Consequently, the most fearful persons with PDN avoided as much as possible physical activities and preferred to stay at home. One participant even prefers to stay in bed as much as possible.

> *Quote I (female, 76 years, oral medication, married, 2 years of PDN, housewife, mobile scooter): I avoid going too far, because then I cannot cope anymore.*

> *Quote II (male, 57 years, oral medication, married, 12 years of PDN, part-time sick leave, wheelchair): I know exactly when the pain attack will come. I start sweating and then it happens. It feels like getting crushed by hydraulic scissors, getting tighter and tighter (...).*

Fear of total exhaustion

A substantial majority of participants experienced one or more situations of complete exhaustion. Usually, this feeling of total exhaustions occurred unexpected and suddenly during daily activities. In these situations, persons with PDN felt powerless, helpless and embarrassed. Additionally, they were not able to continue their activities and were in need for help from others. Therefore, fearful participants mentioned that they avoided exhausting themselves. For example, when walking outside, respondents remain deliberately close to a possibility to sit down.

Quote (male, 57 years, oral medication, married, 12 years of PDN, part-time sick leave, wheelchair): I am not going to exhaust my body. When I move, I am in a lot of pain afterwards. I have to avoid it in any case.

Fear of physical injury

Due to the numbness and/or painful skin sensitivity of the feet, a number of persons with PDN were afraid of developing sores on their feet and lower legs. In the past, they experienced that those sores in most instances hardly healed. All participants avoided walking long distances, despite wearing custom-made orthopaedic shoes. To prevent physical injury, such as sores or severe complaints (e.g., heart conditions), persons with PDN reported to avoid going on excursions or vacation. Furthermore, they did not trust other unknown or foreign health care systems in case medical care would be required.

Quote (male, 56 years, insulin treatment, divorced, 13 years of PDN, incapacity for work, mobile scooter): Actually, I am careful with everything and do not go on holiday to foreign destinations. If something would happen to me, they may not be able to help me.

Fear of falling

All participants acknowledged being afraid of falling when walking on cobblestones, stairs, uneven or slippery surfaces, walking through busy streets, and when using public transportation. They reported that the numbness, pain, and unsteadiness of their legs and feet causes a feeling of instability with makes them cautious and hypervigilant. Therefore, persons with PDN reported to be very hesitant to walk, especially in a crowded environment. Additionally, several participants needed support from their partners, or used walking aids such as a walking stick, walker, or wheelchair.

Quote I (female, 65 years, insulin treatment, married, 8 years of PDN, charity work, no walking aid): I am afraid of falling in the middle of the city centre, all people watching me.

Quote II (male, 51 years, oral medication, married, 7 years of PDN, working in own business, no walking aid): I have to climb over the edge of my bath. This results in life-threatening situations.

Fear of loss of identity

The participants reported to be considerably restricted in daily life activities, housekeeping, work, hobbies, sports, social activities, and traveling. They had become more and more physically limited and increasingly dependent on others. As a result, they said to have

lost meaningful tasks and responsibilities, which caused feelings of loss of purpose in life and loss of their identity. In some cases, these thoughts led to anger and unwillingness to accept the situation and further deterioration, which resulted in performing dangerous activities to prove themselves.

> *Quote I & II (male, 56 years, insulin treatment, living together, 22 years of PDN, sick leave, no walking aid): I am afraid not to be able to stand long enough to finish a conversation. (...) I am afraid of not being able to drive my car to get to work/hobby's/ social activities.*

Fear of negative evaluation

More than half of the participants expressed the fear of being negatively judged by others. This was illustrated by situations in which they felt vulnerable in the presence of others, with a consequence of perceived negative attention and negative judgements. Walking unsteadily, walking with a walking aid, being exhausted, falling, having a hypoglycaemia, and injecting insulin in public were reported as very embarrassing situations. In these situations, other people could make them feel "ill and pathetic", and they did not feel taken seriously. For this reason, activities such as going for a walk and going shopping in public were usually avoided by respondents.

> *Quote I & II (male, 56 years, insulin treatment, living together, 22 years of PDN, sick leave, no walking aid): I do not want to look and feel like an old man (...) I feel less attractive when I have to walk with a walking aid.*

Coping with PDN

Alongside the aforementioned fears, a number of coping strategies were identified, which will be further elaborated in the following paragraphs.

Being active despite PDN

The majority of participants emphasized that remaining physically and socially active despite pain and limitations is of great value. However, most participants preferred not to exercise too often. Examples of activities were engagement in longstanding habits (e.g. daily visit of family), social engagements (e.g. work, voluntary work, care for grandchildren), and participating in public celebrations, such as carnival. Their rationale to stay active was to fulfil social roles to which they felt obliged, receiving appreciation, and having a purpose in life. The majority of participants emphasized that physical efforts must be adapted to personal capabilities. The majority of respondents agreed that remaining physically active helped in preventing further deterioration and becoming overly dependent upon others. Valuable strategies in helping to stay active were a regular daily schedule (e.g. walking the dog at fixed times), and appointments

with others. The participants emphasized that a certain internal motivation in combination with external support is required to remain active. Finally, exercise support by health professionals was perceived beneficial when carefully tailored to the participants' individual needs.

> *Quote I (male, 51 years, oral medication, married, 7 years of PDN, working in own business, no walking aid): I do not let the pain ruin my life. I just do what I think I have to, and often, I go too far. It destroys me, but I benefit from it. I get a feeling of satisfaction. Yes, I still can do this!*

> *Quote II (female, 65 years, insulin treatment, married, 8 years of PDN, charity work, no walking aid): Every day I walk 30 minutes together with my husband. I slowly built this up. Afterwards I feel a lot of pain, but if I would stop doing that, I could walk no longer, soon.*

> *Quote III (female, 61 years, insulin treatment, married, 4 years of PDN, housewife, wheelchair): A little bit of housekeeping, preparing a meal, yes, it costs a lot of effort and pain. But, I want to do that. That is the only purpose I have in my life: caring for my husband and daughter as good as I can.*

Distraction and attention

Importantly, distraction from pain by focusing on a specific activity, hobby, or task was reported to provide pain relief. Some examples of mentioned activities were knitting garments, being involved in interesting tasks and conversations, and participating in aqua jogging lessons. An important characteristic of distraction was that the individuals' attention was focused entirely on the activity, which caused distraction from pain and even pain relief. However, directing attention towards the pain and other complaints led to an increase in pain and other sensations. This phenomenon was reported to often occur during moments of resting.

> *Quote I (male, 70 years, insulin treatment, married, 13 years of PDN, charity work, no walking aid): If you are busy with something you enjoy, it gives you a mental distraction. When I'm working with wood, I feel no pain.*

Avoidance

Avoidance was the most frequently stated strategy to cope with PDN. Activities declined gradually over time by steady reductions in the frequency and intensity (e.g. decrease in walking bouts, distance and speed). Importantly, participants described fears as the primary reasons for avoidance. In particular, participants avoided those activities, which they were not used to do and which were perceived to be too effortful. Furthermore, a number of participants stated that the use of external aid and aids made them lazy (e.g.,

wheelchair, walker, stair elevator). These statements exemplify that environmental factors, such as social support, housing conditions, adaptations in homes, and the availability of aids might also be related to avoidance behaviour and a decrease in physical activity.

Quote I & II (male, 57 years, oral medication, married, 12 years of PDN, part-time sick leave, wheelchair): Diabetes and walking, yes okay, but, I can tell you, it is absolutely not possible to walk with neuropathic pain. That does not work. When you have to walk with neuropathic pain, then you have a bad time. (...) I do not go on a home trainer, cycling uphill, afterwards suffocating in pain, because the therapist wants me to do that. No, I am sorry, that makes no sense to me.

Quote III (male, 56 years, insulin treatment, 22 years of PDN, living together, sick leave, no walking aid): There is much bullying at my work. If I would use a walker, I would be an idiot. I am on sick leave now.

Acceptance and resignation

Acceptance or resignation of complaints was often referred to as an important coping strategy. All participants reported that it was difficult to accept that the pain and restrictions were permanent. They explained acceptance as 'letting things go', 'being satisfied with constraints' and also 'resign oneself with the idea of having chronic pain'. Interestingly, according to the participants, acceptance or resignation of pain and limitations in daily life can be related to both an increase and a decline in motivation to participate in physical and social activities. For example, some participants accepted the pain and by doing so, they were still motivated to look after the grandchildren or to walk the dog, despite the complaints. In contrast, some other persons with PDN stated that they accepted a restricted life in a wheelchair or even in bed, hereby giving in to the pain, and losing the motivation to be physically or socially active. For those participants, physical activity caused an increase in pain, which they perceived an as unbearable and uncontrollable pain.

Quote I (male, 51 years, oral medication, married, 7 years of PDN, working in own business, no walking aid): Well, when you make it too easy for people, then they lean backwards and wait until they get help. But that does not help.

Quote II (male, 72 years, insulin treatment, married, 8 years of PDN, retired, no walking aid): The pain remained, but I have become more positive.

Quote III (male, 57 years, oral medication, married, 12 years of PDN, part-time sick leave, wheelchair): I have no more drive. It is not possible to cope with the pain, you cannot control it. The pain rating is so high! I do not even start exercising anymore.

Discussion

The present study uncovered fears related to diabetes and to pain, and revealed implications that a number of fears and coping strategies of persons with PDN might be related. Fears, such as fear of hypoglycaemia, falling, total exhaustion, as well as fear of increased pain, injury, and negative evaluation seem to inhibit physical and social activities. Prior findings confirmed these relationships with regard to fear of hypoglycaemia, which is known as a widespread phenomenon among persons with DMII, and can cause significant negative consequences for diabetes self-management, including avoidance of physical activity (5, 51).

The data from the present study has illustrated possible relationships between fears and avoidance behaviour. Frequently, persons with PDN reported fear of falling as a reason to avoid walking activities, which is in line with earlier research that found changes in walking patterns and a higher risk of falling in persons with PDN (11, 52). Fear of falling could be considered an adaptive mechanism in persons with PDN, as one may also experience sensory loss, resulting in elevated risk for ulcers and gait impairments. Therefore, having no fear at all could result in increased risks of complications such as injuries and ulcerations. Paradoxically, too much fear of falling can lead to dysfunctional and needless restrictions in daily life (53), which in turn might lead to less physical activity and less favourable overall health outcomes. The fear of falling itself has shown to be a risk factor for falls and injury as it may lead to dysfunctional gait adjustments and can lead to avoidance behaviour, activity restriction and subsequent deconditioning (54). Interestingly low compared to high levels of fear of falling have shown to be protective for falling, irrespective of the presence of balance impairments (53). Kelly et al. (55) discovered that fear of falling was unrelated to the severity of NP. This finding suggests that other reasons than the severity of NP might contribute to a high degree of fear and avoidance behaviour. Studies have shown that exaggerated fear of falling can be treated with a behavioural interventions such as exposure in vivo (56-58). In this treatment, the patient will be exposed repeatedly to a situation in which the fear usually occurs. Absence of aversive consequences will lead to extinction of the specific fear (59).

This study revealed statements about helplessness in connection with fears, which corresponds to previous research, demonstrating associations between catastrophic interpretations of pain and avoidance behaviour in persons with other chronic pain syndromes (60). Sullivan et al. (21) observed that helplessness, a dimension of catastrophizing, was a predictor of pain. Moreover, catastrophic thinking was associated with pain-related disability among persons with NP. A recent study has shown that pain catastrophizing was associated with increased disability and decreased QoL in persons with PDN (19). Interestingly, pain catastrophizing was associated with the subjective

feeling of loss of physical activities due to the pain, while it was not associated with the estimated actual level of activity. Consequently, catastrophic thinking about diabetes and pain-related issues seems to lead to excessive and unnecessary avoidance in persons with PDN.

In this study, the fear of hypoglycaemia was reported as a limiting factor for physical activity. Williams et al. (61) described that experiencing even a single hypoglycaemia symptom has a significant impact on a persons' immediate health status with longer-term consequences, e.g. fear of future hypoglycaemia and self-directed behavioural changes to manage hypoglycaemia symptoms. In our study, participants explained that they tend to keep their glucose levels somewhat higher in order to prevent an episode of hypoglycaemia. This mechanism of keeping the glucose levels within a 'safety margin' has also been described by Sakane and colleagues (62). Di Battista et al. showed that insulin doses may be inappropriately reduced in anticipation or fear of future hypoglycaemia (63). This effect is alarming, as maintenance of tight glycaemic control is of great importance in the (self) management of DMII and the prevention of long-term comorbidities associated with DMII (64). Martyn-Nemeth et al. reported significant associations of fear of hypoglycaemia with glycaemic variability, dietary patterns, and physical activity (65). Furthermore, fear of hypoglycaemia has been reported to be a major barrier to engage in physical activity (66), as there may be a perception that certain activities could lead to a higher risk of hypoglycaemia and difficulties managing it (67). Fear of hypoglycaemia itself has shown to be strongly linked to non-diabetes-related anxiety (68). This is interesting as anxiety symptoms overlap largely with autonomic hypoglycaemia symptoms (sweating, dizziness, palpitations, confusion, being pale, feeling weak, and blurred vision). In this way, hypoglycaemic symptoms could cause an additional trigger for a fear response in people with diabetes (68), or feelings of fear could be confused with feelings of hypoglycaemia, especially if concomitant anxiety symptoms are already present. Overcoming the fear of hypoglycaemia seems to be of great importance in order to engage in physical activity, hereby improving glycaemic control and preventing long-term complications.

Acceptance of personal restrictions might be important in coping with PDN. In our study, acceptance seemed to be associated with the acceptance of pain and active coping on the one hand. On the other hand, acceptance indicated an association with restrictions in daily life, fear of more pain and resignation. Current research suggests that acceptance of pain may play an important mediating role in the relationship between chronic pain and functioning, in the manner that acceptance is associated with better outcomes (69). As is illustrated in our study, participants may refer to 'acceptance' in two opposite ways, resulting in either an active coping or resignation

of the current situation. In the latter interpretation, this so-called 'acceptance' may rather refer to an avoidance coping style. Therefore, it seems to be important to not only address acceptance of pain, but also to further elaborate on this topic during consultation.

As confirmed by Ribu and Wahl (70), persons with PDN were afraid of losing their identity and purpose in life by losing their social roles and responsibilities. Fear of loss of identity arises when the discrepancy between the desired personal situation and the actual situation increases (71). Van Damme et al. (72) state that 'task persistence', and 'holding on to unattainable goals', may result in identity confusion in persons with chronic pain syndromes, which confirms statements taken from persons with PDN. However, remaining physically and socially active within personal capabilities was mentioned as a valuable coping strategy in order to retain identity. Therefore, a reappraisal of goals and expectations can be beneficial (72). Moreover, evidence from Claes et al. (73) illustrated that the pursuit of goals may have an impact on being active despite the pain. Consequently, engaging in appropriate activities, setting attainable goals and the determination to achieve personal goals could be beneficial in managing PDN.

Persons with PDN indicated that they experienced no pain when they were cognitively distracted, which is noteworthy, since medicinal treatments for pain reduction are often insufficient and can have side effects (4, 74). Research confirmed that attention to pain can be modulated by performing demanding tasks, and demonstrated that fear of pain can affect this process (75). In addition, cognitive distraction has been found to be an important coping strategy in persons with PDN, and further research and clinical application is recommended (76, 77).

This study provides insightful findings coming from a qualitative research design. As potential limitation it can be mentioned that the sample size was small, although the aims of conducting focus groups were to explore cognitions and to generate ideas rather than to establish representativeness. Furthermore, as is the case in qualitative research, analysis showed that saturation was reached, meaning that additional FG would not lead to new information. Finally, it should be noted that this study was performed in a specific population with severe PDN complaints in order to get insights into the full range of physical and psychosocial complaints and underlying processes. This selection could have led to an overrepresentation of fears and beliefs in PDN and may not represent the entire group of persons with PDN. At this point, it is not known whether patients with less severe complaints share the same fears that were identified in the present study.

The novelty of this study is that we have aimed to gain more specific information about the content of various fears that can play a role in restrictions in daily life in persons with PDN. The importance of findings can be considerable, since the participants of the present study were a carefully selected, specific sample of experienced experts with high levels of pain and disability despite medical treatment.

Future studies

Various non-pharmacological treatment options have been developed that aim to reduce fear and psychological wellbeing in patients with other chronic pain syndromes (78-81). Research has shown that multidisciplinary rehabilitation interventions that target factors from the different biopsychosocial domains, administered by healthcare professionals from different backgrounds, are more effective than physical or psychological interventions alone (82).

Numerous studies demonstrate that an effective psychosocial remedy against fears is exposure to the object of the fear. An example of a cognitive behavioural treatment modality is exposure in vivo (EXP), which combines physiotherapy with cognitive behavioural therapy (81, 83-85). EXP specifically targets catastrophic (mis)interpretations of bodily symptoms including pain. These fear-reducing techniques are based on experimental and clinical findings that expectancies about the associations between movements and increased pain can be readjusted and reduced by exposing the individual to the feared painful movement (33, 86, 87). EXP treatments have shown to be effective in reducing pain-related fear and the perceived harmfulness of physical activity in various chronic pain conditions, such as chronic low back pain (59, 85, 88) and chronic regional pain syndrome type I (CRPS-I) (59, 81). Whether EXP is applicable in persons with PDN, is currently being investigated in one of our current ongoing clinical studies. We adopted a single-case experimental design in which persons with PDN receive the EXP treatment by our team that has had additional training regarding the risks and special needs of diabetic persons. For example, blood glucose levels are measured pre- and post-treatment, participants are excluded when having pressure ulcers on their feet and they are screened on wearing adequate (orthopaedic) shoes. Next to the pain related fears, also diabetes (hypoglycaemia) related thoughts and fears are assessed, as we believe that they can be challenged in the same way. As mentioned before, the evaluation of fear of hypoglycaemia is not always irrational and some level of concern can be considered appropriate and adaptive (68). Anderbro and colleagues (2015) have suggested that a form of biofeedback training could be helpful in patients with high levels of fear of hypoglycaemia in spite of low levels of hypoglycaemic risk (68). By addressing thoughts and beliefs about blood glucose levels in relation to the actual measurements of blood glucose levels pre- and post-treatment, diabetic persons will learn to recognize which bodily sensations correspond to the actual blood glucose

levels. In a second step, they are encouraged to increase their level of physical activity and apply their recognition skills in novel situations. This sort of training might be a useful addition to an exposure-based treatment for persons with PDN as explained before. In our opinion, EXP programs in PDN are best carried out by experienced behaviour therapists, in combination with physiotherapist (specialized in DM), and under a physician's supervision.

Next to exposure methods for fear-avoidance related patterns, Acceptance and Commitment Therapy (ACT) (89) might also be a promising avenue to assist adaptive coping with PDN. ACT is a treatment approach, which includes a combination of acceptance and mindfulness methods along with activation and behaviour change methods (90). ACT is based on the theory that thoughts, beliefs, rules, and instructions, as well as pain or other psychological experiences can narrow the range of an individual's available responses and present obstacles to healthy behaviour and behaviour change (90). ACT aims to increase psychological flexibility in the context of chronic pain, hereby reducing the influence of personal thoughts, experiences and emotions on daily life functioning. Within this treatment, physical functioning is usually improved according to the principles of graded activity, which is an individualized and submaximal exercise program combined with educational support to enhance self-trust and tolerance to effort (91). Multidisciplinary ACT has shown to be effective in reducing the burden of chronic pain in various pain conditions (78, 92). ACT is mainly focused on acceptance and dealing with pain and its consequences. However, it does not directly target pain related fears or avoidance behaviours.

Conclusion

Based on the data obtained from FG with persons with moderate to severe PDN, diabetes-related fears as well as pain-related fears may have an impact on self-management of persons with PDN. Concepts such as pain catastrophizing, acceptance, goal setting, and cognitive distraction may affect physical activities and social engagements of persons with PDN. The mutual relationship between fears and coping strategies appear to be both functional and dysfunctional.

Based on this study, a few recommendations can be made. For clinical practice, it is recommended to quantify diabetes-related fears as well as pain-related fears, and to take these fears and personal coping strategies into account when treating persons with PDN.

Supplemental Data 1. Final codebook after completing three focus group interviews, based on the agreement between two independent researchers.

1	Walking limitations
2	Barefoot walking
3	Unsteadiness during walking
4	Description of pain (facts)
5	Decrease of pain due to distraction
6	Decrease of pain during/while moving or working (voluntarily)
7	Increase of pain during movements/physical activity
8	Increase of pain as a result of/ in combination with negative emotions
9	Pain during the night when lying in bed
10	Pain when resting (during the day)
11	Pain in different daily situations
12	Attention / focus on pain
13	Experiencing suddenly total exhaustion/ depletion
14	Fatigue
15	Being cautious due to poor vision
16	External locus of control
17	Comorbidity
18	Building up walking distance gradually
19	Learn to live with it
20	Limitations in daily life
21	How to handle physical limitations
22	How to handle negative emotions
23	Depressive feelings
24	Falling (facts)
25	When something goes wrong
26	own limits/ boundaries
27	do not show that you are sick
28	Not want to be seen with a walking aid
29	Do not want others to be worried
30	Do not want that others think that they are pathetic
31	Perception not to be taken seriously
32	Danger/ dangerous situations
33	frustrations
34	Discrepancy between physical goals/ desire and actual physical capabilities
35	Moving slowly
36	Avoidance of physical efforts/ sports
37	Avoidance of working
38	Avoidance of social activities
39	Avoidance of situations that are perceived as unsecure or dangerous (needing safety)
40	Fear of an increase in pain

Supplemental Data 1. Continued.

41	Fear of getting wounds (feet/legs)
42	Fear of losing muscle strengths
43	Being afraid of the loss of exercise/ moving capacity
44	Being afraid of losing social contact
45	Fear of getting dependent on others
46	Being afraid of not succeeding (different situations)
47	Fear of getting a hypo
48	Being afraid of getting a hypo in public space
49	Being afraid of getting exhausted in public space
50	Fear of falling from the stairs (when descending)
51	Fear of falling
52	Being afraid that something unexpected could happen
53	Panic attacks
54	Worries about the future
55	Keeping blood sugar level high consciously (as a form of diabetes management)
56	Loosing strengths (facts)
57	Strengths exercises to prevent loss of strengths
58	Being ashamed
59	consider dying
60	performing tasks that are requested by others
61	performing tasks that are requested by the oneself
62	Needing support from others
63	Physiotherapist
64	Lack of understanding
65	You need to fight
66	Thinking in relative terms
67	Don't want to give up/ doing all that's possible/ taking risks
68	Taking decisions
69	self-discipline
70	environmental factors
71	Advances of medical tools/aids
72	Disadvantages of medical tools/aids
73	Insecurity/ no feeling of control with regard to the blood sugar level
74	insomnia
75	Problems with commuting, travelling, mobility
76	Insights and knowledge about own medical complaints
77	Day schedule (planning)
78	take the initiative yourself
79	Financial issues and consequences
80	Personal motivation 'drive'

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Chapter 3

Perceived physical activity decline as a mediator in the relationship between pain catastrophizing, disability, and quality of life in patients with painful diabetic neuropathy

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Abstract

Background: In order to fully understand the burden of Painful Diabetic Neuropathy (PDN), we investigated the relationship of pain catastrophizing with disability and quality of life in patients with PDN. Furthermore, we studied the mediating roles of physical activity and/or decline in physical activity.

Design & Methods: This questionnaire-based cross-sectional study included 154 patients with PDN. Linear regression analyses, adjusted for age, gender, pain intensity and insulin treatment were performed to assess the association of pain catastrophizing (Pain Catastrophizing Scale, PCS) with the outcome variables disability (Pain Disability Index, PDI) and quality of life (Norfolk Quality of Life Questionnaire Diabetic Neuropathy Version, QOL-DN). The mediating roles of actual physical activity (Physical Activity Rating Scale, PARS) and perceived physical activity decline (PAD) were assessed using mediation analyses according to Baron & Kenny.

Results: This study included 154 patients (62% male). Mean age was 65.7 years (SD=6.6). PCS (M=20.3,SD=13.1) was significantly associated with PDI (M=32.4,SD=17.0; R2=0.356,p<0.001), QOL-DN (M=52.6,SD=26.1;R2=0.437, p<0.001) and PAD (M=7.4, SD=5.7;R2=0.087,p=0.045). PAD acted as a partial mediator in the associations of PCS with PDI and QOL-DN respectively. There was no association of PCS with PARS.

Conclusions: Pain catastrophizing was associated with increased disability and decreased quality of life in patients with PDN. Also, it was associated with a perceived decline in physical activity, which had a mediating role in the association between catastrophizing and disability and quality of life respectively. The present study emphasizes the role of catastrophic thinking about pain and the experienced loss in daily activities due to PDN.

Introduction

Up to 20-60% of patients with Diabetes Mellitus develop Painful Diabetic Neuropathy (PDN) (1). PDN is known to have a negative impact on physical and mental quality of life (QoL) and is associated with socioeconomic consequences including loss of work time (2). Sensory and motor deficits in patients with PDN can lead to less engagement in physical activity, which in turn can further impair psychosocial well-being (3, 4). Research has shown that patients with PDN often suffer from enhanced levels of anxiety, fears and depression (5).

The interpretation of pain and its consequences on daily life are influenced by behavioural and cognitive efforts used in the attempt of dealing with pain. An example of a coping strategy that has received much attention in studies with patients with various chronic pain syndromes, is pain catastrophizing (6-10). Pain catastrophizing is defined as a negative cognitive set brought to bear during actual or anticipated pain experience, as it refers to the process during which pain is interpreted as being extremely threatening (8). It has been suggested that as a function of negative experiences involving pain, catastrophic thinking may lead to the development of a coping style that leads patients to be excessively vigilant to pain-related stimuli, to focus excessively on pain sensations, and to expect that aversive stimuli will result in experiences of heightened pain (11). Pain catastrophizing, as measured with the Pain Catastrophizing Scale (PCS)(12), has been associated with heightened pain experience in patients with different types of neuropathic pain such as postherpetic neuralgia(6), phantom limb pain(7) and pain associated with spinal cord injury (10). It has also shown to have a negative impact on the level of disability, depression and anxiety and increase consumption of analgesic medication and pain-related behaviour (10, 11, 13).

An association of pain catastrophizing with decreased physical activity has been found in groups of patients with whiplash and soft-tissue injuries (14). The association of pain catastrophizing with physical activity, QoL and perceived disability in patients with PDN has not yet been fully elucidated. It is plausible that catastrophic thinking is also associated with a lower level of physical activity and more perceived disability in patients with PDN. The question arises whether catastrophic thinking leads to an experienced decline in physical activity as compared to a patients' habitual activity level, or whether it is associated with the actual level of physical activity. Furthermore, it is unknown whether the level of physical activity affects perceived disability and/or QoL in patients with PDN. The aim of the present study, therefore, was to further unravel the underlying mechanisms linking pain catastrophizing to (perceived) physical activity, disability and QoL in patients with PDN. We hypothesized that pain catastrophizing is associated with perceived disability and decreased QoL in patients with PDN and that these associations are mediated by the experienced decline in physical activity rather than the actual level of physical activity.

Methods

Patients

In this study 154 patients with type II diabetes mellitus, aged > 18 years who suffered from peripheral polyneuropathy were included. Eligibility for this study was based on the following: providing written informed consent, having type 2 diabetes mellitus, aged > 18 years and suffering from peripheral polyneuropathy. Additionally, the Diabetic Neuropathy Symptom Score (DNS)(15) was used to diagnose diabetic neuropathy. This scale consists of 4 items: 1. unsteadiness in walking, 2. pain, 3. burning or aching at legs or feet, prickling sensations in legs or feet and 4. numbness in legs or feet (15). Neuropathic pain in the feet was assessed using the interview section of the Douleur Neuropathique 4 Questions (DN4-interview), which consists of seven items relating to the pain description (burning, painful cold, electric shocks) and to its abnormal sensations (tingling, pins and needles, numbness, itching) (16). DN4 and DN4-interview scores have shown a high diagnostic accuracy for painful diabetic polyneuropathy (16). Patients with a DNS score≥ 1 and DN≥4 for at least three months and being clinically stable, were included. The DNS has been validated for diabetic polyneuropathy and has shown to have a high sensitivity and specificity (15). Patients were excluded if there were other conditions that could lead to pain in the feet and/or damage to the peripheral nervous system and if they were not able to understand the Dutch language.

Procedure

Letters of interest were sent to patients derived from a database of patients with type 2 diabetes from a regional hospital in the south of the Netherlands (VieCuri, Venlo, The Netherlands). In total, a number of 2142 letters of interest were sent to patients randomly selected from the database. A total of 388 letters of interest were returned, of which 237 (61%) patients indicated that they were willing to participate in the study. Of the 151 patients who declined to participate, 94 patients reported the reason: no neuropathic pain (n= 54), type I DM (n=23), death (n=9), personal circumstances (n=4), moved to a different address (n=2), phantom limb pain (n=1), no DM (n=1). Of the 237 patients who received a questionnaire, 183 actually filled in and returned the questionnaire (47% of 388 patients that returned the letter of interest). Inclusion criteria were checked by a research assistant and a physician in rehabilitation medicine independently. Of the 183 patients, 154 met the criteria for inclusion. Informed consent was obtained from all subjects and the experimental protocol was approved by the Medical Ethics Committee of Maastricht University, the Netherlands. The procedure of inclusion is shown in Figure 1.

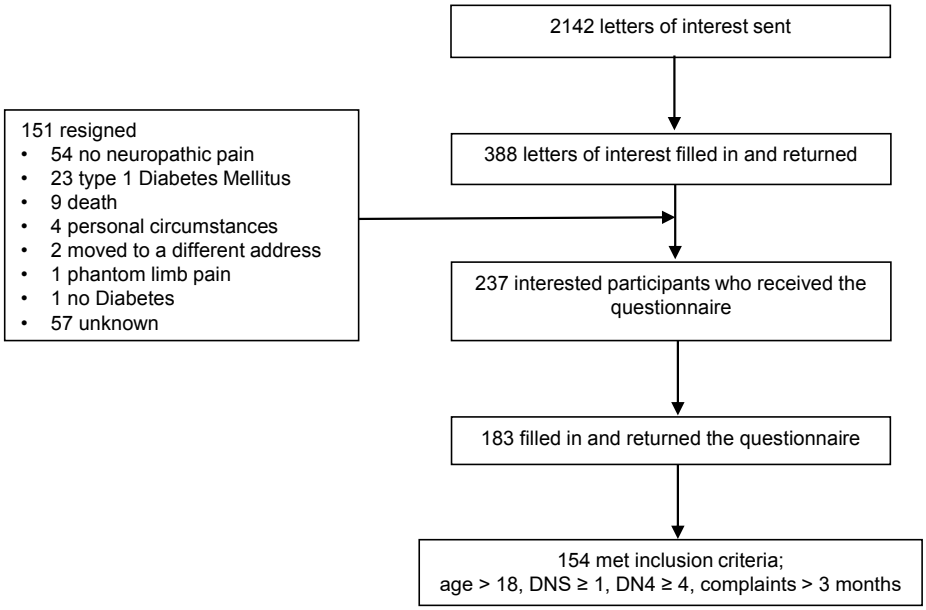

Figure 1. Flowchart of inclusion procedure

Measures

All data were retrieved by self-report questionnaires. Patient characteristics included sociodemographic factors and pain related measures. Behavioural factors were measured using various questionnaires, as is described in the following paragraphs.

1. Patient characteristics

The following factors were assessed; age (years), gender and nationality and having insulin treatment for DM (yes/no).

2. Pain and Pain Catastrophizing

Duration of complaints of neuropathic pain was assessed (months). In addition, pain intensity was measured using a Visual Analogue Scale (VAS), ranging from 0-10. Pain Catastrophizing was measured using the Dutch version of the validated 13-item Pain Catastrophizing Scale (PCS). This questionnaire measures negative thoughts and beliefs during actual or anticipated painful experiences. The items are scored on a five-point Likert scale with scoring possibilities ranging from 'not at all' (score = 0) to 'always' (score = 4). The PCS total score is computed by summing responses to all 13 items and ranges from 0 to 52. High scores indicate that more catastrophic thoughts or feelings are experienced. Psychometric properties of the PCS appeared adequate in previous research: it correlated

highly (r=0.73) with the catastrophizing subscale of the Dutch Pain Cognition List (PCL) and had a good temporal stability (Pearson's r2=0.92) (17). The PCS has shown to have adequate to excellent internal consistency (18).

3. Disability

Perceived disability was measured using the Pain Disability Index (PDI). This 7-item questionnaire investigates the magnitude of the self-reported disability in different situations such as work, leisure time, activities of daily living (ADL) and sports. Each item is scored on a numeric rating scale ranging from 0 (no perceived disability) to 10 (maximum perceived disability). Scores of the individual items were added up to provide the total score. PDI has shown to be internally reliable (Cronbach's alpha = 0.86) and significantly correlated with objective indices of disability such as time spent in bed, psychosomatic symptoms, stopping activities because of pain, work status, pain duration, usual pain intensity, QoL, pain extent and education (r=0.74) (19).

4. Quality of life (QoL)

QoL was measured using the 47-item Norfolk Quality of Life Questionnaire, Diabetic Neuropathy Version, QOL-DN (20), a self-administered questionnaire designed to capture and quantify the perceived impact of diabetic neuropathy on the QoL, physical and psychosocial functioning of patients with diabetic neuropathy. Fourteen of the items are of a health-related, biographical nature and are not scored. Therefore, they were excluded from this study. Items 1-7 (Part I) are an inventory of symptoms of neuropathy in the feet, legs, arms and hands respectively. For each body part separately, the presence of a symptom is scored as 1 and absence of a symptom is scored as 0. Absence of the symptom in all body parts is checked as 'none.' Items 8-35 (Part II) concern Activities of Daily Life (ADL), and are scaled on a 5-point Likert scale ranging from 0 '('not a problem') to 4 ('severe problem'). The 35 scored questions comprise the entire scale and can be grouped according to small fibre, large fibre, and autonomic nerve function symptoms and ADL. Intra-class correlation coefficients have shown to be > 0.9 for most domains (20). Internal consistency of the fiberspecific domains using Cronbach's alpha was considered > 0.6 and up to 0.8 (20). Scores in individual domains (Part I and II) were aggregated to provide a total score.

5. Physical Activity and Perceived Activity Decline

The level of activity was determined using two concepts: physical activity and perceived activity decline (PAD). Physical activity was measured using the Physical Activity Rating Scale (PARS)(21), consisting of 20 daily activities. On a 5-point Likert scale (range 0-4), patients score how often they have performed these activities in the past 2 weeks. To estimate the pain related decline in activities, the PAD question was added to the PARS.

For each activity, patients were asked to indicate how frequently they had performed the specified activity in the last two weeks using the following response categories: never, rarely, now and then, often and very often. Furthermore, patients indicated if they would have performed this specific activity more often if they would not have pain. If the answer was yes for a specific item, one point was counted. On the contrary if the answer was no, the score on that item was zero. The total sum score for 20 activities resulted in a score for PAD; a perceived decline in the level of physical activity after the onset of pain as perceived by the patient, with a theoretical range in PAD of 0–20. The internal consistency (Cronbach's alpha = 0.92) and reliability (ICC = 0.93) of PAD have shown to be good (22).

Statistical analyses

Data were analysed using the Statistical Package for Social Sciences for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). Results for groups (baseline characteristics) were expressed as a mean score and standard deviation. Comparisons between two groups were performed using the Student's t-test for independent samples. To assess the association of pain catastrophizing (PCS) with perceived disability (PDI) and decreased QoL (QOL-DN) linear regression analyses were performed with PDI and QOL as independent variables, adjusted for the study covariates pain intensity, age, gender and insulin treatment (independent variables).

To evaluate the mediating role of PARS and PAD in the association of pain catastrophizing and perceived disability or QoL, multiple linear regression analyses were performed according to Baron and Kenny (23). To illustrate this procedure, the analyses for the mediation of PAD in the association of PCS and PDI is described. In the first analyses PDI was introduced as the dependent variable and PCS, pain intensity, age, gender and insulin treatment as independent variables (step 1). In the second analyses PAD was introduced as dependent variable, with the same independent variables as in the first analyses (step 2). The third analysis resembles the first analysis (PDI dependent variable) with the addition that PAD is added to the earlier set of independent variables (step 3). If PAD acts as mediator in the relation of PCS and PDI, the contribution of PCS should be statistically significant in the first and second analyses, whereas the effect should be attenuated in the third analyses after introduction of PAD. To evaluate the mediating role of PARS in the association with PCS and PDI, and the mediating role of both PARS and PAD in the association with PCS and QOL –DN three identical procedures were performed.

For all multiple linear regression analyses standardized beta coefficients and their significance were tested under the null hypothesis that the coefficient differed from zero. To control for multicollinearity, variable inflation factors (VIF) were checked and should all be below 3. Data was checked for normality and missing values. Mean imputation was performed to account for missing data in total scores.

Results

Baseline characteristics and pain related outcomes

As is shown in table 1, this study included 96 male and 58 female patients with a mean age of 65.7 years (SD=6.6). Mean duration of complaints of PDN was 72.3 months (SD=57.6) and 65% of the participants were on insulin treatment. Pain related variables: mean pain intensity score was 4.8 (SD=2.0), mean PCS score was 20.3 (SD=13.1), mean PDI score was 32.4 (SD=17.0) and mean QOL-DN score was 52.6 (SD=26.1). Activity related variables: Mean PARS score was 45.3 (SD=9.0) and mean PAD score was 7.4 (SD=5.7). There were no differences between men and women on the baseline characteristics or pain related outcomes ($p>0.05$ for all variables, Table 1).

Table 1: Baseline characteristics.

		N	Mean/n	SD / %
Demographic variables	Age	154	65.7	± 6.6
	Gender (Male/Female)	154	96 / 58	62% / 38%
	Insulin Treatment	154	100	65%
Pain related measures	Duration of complaints	144	72.3	± 57.6
	Pain intensity	153	4.8	± 2.0
	PCS	151	20.3	± 13.1
Consequences in daily life	QOL-DN	131	52.6	± 26.1
	PDI	150	32.4	± 17.0
	PARS	152	45.3	± 9.0
	PAD	141	7.4	± 5.7

Data are presented as mean ± SD or n (%), as appropriate. Age (years), Duration of complaints (months), pain intensity (VAS 0-10), PCS: Pain Catastrophizing Scale; Norfolk Quality Questionnaire of Life PDN version; PDI: Pain Disability Index; PARS: Physical Activity Rating Scale; PAD: Perceived Activity Decline.

Step 1: The association between Pain Catastrophizing and Perceived Disability and QoL respectively.

As is shown in the first section of Table 2, PCS significantly contributed to the association with PDI ($\beta=0.311$, $p<0.001$). Furthermore, insulin treatment ($\beta=0.151$, $p=0.028$) and pain intensity ($\beta= 0.375$, $p<0.001$) significantly contributed to the association with pain catastrophizing and perceived disability.

As is shown in the first section of Table 3, PCS was significantly associated with QOL-DN (β= 0.373, p<0.001), indicating a lower QoL in patients who engage in catastrophic thinking. Also, insulin treatment and pain intensity significantly contributed to the association of pain catastrophizing and QoL (β=0.140, p=0.042 and β=0.388, p<0.001 resp.).

Step 2: The association between Pain Catastrophizing and Perceived Activity Decline or Physical Activity respectively.
PCS was significantly associated with PAD (β=0.182, p=0.045), whereas the level of pain intensity showed no contribution to this association (β=0.151, p=0.095) (Table 4). There was no statistically significant association of PCS with PARS, indicating that pain catastrophizing seems to be associated with a perceived decline in physical activity rather than with the actual level of physical activity. Only pain intensity showed a statistically significant contribution to the association with pain catastrophizing and physical activity (β=-0.215, p=0.015)(Table 4).

Step 3A: Mediation analyses of Perceived Activity Decline in the association of Pain Catastrophizing with Disability.
The first and second step of the mediation analyses are presented in paragraph are described above. The mediating role of PAD was analysed in the association of pain catastrophizing and perceived disability. No analyses were performed to investigate the mediating role of PARS, since the obligatory association of PARS with PCS was absent.

The full mediation analysis is shown in Table 2. When introduced as an independent variable, PAD showed to significantly contribute to the association of PCS with PDI (β=0.401, p<0.001). The effects of pain catastrophizing, insulin treatment and pain intensity were all attenuated (β=0.226, p=0.001; β =0.106, p<0.001; and β=0.307, (p=0.100) resp.), indicating that physical activity decline acted as a partial mediator in the association between pain catastrophizing and perceived disability. VIFs were checked and were all below three.

Step 3B: Mediation analyses of Perceived Activity Decline in the association of Pain Catastrophizing with QoL.
To assess whether the association of pain catastrophizing and QoL is mediated by physical activity decline, the same set of analyses were performed. PAD showed to significantly contribute to the association with PCS and QOL-DN (β=0.336, p<0.001) (Table 3). The effects of pain catastrophizing, insulin treatment and pain intensity were again all attenuated after the introduction of PAD (β=0.319, p<0.001; β=0.091, p=0.162 and β=0.343, p<0.001 resp.). This analysis shows that physical activity decline also acted as a partial mediator in the association of pain catastrophizing and QoL. VIFs were checked and were all below three.

Table 2: Mediation analyses for catastrophizing, perceived disability and physical activity decline.

	Dependent variable	Independent variable	R2	Adjusted R2	Standardized β	P-value
1	PDI	PCS	0.356	0.333	0.311	0.000
		Age			0.018	0.791
		Gender			-0.078	0.256
		Insulin Treatment			0.151	0.028
		Pain Intensity			0.375	0.000
2	PAD	PCS	0.087	0.052	0.182	0.045
		Age			-0.053	0.522
		Gender			0.031	0.711
		Insulin Treatment			0.074	0.374
		Pain Intensity			0.151	0.095
3	PDI	PCS	0.482	0.457	0.226	0.001
		Age			0.041	0.518
		Gender			-0.082	0.199
		Insulin Treatment			0.106	0.100
		Pain Intensity			0.307	0.000
		PAD			0.401	0.000

PDI: Pain Disability Index; PCS: Pain Catastrophizing Scale; PAD: Perceived Activity Decline.

Table 3: Mediation analyses for catastrophizing, QoL and physical activity decline.

	Dependent variable	Independent variable	R2	Adjusted R2	Standardized β	P-value
1	QOL-DN	PCS	0.437	0.414	0.373	0.000
		Age			-0.023	0.738
		Gender			0.047	0.497
		Insulin Treatment			0.140	0.042
		Pain Intensity			0.388	0.000
2	PAD	PCS	0.087	0.052	0.182	0.045
		Age			-0.053	0.522
		Gender			0.031	0.711
		Insulin Treatment			0.074	0.374
		Pain Intensity			0.151	0.095
3	QOL-DN	PCS	0.529	0.504	0.319	0.000
		Age			0.012	0.851
		Gender			0.046	0.483
		Insulin Treatment			0.091	0.162
		Pain Intensity			0.343	0.000
		PAD			0.336	0.000

QOL-DN: Norfolk Quality of Life Questionnaire PDN version; PCS: Pain Catastrophizing Scale; PAD: Perceived Activity Decline.

Table 4: Association of pain catastrophizing and physical activity or physical activity decline respectively.

Dependent variable	Independent variable	R2	Adjusted R2	Standardized β	P-value
PAD	PCS	0.087	0.052	0.182	0.045
	Age			-0.053	0.522
	Gender			0.031	0.711
	Insulin Treatment			0.074	0.374
	Pain Intensity			0.151	0.095
PARS	PCS	0.097	0.066	-0.131	0.137
	Age			-0.048	0.548
	Gender			.0079	0.325
	Insulin Treatment			-.0080	0.317
	Pain Intensity			-0.215	0.015

PAD: Perceived Activity Decline; PARS: Physical Activity Rating Scale; PCS: Pain Catastrophizing Scale.

Discussion

Pain catastrophizing is characterized by a tendency to magnify the threat value of pain stimuli, to feel helpless in the context of pain, and by a relative inability to inhibit pain-related thoughts in anticipation of, during or following a painful encounter. Mean PCS scores in this sample of Dutch patients suffering from PDN, were comparable to scores of patients with other pain syndromes (6, 8, 24). We found that pain catastrophizing was associated with increased perceived disability and decreased QoL in patients with PDN. Interestingly, pain catastrophizing was associated with the subjective feeling of loss of physical activities due to pain (perceived physical activity decline) but not the self-reported estimate of one's actual level of activity. Our findings suggest that patients with PDN who catastrophize about their pain experience a greater burden of PDN due to their perceived, but not actual, decline in physical activity.

In the biopsychosocial perspective pain is considered to be of a complex and multifactorial origin, taking into account biological, psychological and social factors, resulting in individual differences in motoric, cognitive and psycho-physiological responses (25). One model within this perspective is the fear-avoidance model, which addresses the way a patient interprets its pain. If pain is interpreted as non-threatening, patients are likely to stay engaged in daily activities. If, however, patients misinterpret pain as being threatening, a vicious cycle of catastrophic thinking may be initiated leading to excessive fear of pain/injury, resulting in avoidance of physical activities, disuse, depression and disability (26, 27). The fear-avoidance model has been extensively studied in patients with chronic low back pain (28), but only limited information is available about the way patients with PDN interpret their pain. In line with the fear-avoidance model, this study shows that pain catastrophizing can induce the feeling of not being able to be physically active rather than affecting the actual level of physical activity, and that this feeling results in perceived disability and a lower QoL in patients with PDN. These results suggest that it is important to address these subjective measures of perceived disability when assessing the effects of chronic pain syndromes on daily life activities and QoL.

It is known that PDN itself has a negative effect on QoL (1). Our results indicate that catastrophic thinking may play a role in this association. Mean QOL-DN score (52.6) was comparable to other studies in patients with PDN (29). Studies in patients with various pain conditions have shown that pain catastrophizing negatively influenced depression and anxiety (10, 24). Furthermore, pain catastrophizing has been associated with increased pain-related disability and behaviour (8, 30). The mean PDI score in our study (32.4) was comparable to scores of patients with other pain syndromes (31). To our knowledge, this study is the first study to link catastrophic thinking with QoL and perceived disability in a sample of patients with PDN.

In order to understand the impact of PDN, it is important to differentiate between perceived disability and physical activity decline. Disability refers to problems in executing daily life tasks and activities. Disability has been defined by the World Health Organization (1980) as any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being (32). Pain-related disability questionnaires focus on the decrease in capacity in the performance and altered performance of regular activities in the daily life of patients with pain. In contrast, physical activity decline is defined as a decrease in the level of physical activity as perceived by the patient, which is relative to a person's activity level before the onset of the pain (33). This study shows that patients who engage in catastrophic thinking experience a greater decline in physical activity, while there was no association between catastrophic thinking and the estimated actual level of physical activity. This is in line with previous studies in patients with low back pain (33, 34).

Perceived decline in physical activity (PAD) acted as a partial mediator in the associations between catastrophic thinking and perceived disability, and catastrophic thinking and QoL respectively. This means that catastrophic thinking is not solely a direct predictor for perceived disability and QoL, but that this association is also partially determined by the feeling of loss in physical activity, which on its turn leads to increased perceived disability (inability to perform an activity) and lower QoL. Patients who catastrophize about pain, probably also catastrophize about their loss in physical activity, which further strengthens them in feeling disabled and having a lower QoL. The identification of pain catastrophizing as a partial mediator is valuable, as it suggests that an intervention that targets pain catastrophizing will indirectly also improve perceived disability and QOL.

In line with previous studies, pain intensity was a significant contributor in the explanation of the association of pain catastrophizing and perceived disability, QoL and physical activity (8, 35). Pain intensity showed no contribution in the perceived decline of physical activity (PAD), suggesting that the perception of activity decline is not pain-induced but is probably based on other mechanisms such as pain catastrophizing.

Insulin treatment is known to be highly burdensome due to the method of administration (injections) and the risks of hypoglycaemia (36). Therefore, insulin treatment can be considered a parameter for the severity of diabetes. As expected, insulin treatment was associated with low QoL and perceived disability. Interestingly, insulin treatment showed a lower β-value in its association with QoL and perceived disability as compared to catastrophic thinking, suggesting that the a catastrophic way of thinking is a greater predictor for the experienced burden caused by PDN, than is insulin treatment. The association of insulin treatment and perceived disability was diminished after the addition of PAD to the model, suggesting that insulin treatment seems to result in the feeling of

not being able to be as physically active as before, which on its turn causes the perceived inability to perform certain activities. Thus, insulin treatment was not a direct predictor for perceived disability.

This study has several limitations. First, potential participants for this study were derived from an already existing database containing patients with type II diabetes. Only 183 out 2142 invited patients filled in and returned the final questionnaire, resulting in a potential self-selection bias. Secondly, diabetes related information is based on self-report. In order to overcome this issue, we used multiple selected items (DNS ≥1 and neuropathic pain in the feet) to identify eligible subjects according to our inclusion criteria. In future studies, PDN should be diagnosed by performing a clinical history and peripheral neurological and vascular examination. Thirdly, there was no information available on diabetes-related complications such as retinopathy or nephropathy. Also scores on physical activity were solely based on self-report and there was no movement registration. It should be noted however, that information on physical activities in the past can only be obtained based on self-report. Future prospective studies using objective physical measurements are advised, in order to avoid the influence of a patients' perception or interpretation. For example, accelerometry could be a useful addition to the PARS questionnaire. Last, this study has a cross-sectional design in which the dependent and independent variables are simultaneously assessed. For this reason, results cannot provide information on a causal relationship or a chronological order of the relationship between pain catastrophizing and the outcome variables.

Most current treatment modalities in PDN are one-dimensional; they solely focus on the disease and/or pain itself and rehabilitation interventions mainly improve physical fitness. This study shows that it is important to not only objectify the daily activity level of a patient with PDN, but also to focus on the perceived change in a patients' activity level. This knowledge can have great implications for the management of patients with PDN, as treatment modalities that focus on pain or physical activity alone most likely will not suffice.

In conclusion, neuropathic pain is a complex and multidimensional condition, which often has a major negative impact on daily life, both physically and mentally. The present study illustrates that patients with PDN who engage in catastrophic thinking experience a loss in physical activity, increased perceived disability and lesser QoL. Based on our results, we stress the importance of integration of psychological aspects such as pain catastrophizing in the treatment of PDN.

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Chapter 4

Anxiety affects disability and quality of life in patients with painful diabetic neuropathy.

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Abstract

Background: Painful Diabetic Neuropathy (PDN) is known to negatively affect psychosocial functioning as expressed by enhanced levels of anxiety and depression. The aim of this study was to specify diabetes and pain related fears.

Methods: This questionnaire-based cross-sectional study included 154 patients with PDN (mean age 65.7±6.6 years). Correlation analyses corrected for age, gender, pain intensity, pain duration and insulin treatment were performed to assess the associations of fear of hypoglycaemia (Hypoglycaemia Fear Survey, HFS), kinesiophobia (Tampa Scale of Kinesiophobia, TSK), fear of pain (Pain Anxiety Symptom Scale, PASS-20), fear of falling (Falls Efficacy Scale-I, FES-I), fear of fatigue (Tampa Scale of Fatigue, TSF), and fear of negative evaluation (Brief Fear of Negative Evaluation Scale, BFNE), with quality of life (QoL) (Norfolk Quality of Life Questionnaire, Diabetic Neuropathy Version, QOL-DN) and disability (Pain Disability Index, PDI), respectively.

Results: In univariate analyses, all fears were independently associated with QOL-DN and PDI ($p<0.001$ for all variables). Linear regression models including all fears and confounders, showed that pain intensity, pain duration and FES-I were significantly associated with QOL-DN ($R2=0.603$). Pain intensity, male gender and FES-I were significantly associated with PDI ($R2=0.526$).

Conclusions: After controlling for confounders, levels of pain intensity, duration of pain and fear of falling were negatively associated with QoL in patients with PDN. Pain intensity, male gender and fear of falling were positively associated with disability. Specifying fears enables us to identify potential targets for behavioural interventions that aim to improve psychosocial well-being in patients with PDN.

Introduction

Peripheral neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the peripheral nervous system (1). Approximately 25-30% of the patients with diabetes mellitus (DM) develop Painful Diabetic Neuropathy (PDN) (2, 3). Patients with PDN report a sharp, stinging, electrical, burning sensation that aggravates at night with numbness or loss of sensation of the involved area (4).

PDN is a complex and multi-dimensional condition which is known to negatively affect psychosocial functioning as expressed by enhanced levels of anxiety and depression, potentially leading to pain related disability (5), which can have a major impact on recreational activities, work, general activities, social activities, mobility, sleep and elevated levels of experienced stress (6). Fear may also negatively influence glycaemic control in diabetic patients (7).

The interpretation of pain and its consequences on daily life are influenced by behavioural and cognitive efforts used in the attempt of dealing with pain(8). Biopsychosocial models regarding chronic pain such as the fear-avoidance model, have been extensively studied in patients with chronic musculoskeletal pain (9, 10), but only limited information is available about the way patients with PDN interpret their pain. For this reason, our research group is currently investigating the role of psychosocial factors on physical activity, disability and quality of life (QoL) in patients with PDN.

Research in the current sample has shown that pain catastrophizing was associated with increased disability and decreased QoL in patients with PDN. Interestingly, pain catastrophizing was associated with the subjective feeling of loss of physical activities due to the pain, while it was not associated with the estimated actual level of activity (11).

In order to gain more insights in the psychological processes that lead to disability and QoL in patients with PDN, we felt that it is important to further investigate and specify anxiety and fears. Improving psychological well-being and especially the level of fear might break this potential vicious cycle in patients with PDN (7).

The first step in specifying PDN related fears was a qualitative study using focus group interviews. In this study, we investigated several PDN related consequences and fears that seemed to inhibit mobility and decrease QoL in patients with PDN. These consequences of PDN were both physical (weakness, pain, physical restrictions), psychological (feelings of loss, feelings of depression, fear, anger, sadness), and social (social withdrawal, isolation, work limitations, lower career opportunities). The patients reported several fears related

to diabetes and pain, such as fear of hypoglycaemia, fear of (increased) pain, fear of total exhaustion, fear of physical injury, fear of falling, fear of loss of identity and fear of negative evaluation (12).

To further quantify these fears, we identified available validated questionnaires that matched these self-reported fears, each measuring one specific element of diabetes-related fear or pain-related fear. From these data we also developed the Painful diabetic neuropathy Anxiety Rasch Transformed Questionnaire (PART-Q30©)(13). In the current study, we have investigated which of these fears showed the largest association with disability and QoL.

Methods

Patients

An invitational letter explaining the study and requesting participation was sent out to a random selection of 2142 patients as part of a registry of patients with type 2 diabetes from a regional hospital in the south of the Netherlands (VieCuri, Venlo, The Netherlands). Eligibility was based on the following: providing written informed consent, having type 2 diabetes mellitus, aged > 18 years, suffering from peripheral polyneuropathy (Diabetic Neuropathy Symptom Score, DNS ≥ 1) (14) and neuropathic pain in the feet (Douleur Neuropathique 4 questions [DN4 ≥ 4]) for at least three months, but being clinically stable. Patients were excluded if there were other conditions that could lead to pain in the feet and/or damage to the peripheral nervous system. Informed consent was obtained from all subjects and the Medical Ethics Committee of Maastricht University, the Netherlands approved the study protocol (11-4-045.4). The full recruitment and inclusion procedure is described elsewhere (11).

Measures

All data were retrieved by self-report questionnaires. Short descriptions of the questionnaires are provided, as they are described in more detail elsewhere (11).

Patient characteristics: The following factors were assessed; age (years), gender (male/female) and having insulin treatment for DM II (yes/no).

Pain: Duration of complaints of neuropathic pain was assessed (months). In addition, current pain intensity was measured using a Visual Analogue Scale (VAS), ranging from 0-10.

Disability: Disability was measured using the Pain Disability Index (PDI). This 7-item questionnaire investigates the magnitude of the self-reported disability in different domains such as work, leisure time, activities of daily living (ADL) and sports. PDI has shown to be reliable (internal consistency, Cronbach's alpha =0.86) and correlates significantly with objective indices of disability such as time spent in bed, psychosomatic symptoms, stopping activities because of pain, work status, pain duration, usual pain intensity, quality of life and education (r=0.74) (15).

Quality of life: QoL was measured using the Norfolk Quality of Life Questionnaire, Diabetic Neuropathy Version, QOL-DN (16), a self-administered questionnaire designed to capture and quantify the perceived impact of diabetic neuropathy on the quality of life, as well as physical and psychosocial functioning. Internal con

Specific fears were measured using the following questionnaires:
Fear of Hypoglycaemia. Fear for hypoglycaemia was measured using the Dutch version of the Hypoglycaemia Fear Survey (HFS). For the purpose of this study, only the 13-item 'worry scale' was used. The internal consistency of this questionnaire has shown to be high (Cronbach's α = 0.92) (17). Temporal reliability (test-retest) has shown to be r=0.74 for the total HFS and r=0.63 for the 'worry scale'(18).

Fear of pain. The short version of the Pain Anxiety Symptom Scale (PASS-20) measures the importance of fear for pain in persistent pain behaviour (19). The PASS-20 has shown strong internal consistency; Cronbach's α for avoidance behaviour = 0.75, for fear = 0.82, for somatic fear = 0.81 and for cognitive fear = 0.86, and total Cronbach's α of 0.91 (19). Test-retest reliability has shown to be good (r=0.86) (20).

Kinesiophobia. Kinesiophobia was measured using the Dutch version of the 17-item Tampa Scale of Kinesiophobia (TSK). Test–retest reliability has shown to range from r=0.64-0.80 (21). The internal consistency of the TSK has shown to be good (Cronbach's α = 0.81) (22).

Fear of Fatigue. Fear of fatigue was measured using the Short Tampa scale for Fear of Fatigue (TSF). Internal consistency of the TSF has shown to be sufficient (Cronbach's α= 0.80)(23) and test–retest reliability has shown to be good (ICC=0.83)(24).

Fear of falling. Fear of falling was measured by the 'Falls Efficacy Scale - International' (FES-I), which measures confidence in performing activities without falling in daily living (e.g. cleaning the house). The internal consistency of the FES-I has shown to be high (Cronbach's α 0.96) and the test-retest reliability has shown to be high (ICC=0.82-0.93) (25, 26).

Fear of negative evaluation. Fear for negative evaluation is measured by the 'Brief Fear of Negative Evaluation Scale' (BFNE, short form)(27). Fear of negative evaluation is defined as fear of negative evaluation as apprehension about others' evaluations, distress over their negative evaluations, avoidance of evaluative situations, and the expectation that others will evaluate oneself negatively (28). Internal consistency of the BFNE has shown to be excellent (Cronbach's α = 0.96) (27). The scale obtained excellent inter-item reliability (α=0 .97) and 2-week test-retest reliability (r =0 .94) (29).

Statistical analysis
Data were analysed using Statistical Package for Social Sciences for Windows, version 22.0. The study questionnaires HFS, PASS-20, TSK, FES-I, TSF and BFNE were scored according to the standard scoring guidelines. Descriptive statistics were used to describe the study

sample; means and standard deviations for normally distributed variables, medians and interquartile ranges for skewed variables and numbers and percentages for categorical variables, as appropriate. Comparisons between two groups were performed using the Student's t-test for independent samples. If there was < 25% nonresponse on a variable, mean imputation was performed to account for missing data in total scores. If there was > 25% nonresponse, the variable was registered as missing value. As data of the HFS, PASS, BFNE and FES-I were skewed, natural logarithmic transformation was applied prior to analyses.

To determine significantly associated variables for the linear regression model for QOL-DN and PDI respectively, Spearman correlation analyses were performed including all confounders (age, gender, insulin treatment, pain intensity and duration of the pain) and all fears (HFS, PASS, TSK, FES-I, TSF and BFNE).

Linear regression models were used to assess which of the fears contributed significantly to QOL-DN and PDI, respectively. First, a baseline model was constructed including all confounders, fears (HFS, PASS, TSK, FES-I, TSF and BFNE) and QOL-DN or PDI respectively. Additionally, stepwise backward regression analyses were performed to construct a final model in which confounders were retained, but the fears HFS, PASS, TSK, FES-I, TSF and BFNE were systematically eliminated. A limit value for elimination in the backward regression analyses was set at $p < 0.05$. In this final model, only statistically significant variables were retained. A two-sided p-value < 0.05 was considered statistically significant. The maximum coefficient of determination (R2) was taken into account for each analysis. All the variable inflation factors (VIF) were checked and had to be < 3.

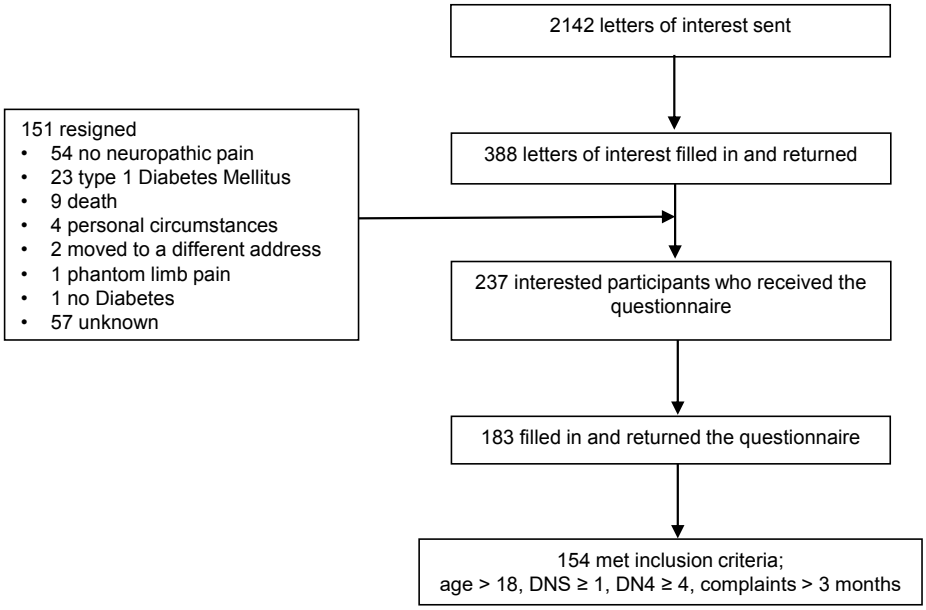

Figure 1. Flowchart of inclusion procedure

Results

Patients

A total of 2142 patients were invited, of which 388 responded and 237 expressed their willingness to participate. Of the 151 patients who resigned, 94 patients/caregivers provided a reason for not participating (no neuropathic pain (n= 54), type I DM (n=23), death (n=9), personal circumstances (n=4), moved to a different address (n=2), phantom limb pain (n=1), or no DM (n=1)). Of the 237 patients who received a questionnaire, 183 actually completed and returned the questionnaire, and of these only 154 patients met the inclusion/exclusion criteria and were eligible to the current study (see figure 1).

Baseline characteristics

Baseline characteristics and descriptive statistics of fear related outcomes are shown in table 1. There were no differences between men and women regarding the baseline characteristics, pain related and fear related outcomes (p>0.05 for all variables, data not shown).

Table 1. Baseline characteristics.

		N	
Demographic variables	Age	154	65.7 ± 6.6
	Gender (Male/Female)	154	96 (62%) / 58 (38%)
	Insulin Treatment	154	100 (65%)
Pain related measures	Duration of complaints	144	72.3 ± 57.6
	Pain intensity	153	4.8 ± 2.0
Consequences in daily life	QOL-DN	131	52.6 ± 26.1
	PDI	150	32.4 ± 17.0
Fears	HFS	151	13.5 (3.5 – 23.0)
	PASS-20	152	25.0 (10.7 – 39.3)
	TSK	149	38.1 ± 8.0
	FES-I	150	27.0 (20.5 – 33.5)
	TSF	153	16.3 ± 5.5
	BFNE	153	11.0 (6.1 – 10.9)

Data are presented as n (%), mean ± SD or median (interquartile range), as appropriate. Age (years); Duration of complaints (months); pain intensity (VAS 0-10). QOL-DN: Norfolk Quality of Life Questionnaire; PDI: Pain Disability Index; HFS: Hypoglycaemia Fear Survey; PASS-20: Pain Anxiety Symptom Scale; TSK: Tampa Scale of Kinesiophobia; FES-I: Falls Efficacy Scale – International; TSF: Tampa Scale of Fatigue; BFNE: Brief Fear of Negative Evaluation Scale.

Correlations and linear backward regression models
Mean imputation was performed for the following variables: QOL-DN (n=29), PDI (n=12), HFS (n=14), PASS (n=13), TSK (n=3), FES-I (n=12), TSF (n=2) and BFNE (n=2).

Spearman correlations were calculated to construct a correlation matrix for all variables and QoL (table 2) and disability (table 3). The results show that each of the fears (fear of hypoglycaemia (HFS), fear of pain (PASS), kinesiophobia (TSK), fear of negative evaluation (BFNE), fear of falling (FES-I) and fear of fatigue (TSF)) significantly correlated with QOL-DN ($p<0.001$ for all variables, table 2) and PDI ($p<0.001$ for all variables, table 3).

Linear regression analyses including all confounders and fears, were performed to assess the association of the fears with QoL and disability, respectively. Duration of complaints, pain intensity and fear of falling were significantly associated with QoL ($\beta=0.131$, $p=0.042$; $\beta=0.239$, $p<0.001$ and $\beta=0.348$, $p=<0.001$ resp.). The final model explained 60.3% of the total variance (adjusted $R2= 0.603$). The full model is shown in Table 4. As mentioned before, mean imputation was performed in 29 cases of QOL-DN. An additional analysis excluding these 29 subjects showed similar results as compared to the analysis including the imputed data; duration of complaints, pain intensity and fear of falling were all significantly associated with QoL ($\beta=0.121$, $p=0.043$; $\beta=0.252$, $p<0.001$; $\beta=0.363$, $p<0.001$ resp.). In addition to this, the fear of hypoglycaemia showed a statistically significant contribution to the association of fears with QoL ($\beta=0.172$, $p=0.027$) and the final model explained 59.2% of the total variance (adjusted $R2=0.592$).

Male gender, pain intensity and fear of falling were significantly associated with disability ($\beta=-0.122$, $p=0.048$; $\beta=0.250$, $p<0.01$ and $\beta=0.443$, $p=<0.001$ resp.). The final model explained 52.6% of the total variance (adjusted $R2=0.526$). The full model is shown in Table 5.

Finally, stepwise backward regression analyses were performed. The final model for QoL and confounders (age, gender, insulin treatment, duration of complaints and pain intensity), showed that fear of fatigue, fear of hypoglycaemia and fear of falling were retained as statistically significant contributing factors ($\beta=0.134$, $p=0.045$; $\beta=0.216$, $p=0.003$ and $\beta=0.385$, $p=<0.001$ resp., data not shown). Also pain intensity showed to have a statistically significant contribution to the model of QOL-DN ($\beta=0.253$, $p<0.001$). The final model explained 60.2% of the total variance (adjusted $R2=0.602$, data not shown). The final model of the stepwise backward regression analysis for disability and confounders, showed that only fear of falling was retained in the model ($\beta=0.540$, $p<0.001$). In this model, pain intensity and gender also showed a statistically significant

contribution to the model (β=0.283, p<0.001; β=-0.135, p=0.025). The final model explained 52.3% of the total variance (adjusted R^2=0.523, data not shown). In both models, age, insulin treatment and duration of complaints showed no statistically significant contribution. In all models, VIFs were checked and were all less than three.

Table 2: Correlation Matrix QoL.

	QOL-DN	Age	Gender	Insulin	Duration
QOL-DN	1.000	-0.037	0.042	0.165	0.375**
Age		1.000	-0.031	-0.005	0.000
Gender			1.000	0.028	0.048
Insulin treatment				1.000	0.116
Duration of symptoms					1.000
Pain intensity					
TSK					
TSF					
HFS					
PASS					
FES-I					
BFNE					

QOL-DN: Norfolk Quality of Life Questionnaire; TSK: Tampa Scale of Kinesiophobia; TSF: Tampa Scale of Fatigue; HFS: Hypoglycaemia Fear Survey; PASS-20: Pain Anxiety Symptom Scale;

Table 3: Correlation Matrix Disability.

	PDI	Age	Gender	Insulin	Duration
PDI	1.000	0.025	-0.081	0.136	0.292**
Age		1.000	0.018	0.051	-0.015
Gender			1.000	0.053	0.020
Insulin treatment				1.000	0.079
Duration of symptoms					1.000
Pain intensity					
TSK					
TSF					
HFS					
PASS					
FES-I					
BFNE					

PDI: Pain Disability Index; TSK: Tampa Scale of Kinesiophobia; TSF: Tampa Scale of Fatigue; HFS: Hypoglycaemia Fear Survey; PASS-20: Pain Anxiety Symptom Scale; FES-I: Falls Efficacy Scale – International;

Pain intensity	TSK	TSF	HFS	PASS-20	FES-I	BFNE
0.491**	0.523**	0.388**	0.582**	0.711**	0.707**	0.458**
-0.009	0.014	0.178*	-0.149	-0.012	0.018	-0.136
0.083	-0.060	-0.167	0.067	0.025	0.048	0.208*
0.068	0.119	0.188*	0.170	0.110	0.184*	0.045
0.226*	0.197*	0.074	0.209*	0.241**	0.322**	0.032
1.000	0.325**	0.149	0.315**	0.441**	0.395**	0.223*
	1.000	0.665**	0.480**	0.583**	0.535**	0.395**
		1.000	0.313**	0.437**	0.366**	0.257**
			1.000	0.639**	0.542**	0.574**
				1.000	0.703**	0.563**
					1.000	0.467**
						1.000

FES-I: Falls Efficacy Scale – International; BFNE: Brief Fear of Negative Evaluation Scale. Correlations are presented as R-values. **= Correlation is significant at the 0.01 level (2-tailed). *= Correlation is significant at the 0.05 level (2-tailed).

Pain intensity	TSK	TSF	HFS	PASS-20	FES-I	BFNE
0.495**	0.484**	0.408**	0.409**	0.610**	0.659**	0.281**
0.008	0.025	0.136	-0.099	0.003	0.024	-0.166
0.035	-0.049	-0.126	0.073	0.004	0.070	0.177*
0.049	0.103	0.124	0.195*	0.095	0.136	0.021
0.257**	0.198*	0.059	0.210*	0.231**	0.277**	-0.007
1.000	0.326**	0.160	0.277**	0.444**	0.404**	0.154
	1.000	0.655**	0.491**	0.603**	0.534**	0.379**
		1.000	0.320**	0.464**	0.415**	0.261**
			1.000	0.642**	0.497**	0.547**
				1.000	0.715**	0.544**
					1.000	0.433**
						1.000

BFNE: Brief Fear of Negative Evaluation Scale. Correlations are presented as R-values. **= Correlation is significant at the 0.01 level (2-tailed). *= Correlation is significant at the 0.05 level (2-tailed).

Table 4: Linear regression analyses of fears and QoL (n=122).

	Standardized Beta	P-value	R2
Age	-0.045	0.467	0.603
Gender	-0.011	0.857	
Insulin Treatment	0.014	0.817	
Duration of complaints	0.131	0.042*	
Pain Intensity	0.239	0.000*	
TSK	-0.036	0.705	
TSF	0.130	0.137	
HFS	0.152	0.062	
PASS	0.078	0.397	
FES-I	0.348	0.000*	
BFNE	0.101	0.175	

Determinants of fears and QOL, as measured with QOL-DN; Norfolk Quality of Life Questionnaire, Diabetic Neuropathy Version. Age (years); Gender (0= male, 1=female); Insulin treatment (0=no, 1=yes); Duration of complaints (months), Pain Intensity (VAS 0-10); TSK; Tampa Scale of Kinesiophobia, TSF; Tampa Scale for Fatigue, HFS; Hypoglycaemia Symptom Scale, PASS; Pain Anxiety Symptom Scale, FES-I; Falls Efficacy Scale – International, BFNE; Brief Fear of Negative Evaluation Scale.

*= $p<0.05$.

Table 5: Linear regression analyses of fears and disability (n=136).

	Standardized Beta	P-value	R2
Age	0.001	0.993	0.526
Gender	-0.122	0.048*	
Insulin Treatment	0.044	0.481	
Duration of complaints	0.055	0.395	
Pain Intensity	0.250	0.000*	
TSK	0.032	0.743	
TSF	0.084	0.334	
HFS	0.029	0.738	
PASS	0.078	0.426	
FES-I	0.443	0.000*	
BFNE	0.006	0.938	

Determinants of Disability as measured with PDI; Pain Disability Index. Age (years); Gender (0= male, 1=female); Insulin treatment (0=no, 1=yes); Duration of complaints (months), Pain Intensity (VAS 0-10); TSK; Tampa Scale of Kinesiophobia, TSF; Tampa Scale for Fatigue, HFS; Hypoglycaemia Symptom Scale, PASS; Pain Anxiety Symptom Scale, FES-I; Falls Efficacy Scale – International, BFNE; Brief Fear of Negative Evaluation Scale. *= $p<0.05$.

Discussion

This study illustrates that patients with PDN seem to suffer from various fears, such as fear of hypoglycaemia, kinesiophobia, fear of pain, fear of negative evaluation, fear of falling and fear of fatigue, and that some of these fears are associated with less QoL and increased disability in patients with PDN. Univariate analyses showed that all these fears were significantly and negatively associated with QoL and were positively associated with disability. More specifically, multivariate analyses showed that fear of falling, duration of complaints and pain intensity were the most important factors being negatively associated with QoL, while fear of falling, male gender and pain intensity were significantly associated with disability in patients with PDN. This study highlights the great burden of PDN in daily life, as reflected by the scores of disability and QoL (30). Our findings could be relevant for clinical practice as it may provide a basis for a theoretical framework on the psychosocial consequences of PDN. This framework enables us to design a treatment strategy that could directly target these fears (e.g. behavioural interventions according to the principles of exposure in vivo (31), and by doing so, could improve physical and psychosocial well-being in these patients.

Chronic pain is a subjective experience that is known to affect cognitive and emotional dimensions (32). Neuropathic pain has shown to be particularly distressing, as it is associated with a high degree of suffering and does not generally decline over time (5). Unfortunately, there is no cure for diabetic neuropathy. Treatment approaches include decelerating the progressive loss of nerve function through maintenance of glycaemic control and pain management (33). Pain medication such as anti-depressants, anti-epileptics and opioids are recommended. However, treatment effects are not always sufficient and side effects occur frequently (34).

In the biopsychosocial perspective, chronic pain is influenced by biological, psychological and social factors, resulting in individual differences in motoric, cognitive and psycho-physiological responses(8). Fears play an important role in the interpretation and experience of chronic pain, as is illustrated by the fear-avoidance model (8). This model proposes a theoretical framework that addresses the way a patient interprets its pain. In general, if pain is interpreted as non-threatening, patients are likely to stay engaged in daily activities. If, however, patients misinterpret pain as being threatening, a vicious cycle of catastrophic thinking may be initiated leading to excessive fear of pain/injury, resulting in avoidance of physical activities, disuse, depression and disability (32). Studies have shown that specific fears such as 'fear of movement' or 'fear of (re)injury' can have a disabling effects in patients with chronic musculoskeletal pain (8) and fear has proven to be a strong predictor for disability and depression on the long run (10). To the best of our knowledge, this is the first study that makes an attempt to specify fears in patients with PDN.

In our study, PDN was associated with a lower QoL (11) and disability (35). This sample of Dutch patients with PDN reported a mean QoL score comparable to other studies in patients with PDN (36). The mean score of disability was comparable to scores of patients with other pain syndromes (37). Greater pain levels in PDN have shown to correspond with higher symptom levels of anxiety and depression, more sleep problems and problems related to physical and mental functioning (6, 38). Furthermore, pain intensity was significantly associated with diminished QoL and disability.

Diabetic neuropathy can lead to sensory and motor deficits, altered gait stability and balance impairments (39), potentially resulting in an increased risk of falling (40). In our study, fear of falling showed to be an important predictor for both disability and QoL as this fear was highly associated with both outcomes in the multivariate analyses. Fear of falling can reduce QoL by causing distress, activity restriction and social isolation (41). Previous research has found a graded relationship between diabetes status and the risk of falling, in which a threefold increased risk of recurrent falls was reported in persons with diabetes compared to persons without diabetes (42). That study concluded that lower extremity pain, amongst which PDN, is one of the major risk factors for falls, together with insulin therapy and high body mass index. Paradoxically, the fear of falling itself has shown to be a risk factor for falls and injury, and can lead to avoidance behaviour, activity restriction and subsequent deconditioning (43). Despite the fact that fear of falling appears to be an adequate protection mechanism in patients with PDN, it also seems to amplify the risk of falling as it may lead to dysfunctional gait adjustments. The current results suggest that it is very important for clinicians to address falling and the fear of falling when treating patients with PDN. Fear of falling is a fear that could be treated with a behavioural intervention such as exposure in vivo (44, 45). In this treatment, the patient will be exposed repeatedly to a situation in which the fear usually occurs. Absence of aversive consequences will lead to extinction of the specific fear (46).

Maintenance of tight glycaemic control is of great importance in the management of DM and the prevention of long-term comorbidities associated with DM (47). However, tight glycaemic control may also increase the number of hypoglycaemic episodes. In clinical practice, treating fear of hypoglycaemia seems to be challenging as studies have shown that experiencing even a single hypoglycaemia symptom has a significant impact on patients' immediate health status with longer-term consequences (e.g., fear of future hypoglycaemia and self-directed behavioural changes to manage hypoglycaemia symptoms) (48). As a result, diabetic patients may tend to maintain their blood glucose levels within a 'safety margin' which is often higher than recommended, hereby maintaining hyperglycaemia (49). In order to reduce the risk of having an episode of hypoglycaemia during exercise, a patient may also avoid physical activity. Therefore, being afraid of a hypoglycaemic

episode can lead to behavioural changes in the management of diabetes and metabolic control, potentially resulting in the aggravation of diabetes related complications such as neuropathy, nephropathy and retinopathy (47). It seems to be of great importance to acknowledge and treat fear of hypoglycaemia in patients with PDN, in order to increase physical activity, QoL and reduce diabetes related complications in the future. In this study, fear of hypoglycaemia was associated with diminished QoL (48) in the stepwise backward regression model and the dataset without the imputed data.

In patients with diabetes, fatigue is reported twice as often as compared to patients without diabetes (50). Fatigue in diabetes is related to poor self-reported health and self-management of diabetes (51). Fear of fatigue showed to be significantly associated with QoL in the in the stepwise backward regression model. Fear of pain, kinesophobia and fear of negative evaluation were all independently associated with QoL and disability, but were not retained in the multivariate analyses.

Age and insulin treatment showed no significant contribution in the associations of fears with QoL or disability. This is in contrast to our previous study in the same sample of patients with PDN, in which we found an association of insulin treatment with pain catastrophizing, QoL and disability, respectively (11). In the latter study we explained this association by the fact that insulin treatment, being a burdensome method of administration, can be considered as a parameter for severity of DM II. Based on these results, we expected that insulin treatment would also be associated with diabetes and/or pain related fears. However, this study suggests that fears do not play a role in this mechanism.

This study has several limitations. First, diabetes related information is based on self-report as subjects were derived from an already existing database containing patients with DM. To improve accuracy, we have used multiple items (DNS >1 and DN4 ≥ 4) to diagnose PDN. Unfortunately, there was no information available on diabetes-related complications such as retinopathy or nephropathy. In future studies, it would be recommended to diagnose PDN based on a clinical history and physical examination. Furthermore, mean imputation was performed on several cases of the variable QOL-DN. Additional analysis excluding the imputed data showed that our results were robust for the fear of falling. The fact that fear of fatigue and fear of hypoglycaemia also contributed to the association of QoL with fears in the sample without imputed data, should be further researched in a new sample. Finally, this study has a cross-sectional design in which the dependent and independent variables are simultaneously assessed. For this reason, conclusions on a causal relationship or a chronological order have to be interpreted with caution.

In conclusion, this study shows that patients with PDN may suffer from different fears that seem to be associated with a significant psychosocial burden. Especially the fear of falling has shown to be an important potential determinant for QoL and/or disability in this study. Despite the limitations of this study, our findings could be relevant to clinical practice as the fear of falling is a fear that can be targeted with treatment, e.g. with behavioural interventions according to the principles of exposure in vivo (31, 52, 53).

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Chapter 5

Painful diabetic neuropathy Anxiety Rasch-Transformed Questionnaire (PART-Q30©)

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Abstract

The association between painful diabetic neuropathy (PDN) and anxiety has been acknowledged using various anxiety scales capturing various fear entities. It has never been examined whether these generally applied anxiety questionnaires could be pooled to construct one overall anxiety metric.

After completion by a cohort of 151 patients with PDN, data obtained from seven generally applied fear scales were stacked (n=88 items) and subjected to Rasch analyses (pre-PART-Q88) to create the Painful Diabetic Neuropathy (PDN) overall Anxiety Questionnaire (PART-Q30©).

We subsequently examined the impact of the final constructed PART-Q30© on disability and Quality of Life (QoL) using the Rasch-Transformed Pain Disability Index (RT-PDI) and the Norfolk Quality of Life Questionnaire, Diabetic Neuropathy version (RT-Norfolk).

The pre-PART-Q88 data did not meet Rasch model's expectations. Through stepwise examination for model fit, disordered thresholds, local dependency and item bias, we succeeded in reducing the data and constructing a 30 items overall anxiety scale (PART-Q30©) that fulfilled all model's expectations, including unidimensionality. An acceptable internal reliability was found (person-separation-index: 0.90). PART-Q30© explained 36% of disability and combined with RT-PDI 63% of QoL (assessed with RT-Norfolk).

Introduction

Approximately a quarter of patients with diabetes mellitus develop painful diabetic neuropathy (PDN) (1, 2). PDN is a complex and multi-dimensional condition, potentially having a major negative impact on daily life, both physically and mentally (3). Moreover, patients with PDN often suffer from enhanced levels of anxiety and depression (4). This negative impact on one's mental situation can result in poorer outcomes such as aggravation of pain related disability (5).

Recent research has shown that PDN is associated with catastrophic thinking, which in turn may lead to a perceived decline in physical activity and reduced quality of life (QoL) (6). Studies of musculoskeletal pain showed that specific fears such as fear of movement or fear of (re)injury can have a disabling effect in patients with chronic pain (7). As presented in the Fear-Avoidance-Model, an explanatory model for pain-related disability, pain-related fear may lead to avoidance behaviour and selective attention to pain-related stimuli (hypervigilance). Moreover, fear has proved to be a strong predictor for disability and depression on the long run (8). Depression and/or fear may also negatively influence the result of treatment of diabetes (9). Improving psychological well-being and especially the level of fear might break this vicious cycle when treating patients with PDN (4, 9).

In PDN, it is unknown which fears contribute most to the level of disability. A recent qualitative study identified various consequences of PDN and fears that inhibit mobility and decrease QoL in patients with PDN (10). These consequences of PDN were physical, psychological and social. Furthermore, patients reported several fears related to diabetes and pain, such as fear of hypoglycaemia, fear of (increased) pain, fear of total exhaustion, fear of physical injury, fear of falling, fear of loss of identity and fear of negative evaluation (10).

Several questionnaires are available to capture these fear qualities, each assumingly measuring one specific element of diabetes-related fears (11, 12) or pain-related fears (13-18). In daily clinical practice, it is not feasible to use all of these questionnaires. Additionally, these measures are ordinal-based constructed and have never been subjected to modern clinimetric evaluation (19-22). It is unknown whether all these fear forms may be related or not, in other words whether there could be an overlap between the questions presented to patients assessing the assumingly different constructs.

In the current study, we aimed to develop a Rasch-transformed overall fear questionnaire by stacking data obtained from seven generally applied scales that assess the various qualities of fear in a cohort of patients with PDN. We hypothesized that a great overlap could be seen between the items enabling us to reduce and simplify fear assessment. We examined the possible impact of the overall fear outcome measure constructed on disability and QoL in patients with PDN.

Materials and Methods

Patient selection

An invitational letter explaining the study and requesting participation was sent out to a random selection of 2142 patients from a registry of patients with type 2 diabetes from a regional hospital in the south of the Netherlands (VieCuri, Venlo, The Netherlands). Eligibility was based on the following: providing written informed consent, having type 2 diabetes mellitus, aged > 18 years, suffering from peripheral polyneuropathy, scoring ≥ 1 on the Diabetic Neuropathy Symptom Score (23) with neuropathic pain in the feet for at least three months, but being clinically stable. Patients were excluded if there were other conditions that could lead to pain in the feet and/or damage to the peripheral nervous system. The protocol was approved by the Medical Ethics Committee of Maastricht University, the Netherlands.

Questionnaires applied in the current study

All data were retrieved through self-reported questionnaires. Fear for hypoglycaemia was measured using a Dutch version of the Hypoglycaemia Fear Survey (HFS) (11). For the purpose of this study, only the 13-item 'worry scale' was used. The short version of the Pain Anxiety Symptom Scale (PASS-20) was used to measure fear for pain in persistent pain behaviour (14). Kinesiophobia was measured using the Dutch version of the 17-item Tampa Scale of Kinesiophobia (TSK) (16). Fear of fatigue was measured using the Short Tampa scale for Fear of Fatigue (TS-Fatigue-S). This shortened questionnaire is based on the TSK in which the word 'pain' is replaced by 'fatigue'(15). Fear of falling was measured by the 'Falls Efficacy Scale - International' (FES-I), which measures confidence in performing activities without falling in daily living (17). Fear for negative evaluation was measured by the 'Brief Fear of Negative Evaluation Scale' (BFNE, short form) (13). Fear of loss of identity was measured on a 10-point Likert-scale. Participants were asked to answer the question "Are you worried that you will not be able to be the person you want to be, due to the neuropathic pain in the feet? If so, to what extend?". Disability was measured using the Pain Disability Index (PDI), which investigates the magnitude of the self-reported disability in different situations such as work, leisure time, activities of daily living (ADL) and sports. (18). Quality of life was measured using the 47-item Norfolk Quality of Life Questionnaire, Diabetic Neuropathy Version (Norfolk-QOL-DN) (12),

Statistical analyses

The following patients' characteristics were collected: gender, age, duration of peripheral neuropathy complaints (months) and insulin treatment (yes/no). Data obtained from the seven selected anxiety measures were stacked to form the so-called preliminary n = 88 items PDN Anxiety measure (pre-PART-Q88) that was subjected and transformed through

Rasch analyses (22), to determine whether model expectations would be met. As previously reported, various aspects were examined including fit statistics, (dis-)ordered thresholds, local (in-)dependency, differential item functioning and unidimensionality (21, 24-26). Item bias was checked on personal factors: gender (female versus male), age category (up to 65 years, 65 to 70 years, and 70 years plus), having insulin (yes/no). The age categories were chosen aiming for an equal distribution among the categories formed. Items or patients not fulfilling these requirements were removed or adjusted to obtain good model fit, hereby creating an interval scale.

Reliability studies were performed by determining the model's person separation index (PSI). A PSI of 0.7 or higher is considered as acceptable, indicating the ability of the final constructed scale to differentiate between at least two groups of patients (25). Explanatory validity for the final Rasch-transformed overall fear measure was also examined by determining the association between fear leading to disability and to QoL reduction. Data for the PDI and Norfolk quality of life measures were separately examined and transformed as much as possible through Rasch analyses aiming to meet model fit, if possible (RT-PDI and RT-Norfolk as the dependent variables). The impact of the overall fear on both dependent variables was examined separately. Overall fear scale combined with RT-PDI explaining QoL reduction (as assessed with the RT-Norfolk) was also investigated. Correlation was examined using linear regression studies with restricted cubic splines on the independent variable for best model fit (expressed as the proportion of variance R2) (27). Analyses were performed using Stata Statistical Software 12.0 for Windows and Rasch unidimensional measurement model (RUMM2030) (28).

Results

Patients

A total of 2142 patients were invited to participate, of which 237 expressed their willingness to participate. Of these patients, 183 actually completed and returned the questionnaire, and of these only 151 patients met the inclusion/exclusion criteria and were eligible to the current study. Eligible patients had a mean age of 67 years (SD 6.3, range 47-84 years), 62% were females, the mean duration of peripheral neuropathy complaints was 6.2 years (SD 4.9, range 0.5-25 years), and 66% were on insulin treatment.

Initial Rasch analyses of the pre-PART-Q88

The preliminary 88-item stacked fear scale (pre-PART-Q88) did not meet Rasch model requirements. A significant deviation from model's expectations was seen for both item's and person's fit residual statistics, particularly for the standard deviation (SD) (mean for items: 0.321, SD: 2.043, mean for persons: -0.140, SD: 2.364). Item-trait interaction also showed a significant Chi-square probability ($p<0.00001$), indicating no invariance. Most items (60 of the 88) had disordered thresholds. There were 237 correlations seen between the items' residuals (Spearman Rank coefficient: $\rho \geq 0.3$). All eight items as part of the brief fear of negative evaluation scale were correlated with each other (ranging from ρ: 0.31–0.79).

Data handling of the pre-PART-Q88 to fit Rasch modelling

Throughout the analyses, we continuously monitored the class intervals and thresholds. Since most items showed disordered thresholds, we have decided to systematically rescore all items that eventually led to an overall uniform three response options. After this, no items except 1 showed disordered thresholds. This item was subsequently removed (n = 87 items remaining). Several items demonstrated significant misfit statistics and/or fit residuals exceeding ± 2.5 boundaries. A total of 11 misfitting items were stepwise removed (n = 76 items remaining). All item sets with residual correlations ≥ 0.30 were evaluated starting with the highest correlations (≥0.7, ≥0.6, … up to ≥0.30). Of each item set, the item showing less clinical relevance combined with the most over- or under-discrimination on its category probability curve was removed. Eventually, a total of 45 items were one by one removed (31 items remaining). One item (someone with my situation is advised not to perform physical activities) demonstrated item bias on person factor gender and was removed (30 items remaining). After this, the item's fit residual statistics improved considerably (mean: -0.069, SD: 0.982), but the person's fit residual statistics still deviated substantially from model expectations (mean: -0.382, SD: 1.774). Based on this observation, we stepwise removed a total of n = 16 patients having residuals exceeding ± 2.5. After this, a good model fit was obtained for the final 30-item PART-Q30©, having no misfit statistics or item's and person's residuals exceeding ±2.5, no differential item functioning, and no

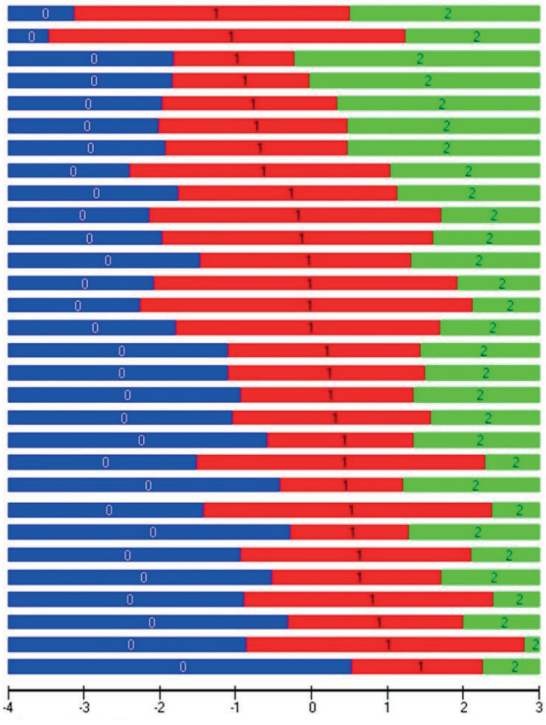
local dependency (item fit residuals: mean 0.050, SD 0.940; person fit residuals: mean -0.134, SD 1.068, item-trait interaction Chi-square p-value: 0.46, degrees of freedom (DF) 60). Acceptable unidimensionality was obtained for the PART-Q30© using two subsets of items (4 most positively loaded versus 4 most negatively loaded items; independent t-tests between the two groups of items: 0.068 (95%-CI: 0.031-0.105)). The item "worried for walking up or down a ramp" was the easiest item to perform, while "worried for answering the telephone before it stops ringing" was the most difficult (Figure 1). Only four patients demonstrated floor effect; there was no ceiling effect.

Transforming the PDI and Norfolk-QOL-DN through Rasch analyses

Rasch-Transformation of the Norfolk (RT-Norfolk)

The 35-item Norfolk questionnaire was subjected to Rasch analyses and did not meet model's expectations. In particular, item's residual statistics deviated (mean -0.190, SD 2.416). The person's residual statistics were acceptable (mean -0.138, SD 1.239). The item-trait interaction showed a significant Chi-square probability ($p<0.00001$), indicating no invariance. Disordered thresholds were seen in all except 3 items.

Figure 1. Painful diabetes neuropathy Anxiety Rasch-Transformed 30-item scale (PART-Q30©)



Item	Location	SE	FitResid	Chi-square
fes15	-1,301	0,176	0,242	1,006
pass20	-1,106	0,2	-0,711	1,771
tsk9	-1,02	0,144	1,258	2,988
tsk5	-0,923	0,146	0,874	2,839
tsk11	-0,811	0,154	2,327	6,312
pass16	-0,762	0,156	0,481	0,514
tsk6	-0,713	0,155	0,157	2,712
pass1	-0,672	0,17	-0,016	0,101
fes9	-0,309	0,166	0,056	0,352
pass14	-0,209	0,18	-0,937	0,72
pass6	-0,173	0,174	-0,543	2,195
tsf3	-0,072	0,167	0,645	2,343
pass5	-0,068	0,181	-0,802	2,847
pass17	-0,055	0,188	-1,555	7,82
ahv1	-0,042	0,175	1,723	0,09
ahv17	0,17	0,173	0,429	0,119
pass8	0,201	0,17	1,292	2,097
pass19	0,213	0,169	-0,268	0,208
fes13	0,277	0,173	-0,867	2,629
bfn7	0,389	0,173	0,371	0,232
pass2	0,396	0,181	-0,532	1,653
fes2	0,41	0,176	0,555	2,386
pass7	0,486	0,184	-0,861	2,142
pass9	0,509	0,178	-0,904	0,701
tsk2	0,59	0,18	1,054	2,124
fes6	0,597	0,181	-1,478	3,761
bfn8	0,757	0,184	0,533	0,05
ahv6	0,856	0,189	-0,251	3,967
pass15	0,98	0,189	0,167	0,778
fes10	1,404	0,229	-0,925	2,893

◂ Legend to Figure 1: Threshold map of the final 30 items as part of the PART-Q30©. The map shows the expected response for each item related to the ability of the patients.

Description of items: fes15: How concerned are you that you will fall, while walking up or down a slope?; pass20: I find it hard to concentrate when I am in pain; tsk 9: I am afraid of injuring myself accidentally; tsk5: People are not taking my medical condition seriously enough; tsk11: I would not have this much pain if there was not something potentially dangerous going on in my body; pass16: I try to avoid activities that cause pain; tsk6: My pain has put my body at risk for the rest of my life; pass1: I think that if my pain gets too severe, it will never decrease; fes9: How concerned are you that you will fall, while reaching for something above your head or on the ground; pass14: When I hurt I think of the pain constantly; pass6: I will stop any activity as soon as I sense pain is coming; tsf3: My fatigue has put my body at risk for the rest of my life; pass5: I can't think straight when I am in pain; pass 17: I find it difficult to calm my body down after periods of pain; ahv 1: How often have you have worried about not recognizing/realizing I am having a reaction because of low blood sugar; ahv17: How often have you worried about having a reaction while asleep because of low blood sugar; pass8: As soon as pain comes on I take medication to reduce it; pass19: When pain comes on strong I think that I might become paralyzed or more disabled; fes13: How concerned are you that you will fall, while walking in a place with crowds; bfn7: I am frequently afraid of other people noticing my shortcomings; pass2: When I feel pain I am afraid that something terrible will happen; fes2: How concerned are you that you will fall, while getting dressed or undressed; pass7: Pain seems to cause my heart to pound or race; pass9: When I feel pain I think I might be seriously ill; tsk2: If I were to try to overcome my pain, my symptoms would increase; fes6: How concerned are you that you will fall, while getting in or out of a chair; bfn8: I often worry that I will say or do the wrong things; ahv6: How often have you worried about appearing stupid or drunk because of low blood sugar; pass15: Pain makes me nauseous; fes10: How concerned are you that you will fall, while going to answer the telephone before it stops ringing. The item "worried for walking up or down a ramp" was the easiest item to perform, while " worried for answering the telephone before it stops ringing" was the most difficult to accomplish.

The following steps were taken aiming to transform the ordinal-based Norfolk-QOL-DN to meet Rasch model's expectations. No differential item bias was seen on person factors. First, all items were rescored based on the categories frequency distribution to three response options, hereby eliminating all disordered thresholds seen. Second, 9 items were deleted based on significant misfit statistics or fit residuals exceeding ± 2.5 (n = 26 items remaining). Third, 9 items were stepwise removed based on local dependency seen with corresponding residuals (n = 17 items remaining). The final 17-item RT-Norfolk fulfilled all Rasch model expectations (see Table 1; item fit residuals: mean -0.087, SD 1.071; person fit residuals: mean -0.203, SD 1.011; item-trait Chi-square probability: p=0.11, DF 34; PSI 0.85; acceptable unidimensionality: independent t-tests between the 4 most positively loaded and the 4 most negatively loaded items: 0.08 (95%-CI: 0.045-0.115)). The corresponding Logits for all patients on the final RT-Norfolk were extracted for correlation purposes with the fear scores obtained with the PART-Q30© (Table 1).

Table 1: Rasch-Transformed 17-item Norfolk questionnaire (RT-Norfolk)

Item	Location	SE	FitResid	DF	ChiSq
I0013	-1.373	0.165	-0.5	137.03	0.21
I0014	-1.203	0.162	-1.317	135.18	4.374
I0008	-1.133	0.155	1.158	137.96	8.728
I0007	-0.996	0.154	0.462	132.4	0.966
I0015	-0.804	0.151	-1.219	135.18	1.857
I0028	-0.789	0.163	-1.537	137.96	3.111
I0002	-0.782	0.232	-0.29	137.96	3.717
I0033	-0.281	0.155	-1.77	139.81	4.333
I0006	-0.06	0.181	-0.127	122.22	1.075
I0020	0.283	0.152	1.669	139.81	4.917
I0018	0.363	0.157	0.603	137.96	0.32
I0022	0.651	0.165	-1.158	137.03	2.415
I0021	0.81	0.17	0.485	137.96	2.628
I0004	0.881	0.187	1.681	114.81	1.443
I0026	1.205	0.178	-0.108	138.88	1.338
I0019	1.558	0.211	0.53	138.88	2.137
I0010	1.67	0.206	-0.048	137.96	0.934

Legend Table 1: Item 13: Have you felt unsteady on your feet when you walk?; Item 14: Have you had any problem getting out of a chair without pushing with your hands?; Item 8: Has pain kept you awake or woken you at night?; Item 7: Have you had any weakness in feet/legs/hands/arms/ none; Item 15: Have you had a problem walking down stairs?; Item 28: Have you accomplished less than you would like?; Item 2: Have you had the feeling of tingling, pins and needles in feet/legs/ hands/ arms/none; Item 33: To what extent has your physical health interfered with your normal social activities with family, friends, neighbours, or groups?; Item 6: Have you had deep pain in feet/legs/hands/arms/ none; Item 20: Have you had a problem with diarrhoea and/or loss of bowel control?; Item 18: Have you been unable to tell hot from cold water with your feet?; Item 22: How much difficulty have you had with bathing/showering?; Item 21: Have you had a problem with fainting or dizziness when you stand?; Item 4: Have you had other unusual sensations in feet/ legs/hands/arms/none; Item 26: How much difficulty have you had using eating utensils?; Item 19: Have you had a problem with vomiting, particularly after meals (but not due to flu or other illness)?; Item 10: Have you burned or injured yourself and been unable to feel it?. The final 17-item RT-Norfolk fulfilled all Rasch model expectations (item fit residuals: mean -0.087, SD 1.071; person fit residuals: mean -0.203, SD 1.011; item-trait Chi-square probability: p=0.11, DF 34; PSI 0.85; acceptable unidimensionality: independent t-tests between the 4 most positively loaded and the 4 most negatively loaded items: 0.08 (95%-CI: 0.045-0.115)).

Rasch-Transformation of the PDI (RT-PDI)

The same procedure was adopted aiming to transform the 7-item 11-response options PDI through Rasch analyses. The PDI did not meet model's expectations. In particular the item fit residuals SD deviated significantly from model's expectations (mean 0.339, SD 3.057 (SD should be around 1)), while person fit residuals were acceptable (mean -0.321, SD 1.296). Four items demonstrated significant misfit statistics or fit residuals exceeding ± 2.5 (see Figure 2). Five of the seven items demonstrated disordered thresholds. Three items demonstrated differential item functioning on person factor gender. Based on all these observations, we were unable to transform the PDI to meet model's requirements. However, we have decided to use the obtained Logits for each patient from the initial Rasch analyses, hereby creating an interval measure (RT-PDI), although not perfect. Removing the items would ultimately lead to a scale of only two items that would not be representative.

Reliability and explanatory validity studies

The PSI of the PART-Q30© was good (0.90). Figure 3 shows the proportion of variances that were obtained from the regression studies for the PART-Q30© explaining RT-PDI, RT-PDI on RT-Norfolk, and the PART-Q30© combined with RT-PDI explaining RT-Norfolk. Approximately 1/3 (R2=0.36) of disability was explained by fear symptoms. Almost half of the experienced QoL reduction by the patients with PDN was explained by fear (R2=0.45). Fear combined with disability explained approximately 2/3 (R2=0.63) of QoL scores as assessed with the RT-Norfolk (Figure 3).

INDIVIDUAL ITEM-FIT for Analysis Name RTPDI1 - Item-Person Fit Residual [Ascending Order]

	Seq	Item	Type	Location	SE	FitResid	DF	ChiSq	DF	Prob
4	4	I0004	Poly	0,029	0,048	-2,160	110,73	12,976	2	0,001523
3	3	I0003	Poly	0,015	0,043	-2,003	117,34	13,160	2	0,001388
1	1	I0001	Poly	0,006	0,047	-1,205	115,68	13,705	2	0,001058
2	2	I0002	Poly	-0,435	0,048	-1,121	117,34	8,167	2	0,016847
6	6	I0006	Poly	0,435	0,044	-0,596	116,51	1,354	2	0,508252
7	7	I0007	Poly	0,209	0,042	4,270	116,51	12,127	2	0,002327
5	5	I0005	Poly	-0,258	0,040	5,188	109,90	49,582	2	0,000000

Figure 2. Initial findings after subjecting the 7-item 11-response options PDI to Rasch analyses. PDI: pain disability index. The purple highlighted sections show significant misfit statistics for 3 items, the green highlighted sections show 2 items with fit residuals > +2.5, which deviates from model requirements.

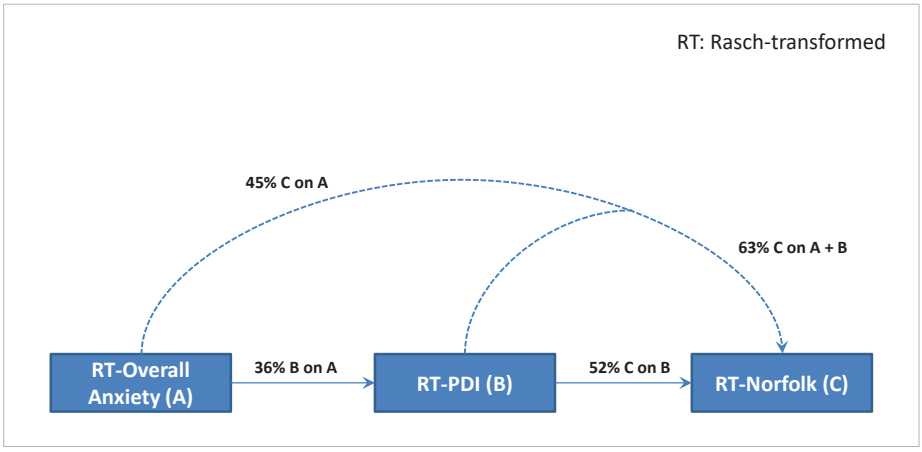


Figure 3. Regression studies linking anxiety, disability, and quality of life with each other in patients with PDN. PDN: painful diabetic neuropathy. RT: Rasch transformed, PDI: painful disability index. The RT-PDI and RT-Norfolk were the dependent variables. The proportion of variance was expressed in percentages.

The full version of the Painful diabetic neuropathy Anxiety Rasch Transformed Questionnaire (PART-Q30©) is shown at the end of this chapter. In our study we used the Dutch versions of the questionnaires. The items in the PART-Q30© were derived from the original validated English questionnaires (11-18).

Discussion

The current study presents the construction of an overall Painful Diabetic Neuropathy (PDN) Anxiety Rasch-Transformed 30-item questionnaire (PART-Q30©) that was derived from pooled and stacked items from seven generally applied fear outcome measures (11-18). The PART-Q30© fulfilled all Rasch model expectations and explained approximately 1/3 of disability and almost half of the QoL reduction as experienced by the patients with PDN.

The newly constructed PART-Q30© questionnaire consists of three items of the HFS questionnaire, 13 items of the PASS-20, five items of the TSK, six of the FES-I, one of TSF and two from the BFNE questionnaire. Interestingly, the final items retained in the PART-Q30© cover almost all fears that were identified in our qualitative study (10). Only one item, the fear of loss of identity, dropped out of the analyses. In this study, we achieved to create an overall anxiety questionnaire for patients with PDN, hereby covering various domains of PDN related anxieties and fears, but still being unidimensional. The reduction of the items from 88 to 30 with a uniform response option will certainly reduce the burden in the assessment of patients and simplify anxiety assessment in PDN.

This new questionnaire can be applied in clinical practice to identify the impact of specific disabling fears for the individual patients based on a relatively simple procedure existing of 30 items to evaluate. With this information, it will be possible to identify the most disabling fears for patients with PDN. This knowledge could result in targeting the most disabling fears per patient with an intervention such as graded exposure in vivo (29). Currently, no specific graded exposure treatment is available for PDN. Further research can lead to a treatment protocol including targets for both diabetes and pain related fears.

The Pain Disability Index (PDI) and the Norfolk Quality of Life Questionnaire, Diabetic Neuropathy Version (Norfolk-QOL-DN) are both CTT-based scales with ordinal measures. In our analyses, we were unable to transform the PDI and Norfolk-QOL-DN to meet the model's requirements. Removing the items would lead to a scale of too little items, which would not be representative. In order to overcome this problem, interval measures were created (RT-PDI and RT-Norfolk) using obtained Logits for each patient from the initial Rasch analyses. Interval measures have the advantage of having a fixed unit, enabling proper parametric analyses.

This study has several limitations. Since the study was based on self-report by questionnaires, we also had to rely on self-report to set the diagnosis PDN. No actual physical measurements could be performed to confirm the diagnosis PDN. This study was performed in the Netherlands and cross-cultural validation should be performed

as cultural factors may influence anxiety in PDN. Only a small number of the invited patients (n=2142) filled in the questionnaire (n=183) and were eligible (n=151). It is not known whether anxious people are more likely to be willing to participate. We plan to examine the applicability and clinimetric properties of the newly constructed PART-Q30© in a larger cohort of patients with PDN to determine its applicability and examine the validity and reliability of items' weight and patients' location using the new three response options. Future longitudinal studies are needed to investigate the constructed measures of the PART-Q30© in patients with PDN, and to investigate the PART-Q30©'s responsiveness to detect changes in the level of fear in PDN undergoing e.g. a new therapeutic intervention.

Full version of the Painful diabetic neuropathy Anxiety Rasch Transformed Questionnaire (PART-Q30©).

Worries about low blood sugar

Please indicate how often you have worried about each item because of low blood sugar, in the past 4 weeks.

	Never		Always
1. Not recognizing/realizing I am having a reaction.	1	2	3
2. Appearing stupid or drunk.	1	2	3
3. Having a reaction while asleep.	1	2	3

Fears about pain and its consequences in daily life

Please indicate how often you experience the following thoughts about your pain.

	Never		Always
4. I think that if my pain gets too severe, it will never decrease.	1	2	3
5. When I feel pain I am afraid that something terrible will happen.	1	2	3
6. I can't think straight when I am in pain.	1	2	3
7. I will stop any activity as soon as I sense pain is coming.	1	2	3
8. Pain seems to cause my heart to pound or race.	1	2	3
9. As soon as pain comes on I take medication to reduce it.	1	2	3
10. When I feel pain I think I might be seriously ill.	1	2	3
11. When I hurt I think of the pain constantly.	1	2	3
12. Pain makes me nauseous.	1	2	3
13. I try to avoid activities that cause pain.	1	2	3
14. I find it difficult to calm my body down after periods of pain.	1	2	3
15. When pain comes on strong I think that I might become paralyzed or more disabled.	1	2	3
16. I find it hard to concentrate when I am in pain.			

Fears about your pain

Please indicate to what extend you agree or disagree with the following statement:

	Disagree		Agree
17. If I were to try to overcome my pain, my symptoms would increase.	1		3
	1		3
18. People are not taking my medical condition seriously enough.	1		3
	1	2	3
19. My pain has put my body at risk for the rest of my life.	1	2	3
20. I am afraid of injuring myself accidentally		2	
21. I would not have this much pain if there was not something potentially dangerous going on in my body.		2	
		2	

Full version of the Painful diabetic neuropathy Anxiety Rasch Transformed Questionnaire (PART-Q30©).

Worries about falling

For each of the following activities, please indicate how concerned you are that you might fall if you do this activity.

	Disagree		Agree
22. Getting dressed or undressed.	1	2	3
23. Getting in or out of a chair.	1	2	3
24. Reaching for something above your head or on the ground.	1	2	3
25. Going to answer the telephone before it stops ringing.	1	2	3
26. Walking in a place with crowds .	1	2	3
27. Walking up or down a slope.	1	2	3

Worries about fatigue and negative evaluation

Please indicate to what extend you agree or disagree with the following statement:

	Disagree		Agree
28. My fatigue has put my body at risk for the rest of my life.	1		3
29. I am frequently afraid of other people noticing my	1	2	3
shortcomings.	1	2	3
30. I often worry that I will say or do the wrong things.		2	

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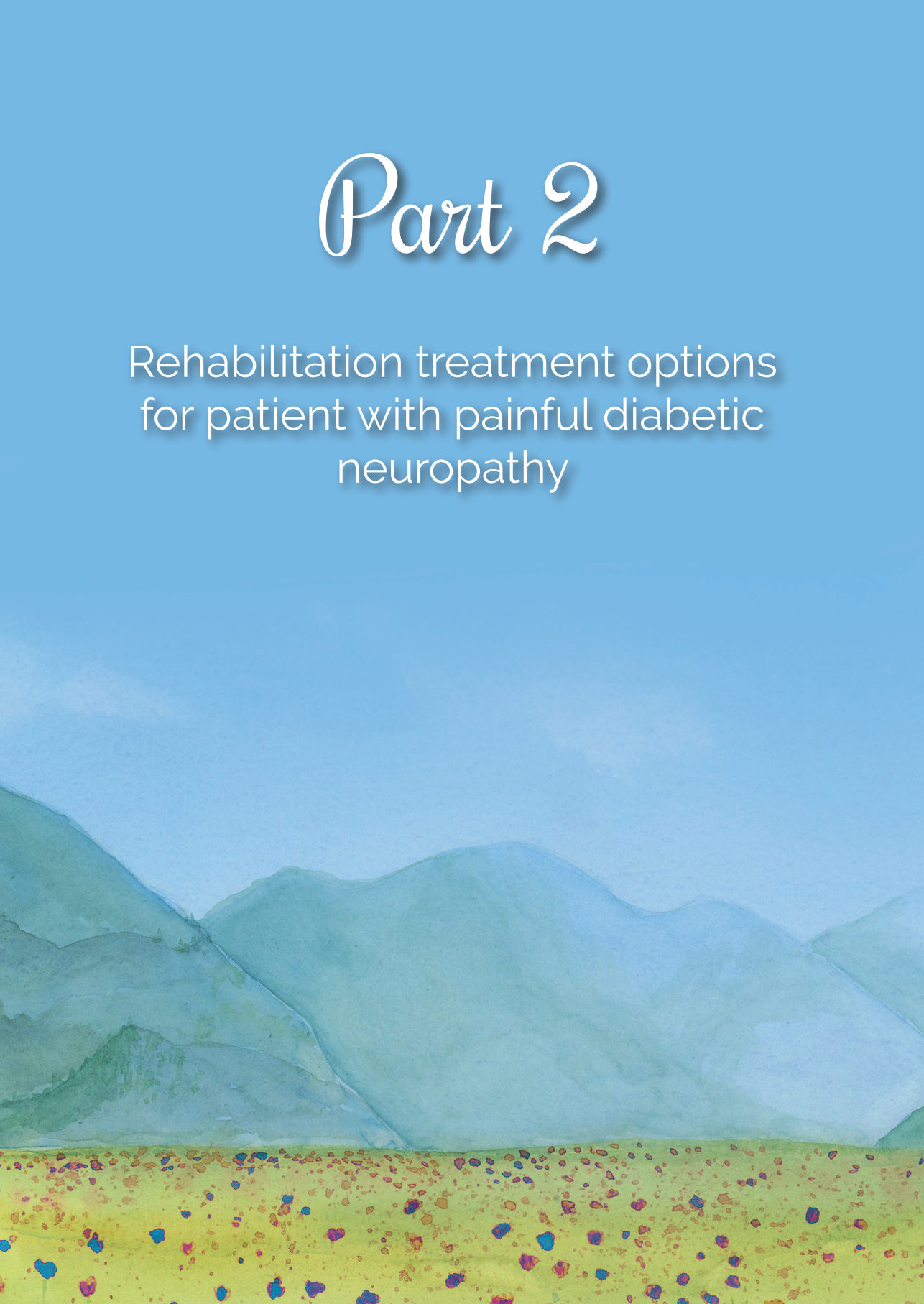
Part 2

Rehabilitation treatment options for patient with painful diabetic neuropathy



Chapter 6

The effect of exercise therapy combined with psychological therapy on physical activity and quality of life in patients with painful diabetic neuropathy: A systematic review

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Abstract

Background: Approximately 25% of patients with diabetes mellitus type 2 (DMII) develop painful diabetic neuropathy (PDN). PDN is known to affect both mental and physical wellbeing, resulting in anxiety, depression, low quality of life and physical disability. Pharmacological treatment of PDN aims at pain relief and is often ineffective and/or has many side effects. Rehabilitation treatment modalities that are designed to help the patient deal with PDN related complaints, are mostly focussed on either physical (e.g. exercise therapy) or psychological aspects (e.g. cognitive behavioural therapy, CBT). There is emerging evidence that PDN can be approached from a biopsychosocial perspective, in which physical and psychosocial aspects are integrated. From this biopsychosocial approach it is plausible that integrated treatment modalities such as acceptance commitment therapy (ACT) or exposure in vivo (EXP) could be effective in patients with PDN.

Objective: To provide an overview of the current evidence on the effects of rehabilitation treatments that combine exercise therapies with psychological therapies in order to improve physical activity (PA) and quality of life (QoL) in patients with PDN.

Methods: Systematic review of the current literature. EMBASE, MEDLINE, Medline In-Process citations & e-Pubs ahead-of-print, Pedro, Web of Science, PsycINFO, CENTRAL, PubMed and Google Scholar were searched. All studies on interventions combining exercise therapy with psychological interventions in patients with PDN, aged >18 years, were included. Outcome measures were PA, QoL.

Results: The search resulted in 1603 records after removing duplicates. After screening on titles and abstracts, 100 records remained. From these, not one study reported on interventions that combined exercise therapy with psychological interventions. Through a secondary hand search, a total of 3 reviews were identified that described a total of 5 studies regarding either physical or psychological interventions in patients with PDN. These studies reported moderate effects of 1) mindfulness meditation on QoL, 2) CBT on pain severity, 3) mindfulness-based stress reduction intervention on function, health-related QoL, pain catastrophizing and depression, 4) aerobic exercise on QoL and 5) Tai Chi on glucose control, balance, neuropathic symptoms, and some dimensions of QoL in patients with PDN. All studies were of a moderate quality, and results should be interpreted with caution.

Conclusions: Based on increasing knowledge in the domain of chronic pain, it could be assumed that integrated rehabilitation treatments for patients with PDN are beneficial. There is no literature to support this and more research should be done on integrated biopsychosocial interventions in patients with PDN.

Implications: This empty review highlights the importance that more research should be done on integrated biopsychosocial interventions in patients with PDN. Currently, our research group is performing a study on the effects of EXP treatment in patients with PDN.

Introduction

Approximately 25% of patients with diabetes mellitus type 2 (DMII) develop painful diabetic neuropathy (PDN)(1), characterized by pain, paraesthesia and sensory loss (2-4). Currently, the treatment of PDN is mainly pharmacological (5). Side effects occur and/or the effects are often limited (6).

PDN can have far-reaching consequences in daily life (7, 8). It can lead to sensory loss, the development of pressure ulcers (PU's), balance impairments, an altered gait with potentially an increased risk of falling (9, 10). This leads to a more sedentary lifestyle (7) with impaired levels of physical activity (10-12), less engagement in social activities, dependency on others, social isolation, depression and as a result decreased quality of life (13-16). Depression in turn, can amplify diabetic complications related to suboptimal glycaemic control (17). Furthermore, patients with PDN can suffer from anxiety and fears, such as fear of pain, fear of falling, fear of disturbed glucose regulation, leading to persistence of the consequences of PDN (11, 18-20). It seems likely that the overall QoL of patients with PDN can be improved when comorbid anxiety and negative emotions are adequately screened, diagnosed and treated (11, 18, 19, 21).

Increasing physical activity in patients with DM is known to have favourable effects on diabetes-related outcomes (22, 23), such as improved blood sugar control, decreased body fat, and an improved body reaction to insulin therapy (23, 24). Aerobic exercise has shown to improve the QoL in patients with PDN (25). Unfortunately, dropout rates in physical exercise programmes are high (up to 45%), due to the occurrence of PU's, overuse injuries and lack of motivation (26, 27). Therefore, an interdisciplinary therapeutic approach that targets physical and emotional factors has been recommended (15, 16, 18, 28, 29).

Since patients with PDN frequently share the comorbidities of depression and fear (and as a consequence disability) with other chronic pain populations (11, 21), it seems apparent to integrate the knowledge obtained in the treatment populations with other pain syndromes into the field of PDN. Within the Fear-Avoidance-Model (FAM) (30), chronic pain is approached from a biopsychosocial perspective. The model states that negative exaggerated or irrational thoughts (catastrophizing) and fears can give rise to avoidance behaviour, which can lead to significant health consequences such as disuse, disability and depression, further fuelling the vicious cycle of chronic disabling pain (31, 32). In line with the FAM model, one could hypothesize that a physical intervention or psychological treatment alone will not suffice to restore QoL and participation in daily life, as these treatment address only one ('bio' or 'psycho') component of the model. Research has shown that multidisciplinary rehabilitation

interventions that target factors from all biopsychosocial domains, administered by healthcare professionals from different backgrounds, are more effective than physical or psychological interventions alone (33).

The aim of this study was to provide an up-to-date overview of the current evidence on the effects of rehabilitation interventions that combine exercise therapies with psychological therapies in order to improve physical activity (PA) and quality of life (QoL) in patients with PDN.

Methods

The review protocol was registered with PROSPERO (CRD42018081664).

Eligibility criteria: Studies on interventions combining exercise therapies with psychological therapies in patients with a clear diagnosis of PDN (DM I & II), aged > 18 years were included in this systematic review. Primary outcome measures were physical activity and QoL.

Search: Ovid's EMBASE, MEDLINE, Medline In-Process citations & e-Pubs ahead-of-print and PsycINFO and in Pedro, Web of Science, CENTRAL in Wiley and PubMed (for the newest publications), were searched. Google Scholar was searched for on-going research. A full overview of search terms in Embase is provided in Supplemental data 1. Subject headings and truncations were modified per database.

Selection of studies: Primarily, randomized controlled trials (RCT's) were included. In case no RCT's were available other study types were included, in order of preference: cohort studies, case control, cross over studies, observational studies, single case studies, cross-sectional study and experimental studies. Study selection was performed by two reviewers (CvL and SQ). First, both reviewers selected articles for relevance based on title and abstract. Of all articles that appeared to be relevant, the full text articles were retrieved. Of all duplicates, just one was included. The reference lists of all retrieved articles were hand searched for additional references. Consensus meetings were held to resolve disagreements. If disagreement persisted a third reviewer could be consulted (RS).

Quality assessment: The Cochrane Risk of Bias tool for randomized controlled trials and ROBINS-I for non-randomized studies and interventions was used (34).The individual results were compared by two reviewers (CvL and SQ) and disagreements were resolved through discussion when needed. A third reviewer (RS) was available if consensus could not be reached. Data extraction and reporting of data: Data extraction was performed by two reviewers (CvL and SQ) independently. Due to the expected heterogeneity of the concepts of PA and QoL, a narrative summary of all included studies was given. Information on study characteristics (number of participants, gender, age, type of DM, duration of PDN), descriptions of the intervention and control arm, duration of follow up and the data on the outcome measures PA and QoL was extracted from the selected articles.

Results

The search resulted in 1603 records after having removed 23 duplicates. After screening on title and abstract, 100 records remained for full text reading and 1503 articles were excluded. The reasons for exclusion were related to: wrong diagnosis (n=1029, e.g. chemotherapy induced peripheral neuropathy, non-specific chronic pain, diabetic neuropathy without pain), study design (n=223, e.g. descriptive reviews), type of intervention (n=180, e.g. pharmacological), different outcome measures (n=47, e.g. improvement of balance disorders and uncertain gait). From the 100 remaining potentially relevant studies, 96 full texts could be retrieved. After full text reading, additional articles were excluded because of not fulfilling the criteria as set on diagnosis (n=44), study design (n=28), type of intervention (n=24). By contacting the authors of the non-retrievable studies, we obtained 1 additional study, which was excluded since this article did not fulfil the criteria set for intervention. At the end of our study selection, not one study that answered our research question could be included. Therefore, no quality assessment was performed. Figure 1 illustrates the study selection.

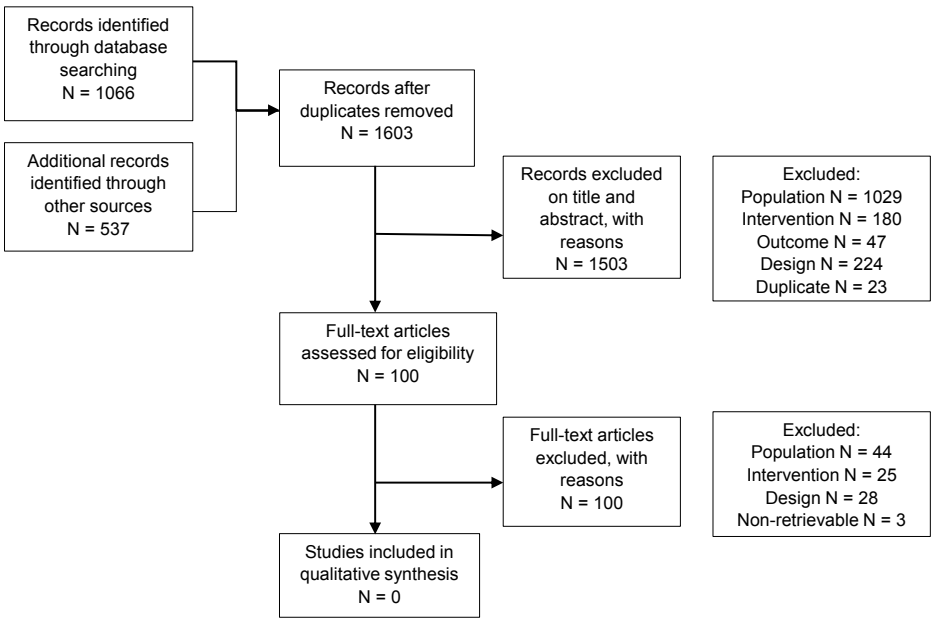

Figure 1: flowchart of study selection

Through hand search of the 100 selected articles, we identified a total of 8 articles that reported on the effectiveness of either a physical or a psychological intervention in patients with PDN (5 RCT's, 3 reviews). The full overview of these articles with its study characteristics and outcomes is presented in Supplemental data 2.

In short, we identified two studies that investigated exercise based treatments for patients with PDN. A RCT by Dixit et al (2013) (25) showed the positive effects of aerobic exercise compared to usual care, with statistically significant improvement on the following domains of the Quality of Life in Neurological Disorders (NeuroQoL) scale: QoL total score, pain subscale, reduced feeling/sensation, sensory motor symptoms and restrictions in daily life activities subscales (25, 35). A pretest–posttest quasi-experimental design by Ahn et al (2012), reported the positive effect of Tai Chi on glucose control, balance, neuropathic symptoms, and the following dimensions of QoL (Short Form 36 Health Survey (SF36)): bodily pain subscale, physical functioning, role physical, role emotional, social function) in diabetic patients with neuropathy compared to no intervention (36). We identified 3 RCT's that focused on psychologically based treatments. Teixeira (2010) et al., investigated the effect of mindfulness meditation on QoL in patients with PDN compared to care as usual and found no effects symptom related quality of life, measured with NeuroQol and Neuropathic pain scale (NPS) (37). Otis et al. (2013) reported that pain severity and pain interference, measured with the West Haven Yale Multidimensional Pain Inventory (WHYMPI) decreased in the CBT group compared to treatment as usual (38). Nathan et al. (2017) showed that a mindfulness-based stress reduction resulted in significant improvement in function, better health-related quality of life, and reduced pain catastrophizing, and depression compared to those receiving usual care (39). Results of all studies should be interpreted with caution, as they were of moderate quality. In 2015, a review was published by Davies et al (2015)(40), which described the studies by Ahn(36), Teixeira (37), Otis (38) and Dixit (25). Reviews by Rosenberg et al. (2015)(5) and Castelnuovo et al. (2016)(41), discussed the work of Otis(38).

Discussion

The aim of this systematic review was to provide an overview of the current literature regarding the effectiveness of treatments that combine exercise therapy with psychological therapy for the improvement of physical activity and QoL of patients with PDN. Although studies in the domain of chronic pain suggest that a multidisciplinary therapeutic approach based on the biopsychosocial model could be effective in improving physical activity and QoL in patients with PDN, this systematic review of the literature revealed no studies that described or tested treatments that combine exercise therapy with psychological treatment modalities. This so called empty review shows that the biopsychosocial approach in the treatment low levels of physical activity and QoL in patients with PDN is a rather unexplored topic and that studies on the effectiveness of multidisciplinary treatments are needed.

Consequences of PDN can be physical (sensory loss, weakness, pain, physical restrictions), psychological (feelings of loss, feelings of depression, anger, sadness), and social (social withdrawal, isolation, work limitations, lower career opportunities) (12). PDN has shown to be associated with catastrophic thinking, increased disability, diminished quality of life, depression and anxiety (11, 21, 42, 43). A recent study by our group identified specific fears related to diabetes and pain that showed to be important predictors of physical and social activities; e.g. fear of hypoglycaemia, fear of (increased) pain, fear of total exhaustion, fear of physical injury, fear of falling, fear of loss of identity and fear of negative evaluation (11). Negative feelings can enhance pain experience and amplify the risk for diabetic complications, again leading to less physical activity and diminished health related quality of life (QoL), creating a vicious cycle (11, 16, 17, 44). Research has shown that multidisciplinary rehabilitation interventions that target all factors from the different biopsychosocial domains, administered by healthcare professionals from different backgrounds, are more effective than physical or psychological interventions alone (33).

In this review, we identified 5 studies that reported on the effectiveness of treatments for PDN that are either psychological treatments or exercise interventions alone (25, 36-39). The results regarding the effectiveness of psychological treatments are not conclusive. A positive, however not statistically significant effect of mindfulness meditation on QoL was found in patients with PDN compared to care as usual (37).

CBT seems to have positive effects on pain severity (38). A mindfulness-based stress reduction intervention showed improvement in function, better health-related QoL, and reduced pain catastrophizing and depression (39). We also found limited evidence for exercise-based treatments. Aerobic exercise showed to have positive effects on peripheral

neuropathy symptoms (25). Beneficial effects of Tai Chi on glucose control, balance, neuropathic symptoms, and some dimensions of QoL were found (36). However, none of these studies supports or rejects a multidisciplinary and/or biopsychosocial approach for PDN.

A combined physical and cognitive behavioural treatment modality with a potential positive effect is exposure in vivo (EXP) (45-48). EXP aims to decrease pain-related disability by specifically targeting irrational thoughts and fears about pain and its consequences (30, 49, 50). EXP treatments have shown to be effective in reducing pain-related fear and the perceived harmfulness of physical activity in various chronic pain conditions, such as chronic low back pain (48, 51, 52) and complex regional pain syndrome type I (CRPS-I) (47, 51). Another combined physical and cognitive behavioural treatment modality is Acceptance and Commitment Therapy (ACT)(53). ACT includes a combination of acceptance and mindfulness methods along with activation and behaviour change methods. Multidisciplinary ACT has shown to be effective in reducing the burden of chronic pain in various pain conditions (53, 54). In this review, we have found no articles that discussed EXP or ACT. Currently, our group is conducting a clinical study in single-case-design to test the effectiveness of an EXP treatment that was specifically designed for the needs and risks of patients with PDN (ActiFeeT, NCT03066570).

There are a few limitations of the current study that should be mentioned. For this systematic review, the search was focused on combined treatments (exercise and psychological). Within the set of articles retrieved, we identified 8 articles that discussed exercise or psychological therapies alone. It should be noted that this was not our primary research question and therefore the listing may not be complete. We evaluated the option of performing a new search with the or option, but decided not to do this, as this work has already been done by Davies et al. in 2015 (55). By performing a thorough hand search through all databases, we identified only 1 article that was published after the review of Davies et al. (Nathan, 2017 (39). We added this article to our results. Furthermore, we could not retrieve the full text of 3 remaining articles. Based on the abstracts, we did not expect any added value of these articles (wrong diagnosis and/or design).

In conclusion, PDN is a multifactorial disease in which pain, balance disorders, gait disturbance and fear/ avoidance behaviour can significantly limit daily life activities QoL. Current care, mostly based on pharmacotherapy, physical training and/or psychological support, seems insufficient to increase physical activity and regain normal daily functioning. Although studies suggest that a multidisciplinary therapeutic

approach could be effective in improving daily life functioning and QoL in patients with PDN, this systematic review of the literature revealed no studies that describe or test treatment modalities that combine exercise therapy with psychological treatment. This empty review highlights the need for studies on the effectiveness of multidisciplinary treatments such as EXP or ACT.

Supplemental data I: search strategy

Embase (Ovid)	
1	exp Diabetes Mellitus/ (808315)
2	(T2dm or TiiDM or Tii-DM or “type 2 DM” or “type ii DM” or DM2 or DM-2 or T2-DM or NIDDM).ti,ab,ot. (42064)
3	(T1dm or TiDM or Ti-DM or “type 1 DM” or “type i DM” or DM1 or DM-1 or T1-DM or IDDM).ti,ab,ot. (20461)
4	(diabet$ or prediabet$ or pre-diabet$).ti,ab,ot. (777536)
5	or/1-4 (953889)
6	Neuralgia/ (7653)
7	Pain/ (273606)
8	Chronic Pain/ (48677)
9	(Neurodynia$ or neuralgi$ or (Nerve$ adj3 Pain$) or (chronic adj3 pain$)).ti,ab,ot. (93439)
10	or/6-9 (355944)
11	5 and 10 (12846)
12	exp diabetic neuropathies/ (21195)
13	(neuropath$ or polyneuropath$ or poly-neuropath$ or third nerve pals$ or mononeuropath$ or mono-neuropath$ or “mononeuritis multiplex”).ti,ab,ot. (172719)
14	(pain$ adj5 (diabet$ adj3 (amyotroph$ or radiculopath$ or Neuralgia$))).ti,ab,ot. (175)
15	(Distal symmetrical polyneuropath$ or DSPN).ti,ab,ot. (313)
16	(diabetic peripheral neuropath$ or DPN).ti,ab,ot. (4460)
17	or/12-16 (181145)
18	11 or 17 (189921)
19	exp kinesiotherapy/ (65978)
20	passive movement/ (3186)
21	resistance training/ (12124)
22	rehabilitation/ (72630)
23	hydrotherapy/ (3751)
24	physical medicine/ or physiotherapy/ (82650)
25	((strength or weight bearing or resistance or aerobic) adj3 (training$ or exercise$)).ti,ab,ot. (32403)
26	(passive adj3 (movement$ or motion$)).ti,ab,ot. (6217)
27	((exercis$ or motion or resistan$ or activity or aerobic) adj3 therap$).ti,ab,ot. (55340)
28	(hydrotherap$ or hydro-therap$ or ((kneipp or water immersion) adj3 (therap$ or treatment$))).ti,ab,ot. (1343)
29	(physical$ adj3 (therap$ or conditioning)).ti,ab,ot. (32378)
30	(physiotherap$ or physio-therap$ or physiatrics).ti,ab,ot. (36392)
31	or/19-30 (309856)
32	Behavior Therapy/ (41305)
33	exp exposure therapy/ (1171)
34	exp cognitive therapy/ (43221)
35	mindfulness/ (4060)

Supplemental data I: Continued

Embase (Ovid)	
36	Occupational Therapy/ (20132)
37	Relaxation Therapy/ (9864)
38	neurofeedback/ (1970)
39	exp Psychotherapy/ (232471)
40	"acceptance and commitment".ti,ab,ot. (840)
41	(behavio?r$ adj3 (therap$ or treatment$ or training)).ti,ab,ot. (51529)
42	(Neurofeedback or Neuro-feedback).ti,ab,ot. (1591)
43	(Imaginal Flooding or desensitization or desensitisation).ti,ab,ot. (27339)
44	(occupational$ adj3 (therap$ or treatment$ or training)).ti,ab,ot. (19063)
45	(ergotherap$ or ergo-therap$).ti,ab,ot. (872)
46	(relaxation adj3 (therap$ or treatment$ or method$ or technique$ or technic$)).ti,ab,ot. (6113)
47	(cognitive adj3 (therap$ or treatment$)).ti,ab,ot. (33088)
48	(eeg adj3 (biofeedback or bio-feedback or neurofeedback or neuro-feedback)).ti,ab,ot. (465)
49	((implosive or relaxation) adj3 (therap$ or treatment$)).ti,ab,ot. (2615)
50	or/32-49 (315965)
51	31 and 50 (25734)
52	(Exposure adj3 (therap$ or treatment$)).ti,ab,ot. or exposure therapy/ (13447)
53	"Exposure in vivo".ti,ab,ot. (1016)
54	(graded adj3 (exposure or activity or exercis$)).ti,ab,ot. (4571)
55	or/52-54 (18810)
56	51 or 55 (44225)
57	18 and 56 (673)
58	animal/ or animal experiment/ (3960625)
59	(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6635551)
60	58 or 59 (6635551)
61	exp human/ or human experiment/ (19079358)
	60 not (60 and 61) (5172695)
63	(letter or editorial).pt. (1544446)
64	57 not (62 or 63) (630)

Supplemental data 2. Results of hand search.

No	Author	Study design	Participants	Sample size	Intervention
1	Ahn et al. 2012	Quasi-experimental controlled trial with pretest – post test	Intervention: n=20, age 66.1 (6.4) years, 12 male, all DM2 Control: n=19, 62.7 (7.5) years, 8 male, all DM2	N=39	Exercise intervention. 12 weeks of Tai Chi 2×1 hour per week, 40 minutes Tai Chi + 15 minutes Qigong.
2	Dixit et al. 2013	RCT	Intervention: n=40, age 54.4 (1.2) years, 22 male, all DM2 Control: n=47, 59.4(1.2) years, 31 males, all DM2	N=87	Exercise intervention. 8 weeks aerobic treadmill exercise at 40-60% of HRR, 5-6 days per week, 150–360 exercise min/week.
3	Otis et al. 2013	RCT	Intervention: n=11, 62 (11) years, all male, all DM2 Control: n=8, 63 (11.6) years, all male, all DM2	N=19	Psychological intervention. 11 sessions of individual CBT, 1-hour session.
4	Teixeira et al. 2010	RCT	All participants n=20: 74.6 (10.8) years, 5 male, all DM2	N=20	Psychological intervention. Mindfulness relaxation: 1 h session + audio CD for home practice.
5	Nathan et al. 2017	RCT	Intervention: n=30, 59.7 (9.1) years, 15 male, 24 DM2 Control: n=32, 58.9 (8.7) years, 12 male, 24 DM2	N=62	Psychological intervention. Community-based group intervention that was based on MSBR. 9 sessions: 8 weekly 2.5h sessions and 1 6h session.
6	Davies et al. 2015	Systematic review	NA	NA	NA

Control arm	Outcomes	Results
Treatment as usual.	SF36	Bodily pain subscale improvement: p = 0.009. Physical functioning improvement: P = 0.028. Role physical improvement: p = 0.006 Role emotional improvement: P = 0.002. Social function improvement: P = 0.001. All other SF36 subscales no difference: p>0.1.
Education for foot care and diet, weekly physician appointment	NeuroQoL	Quality of life total score improvement: p < 0.001. Pain subscale improvement: p = 0.03. Reduced feeling/sensation improvement, sensory motor symptoms and restrictions in daily life activities subscales improvement: all p < 0.001
Treatment as usual	WHYMPI	Pain severity decreased in CBT group: mean 1.08 (0.79), control arm was unchanged, mean 0 (0.51), p < 0.1. Pain interference declined in CBT group: mean 1.35 (SD 1.22), while control arm increased mean 0.22 (SD 0.73), p < 0.5.
Nutritional advice 1h + food diary for 4 weeks	NPS NeuroQoL	No significant difference in overall, symptom related or pain quality of life.
Waiting list with treatment as usual	BPI PHQ-9 PGIC POMS-2A PSS PCS SF-12 NeuroQoL SDScA BSRQ HbA1C	MBSR showed statistically significant improvement in function, better health-related quality of life, and reduced pain catastrophizing, and depression compared to those receiving usual care. BPI interference score decreased: absolute difference 41.4%, P = 0.02. PGIC score improved: absolute difference 40.5%, P = 0.007. All secondary outcome measures, except SF-12 role emotion and HbA1C showed improvement 12 weeks after the course.
NA	NA	Systematic review with the objective to establish the effectiveness of physical activity and psychological coping strategies for PDN. Discusses studies 1, 2, 3 and 4.

Supplemental data 2. Continued

No	Author	Study design	Participants	Sample size	Intervention
7	Rosenberg et al. 2015	Descriptive review	NA	NA	NA
8	Castelnuovo et al. 2016	Descriptive review	NA	NA	NA

BPI; Brief Pain Inventory; BSRQ, Blood Sugar Reactions Questionnaire; CBT, Cognitive behavioural therapy; DM2, Diabetes mellitus type 2; HbA1c, Haemoglobin A1c; HRR, Heart rate reserve; MSBR, mindfulness-based stress reduction; NA, not applicable; NPS, Neuropathic pain scale; NTSS, Neuropathy total symptom score; NeuroQol, Quality of Life in Neurological Disorders; PCS, Pain Catastrophizing Scale;

	Control arm	Outcomes	Results
	NA	NA	Descriptive review of the literature discussing treatment of painful diabetic peripheral neuropathy. Discusses study 3.
	NA	NA	Descriptive review with the aim to determine the psychological factors which are associated with or predictive of pain secondary to neurological conditions and to assess the influence of these aspects on the outcome of neurorehabilitation. Discusses study 3.

PDN, Painful diabetic neuropathy; PGIC, Patient Global Impression of Change; PHQ-9, Patient Health Questionnaire; POMS-2A, Profile of Mood States-2A RCT, randomized controlled trial; SD, Standard deviation; SDSCA, Summary of Diabetes Self-Care Activities; SF-36, Short Form- 36 Health Survey; SF-12, Short Form-12 Health Survey version 2; WHYMPI, West Haven Yale Multidimensional Pain Inventory.

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Chapter 7

Biopsychosocial Rehabilitation treatment 'Exposure in vivo' in patients with Painful Diabetic Neuropathy: Development of a treatment protocol

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Abstract

Introduction: Painful Diabetic Neuropathy (PDN) is known to be associated with low quality of life (QoL), depression and anxiety. Treatment modalities that help patients cope with their pain and pain-related disability, are needed. Exposure in vivo (EXP) has shown to be effective in increasing functional ability and QoL in patients with other chronic pain syndromes.

Protocol: This 8 weeks EXP treatment protocol was specifically adapted to the needs and risks of patients with PDN who are limited in the performance of daily life activities due to PDN related fears. New screening tools were developed for patients with PDN. The Painful Diabetic Neuropathy Anxiety Rasch-Transformed Questionnaire (PART-Q30) identifies specific PDN related fears (e.g. fear of hypoglycaemia). A customized version of the Photograph-series Of Daily Activities (PHODA-PDN) detects PDN related fear-eliciting activities in each individual patient. During EXP, catastrophic interpretations regarding painful stimuli are challenged and corrected, hereby diminishing pain-related fear and enabling the patient to reengage in daily life activities. An interdisciplinary team provides EXP in 1-hour sessions twice a week.

Discussion: To the best of our knowledge, this treatment protocol is the first EXP intervention that was specifically adapted to the needs and risks of patients with PDN.

Introduction

The increasing incidence of diabetes mellitus represents a serious challenge for the medical profession all over the world. Diabetic neuropathy (DN) is present in up to 50% of all chronic diabetic patients and is a major cause of morbidity and mortality (1). In the United States alone, the total costs associated with DN are USD 10.9 billion a year (2).

Up to 25% of the diabetic patients develop painful diabetic neuropathy (PDN), characterized by pain, paraesthesia and sensory loss (3). Sensory loss can lead to the development of pressure ulcers (PU's), balance impairments, an altered gait with potentially an increased risk of falling (4) and impaired levels of physical activity (5). Reduced mobility can lead to restrictions in daily and social activities, dependency on others, depression and as a result decreased quality of life (QoL) (6). Depression in turn, can amplify diabetic complications related to suboptimal glycaemic control (7).

An increasing number of studies has shown that a substantial part of patients with diabetes with PDN suffer from anxiety and fears, such as fear of pain, fear of falling, fear of disturbed glucose regulation, thereby avoiding physical activity (8). Current care, mostly based on pharmacotherapy and physical training, seems to ignore the debilitating role of those fears in increasing physical activity and regaining normal daily functioning (9). It is well known that increasing physical activity in patients with DM has favourable effects on diabetes-related outcomes (10). However, dropout rates in physical exercise programmes are high, with rates up to 45% (11). An interdisciplinary therapeutic approach has therefore been recommended in order to improve daily life functioning (12).

Since patients with PDN frequently share the comorbidities of depression and fear (and as a consequence disability) with other chronic pain populations (13), it seems apparent to integrate the knowledge obtained in populations with other pain syndromes into the field of PDN. An example of a cognitive behavioural treatment modality for patients with chronic pain is exposure in vivo (EXP), which is based on the principles of classical conditioning (14). EXP aims to decrease pain-related disability by specifically targeting irrational thoughts and fears about pain and its consequences (15). EXP has shown to be effective in improving functional ability and QoL, and to reduce pain-related fear and the perceived harmfulness of physical activity in patients with various chronic pain conditions (14, 16-18). EXP has also shown to be cost-effective (19, 20).

We have developed an 8 weeks EXP treatment that was specifically adjusted to the needs and risks of patients with PDN. It has a unique multidimensional approach on improving daily functioning and contains methods derived from research in psychology,

behavioural sciences, physical therapy, diabetes care and rehabilitation medicine. In this interdisciplinary rehabilitation treatment, physicians in rehabilitation medicine, physiotherapists, occupational therapists and psychologists are involved. In this paper we present the treatment protocol of this EXP treatment for patients with PDN.

Protocol

Protocol development

At Adelante, location Maastricht University Medical Centre, EXP treatment is embedded in the usual care for patients with chronic pain syndromes such as CRPS-I and chronic low back pain who report substantial pain-related fear, and fear of movement/(re)injury in particular (14, 15). The EXP treatment is highly structured, protocolled, individually tailored, and aims to restore a normal pattern of daily functioning (15). The current EXP treatments are designed for chronic pain conditions that generally have no medical risks or restrictions regarding physical activity. PDN however, can present with potential risks for injury, PU's and/or hypoglycaemia, which can make EXP unsuitable for patients with PDN. Also, the behavioural and psychosocial processes in patients with PDN could differ from the more unspecific chronic pain syndromes such as chronic low back pain. This paragraph presents the theoretical framework and procedures that were used to customize the already existing EXP treatment to the needs and risks of patients with PDN.

In order to gain more insights into the perceptions, fears and consequences of PDN in daily life, the project started with a qualitative study (21). Three focus groups with each four patients with PDN were performed. Patients reported to suffer from substantial pain, disability, polyneuropathy and diminished QoL. The consequences of PDN showed to be physical (weakness, pain, physical restrictions), psychological (feelings of loss, feelings of depression, anger, sadness), and social (social withdrawal, isolation, work limitations, lower career opportunities). Furthermore, patients reported several fears related to diabetes and pain that could be important predictors of physical and social activities, such as fear of hypoglycaemia, fear of (increased) pain, fear of total exhaustion, fear of physical injury, fear of falling, fear of loss of identity and fear of negative evaluation. Fear seemed to be associated with different types of avoidance behaviour; patients avoided various activities, were less physically active and withdrew themselves from performing activities (21). A second study in a cross sectional design by our group showed that PDN was associated with catastrophic thinking, which in turn led to a perceived decline in physical activity, increased disability and less QoL (13). The identification of these fears enabled us to determine potential specific PDN-related targets for the behavioural intervention (5).

Treatment Protocol

The 8 weeks treatment is specifically designed for persons with PDN, aged > 18 years, who experience PDN related fears and want to improve their level of activity and QoL. During the EXP treatment, patients with PDN are guided to learn and recognize which bodily sensations correspond to actual PDN related risks such as falling or current blood glucose levels. This is done by addressing thoughts and beliefs about the bodily sensations in

relation to actual measurements (e.g. clinimetric parameters, blood glucose levels pre- and post-treatment). Then, patients are encouraged to increase the level of physical activity and apply their recognition skills in novel situations.

A treatment team consisting of a psychologist, occupational therapist, physiotherapist and a rehabilitation physician, all experienced in the cognitive-behavioural rehabilitation of patients with chronic pain, provides the EXP treatment. All team members should be trained on the risks and special needs of diabetic patients. For example, if a patient has a high risk of developing an episode of hypoglycaemia, blood glucose levels should be measured pre- and post-treatment. Furthermore, the physician and team members have to be aware of the risk of developing PU's and should be able to identify PU's timely.

The EXP treatment protocol consists of three parts; 1) intake by rehabilitation physician, 2) an extensive one-day screening and 3) the actual 8 weeks EXP treatment. The full treatment will be discussed in the following paragraph. Table 1 provides an overview of the treatment protocol.

Table 1. Schematic overview of the Exposure in vivo Treatment Protocol for patients with PDN.

Treatment	
Medical Consultation incl. Physical Examination	Rehabilitation Physician
Screening	
· Physical Examination	Physical Therapist
· Behavioural Analyses	Psychologist and Physical Therapist
· Goal Identification (COPM)	Occupational Therapist
· Graded Hierarchies (PHODA-PDN)	Psychologist Therapist
· Medical education about PDN	Rehabilitation Physician
· Education about chronic pain	Rehabilitation Physician, Psychologist and Physical Therapist
Treatment *8 weeks; one hour sessions, twice a week*	All members of treatment team
Team meetings *In week 3 & 7*	All members of treatment team
Final consultation	Rehabilitation Physician
Aftercare *After 6 weeks and 3 months*	Rehabilitation Physician

PDN: Painful Diabetic Neuropathy; COPM: Canadian Occupational Performance Measure; PHODA-PDN: Photograph-series Of Daily Activities-PDN.

Intake by rehabilitation physician

During the intake session, the rehabilitation physician takes a full medical history and assesses the current PDN related complaints, risks and medication. Topics such as hypoglycaemic episodes, (the risk for) PU's and withdrawal/ reduction of pain medication are discussed.

Physical examination: A thorough physical examination of the lower extremity is performed. Peripheral polyneuropathy is checked and classified based on a standardised clinical neurological examination (CNE) in which a CNE score > 5 indicates the presence of peripheral neuropathy and a score of > 15 is considered severe peripheral neuropathy (22). The CNE score is determined by examining the Achilles tendon reflex, vibration awareness, sharp–blunt discrimination, touch sense, position sense at the hallux and manual assessment of extensor muscle strength of the hallux and flexor muscle strength of the foot in which all items are scored as either normal, impaired or absent (0–2 points). In addition, the scoring of light touch sense is related to the anatomical level below which it is impaired (toe, mid-foot, ankle, mid-calf and knee) (0–5 points). Previous research has shown that EMG and CNE scores resulted in the same diagnosis of distal polyneuropathy in DMII patients (23, 24). All patients are screened on PU's on their feet and on wearing adequate (orthopaedic) shoes. Also, walking abilities are tested. Based on the findings, the rehabilitation physician decides whether the patient can receive the treatment. If the risks of injury are considered too high, the patient will be excluded.

Elaboration on PDN related fears: The rehabilitation physician screens for pain and diabetes related fears that may inhibit the patient in performing daily activities. The PARTQ-30 is used to determine and quantify the impact of these specific disabling fears. Based on the results of our qualitative studies, our group developed the Painful Diabetic Neuropathy Anxiety Rasch-Transformed Questionnaire (PART-Q30©)(25). This 30-item questionnaire can easily be applied in clinical practice and identifies the impact of specific disabling fears for the individual patient based on a relatively simple procedure (25). An elaboration of the current level of physical activities and participation in daily life is performed, according to the International Classification of Functioning (ICF) – model (26).

Table 2. Eligibility criteria for exposure in vivo treatment

1. Patients experience PDN related fears that limit the patient in daily life activities.
2. The patient has relevant treatment goals aimed on participation in daily life.
3. The patient is committed and motivated to undergo the 8 week treatment programme.
4. There are no medical or psychological restrictions to participate (e.g. pressure ulcers, high injury risks, comorbid severe depression).

When PDN related fears are present and cause limitations in participation in daily life activities, the rehabilitation physician will provide more information on the EXP treatment. Then, a short elaboration on possible treatment goals is performed. The patient is eligible for EXP treatment when he/she meets all 4 eligibility criteria; 1) there are PDN related fears that limit the patient in daily life activities; 2) the patient can formulate relevant treatment goals aimed at participation in daily life; 3) the patient is committed and motivated to undergo the 8 weeks treatment programme; and 4) there are no medical or psychological restrictions to participate (e.g. PU's, high injury risks, comorbid severe depression). Eligibility criteria are presented in Table 2.

Screening
The screening consists of a behavioural analyses by the psychologist, an observation during activities and physical examination by the physical therapist, goal identification by the occupational therapist, a team meeting with the physician and all therapists, and a final educational session with all team members and the patient.

Behavioural analysis:. The aim of this session by the psychologist is to complete a behavioural, cognitive and psycho-physiological analysis of the problems associated with PDN. The Hospital Anxiety and Depression Scale (HADS) (27) and Pain Catastrophizing Scale (PCS) (28) are administered. The psychologist focusses on the patient's catastrophic interpretations and fears related to PDN. The assessment also includes information about any antecedents (situational or internal, episodes of hypoglycaemia, recurrent falls etc.) of pain-related fear and about direct and indirect consequences. The screening could also include other areas of life stress, as they might increase arousal levels and indirectly also fuel pain-related fear.

Observation during activities: The intake session with the physical therapist comprises a physical examination and an observation of the specific body movements during various activities. During this observation there is also a special attention to behavioural responses to specific activities (e.g. fear or avoidance). Whenever there are physical complaints or restrictions, these will be noted in the medical file.

Goal identification: PDN can have profound effects on a patient's life (5, 29) and the repeated interference with tasks that are essential to achieve various life goals and maintain a role in society, will impact on their sense of self, both their current self and perhaps more importantly their plans and ideas about who they might become (30). The occupational therapist emphasizes that EXP does not primarily aim at reducing pain, but at the restoration of functional abilities through which patients' capacity to live according to their life values can be restored. The patient is invited to formulate his/her

own treatment goals together with the occupational therapist. The Canadian Occupational Performance Measure (COPM) is used by the occupational therapist to assess perceived limitations in activities and participation and to aid the goal formulation process. The patient and occupational therapist agree on one or more realistic and specific goals that are formulated in positive terms. Activities (e.g. walking on uneven ground) that are in line with these goals (e.g. running errands) will be included in EXP.

PHODA-PDN: A listing of fear-eliciting activities is made using the Photograph-series Of Daily Activities (PHODA) (31, 32). This is a standardized method during which patients are requested to judge the perceived harmfulness of various physical daily life activities represented by photographs. Using a thermometer, the patient rates each picture between zero to 100 regarding harmfulness (zero represents the situation which is not harmful for the lower extremity; 100 represents the situation which is absolutely damaging the lower extremity). Based on the associations between activities and expected negative outcomes (amputation, exhaustion etc.), individually tailored behavioural experiments can be developed (31). For this treatment protocol, the PHODA for lower extremities was specifically adapted with additional photographs of PDN related fears, resulting in the PHODA-PDN. These fears included fear of hypoglycaemia, fear of falling, fear of amputation, fear of pain, fear of exhaustion, fear of injury, fear of social isolation and fear of loss of identity (13, 21).

Within the theory of classical conditioning, conditioned responses (CR), for example fears, occur when an unconditioned stimulus (US) is paired to a conditioned stimulus (CS). In PDN, the feared catastrophic consequence can be considered the US, while the activity in which the fear occurs is the CS. E.g.: 'If I walk up a flight of stairs (CS), I will fall and break my leg (US)'. EXP treatment will then target the CS, providing a new experience for the patient: no catastrophic consequence occurs. In the example, the patient will experience that he can walk up a flight of stairs (CS) without falling and breaking his leg (no US). This newly learned association (CS-no US) will then increase the likelihood that the patient will no longer avoid walking up a flight of stairs in future situations. The original PHODA is designed to represent activities (CS's) that may be considered harmful (US's). However, the fears that were identified in our previous studies (fear of falling, fear of hypoglycaemia etc.) are mostly feared consequences (USs), rather than specific activities (CSs). To overcome this issue, the PHODA-PDN is used in 2 phases. First, the patient identifies which PDN related feared consequences (US) were present (e.g. fear of hypoglycaemia or fear of amputation). After this, the pictures of PDN related fears is paired with pictures of activities from the original version of the PHODA (CSs). In this way, we could determine during which activity (CS) this PDN related fear (US) occurred (e.g. walking on uneven ground).

Team meeting: After these sessions, there is a meeting with the treatment team including the rehabilitation physician, without the patient. The team summarizes and elaborates on all the information that was obtained. In this meeting, the treatment team will make a final judgement as to whether the patient is eligible for EXP treatment. Directly after this, there is a final session with the patient, rehabilitation physician and physiotherapist during which the patient will be informed about the eligibility for EXP treatment. When the patient is eligible, the screening finishes with an educational session.

Educational session: The patient receives an educational session with the rehabilitation physician, psychologist and physiotherapist. This educational session comprises a medical education on PDN and an explanation about the FAM and treatment rationale.

Medical education: The rehabilitation physician elaborates on the aetiology of diabetes and PDN and the medical consequences and risks. He/she stresses the importance of adequate glycaemic control and physical activity. The aim of this educational session is to provide information and clarify any potential misconceptions regarding diabetes, pain and physical activity. Table 3 shows which topics should be addressed during this session. At the end of the session, the patient should be informed and aware of his/her medical condition on the one hand, and on the other hand, should realize that physical activity is important for good glycaemic control, and is not harmful when performed in the correct way.

Education of FAM: Using their own individual symptoms, beliefs and behaviours in relation to their pain complaints, patients are given a careful explanation of the FAM (33) by the psychologist. Pain catastrophizing, pain related fears, diabetes related fears, avoidance and safety behaviours are discussed. The treatment team illustrates the paradoxical and dysfunctional effects of these coping strategies. In addition, the team stresses the risks of this behaviour, as it can lead to a higher risk of developing diabetes related complications in the long run. One of the major goals of the educational session is to help the patient understand that the consequences of PDN, in his/her case, are catastrophically overestimated and that physical activity is beneficial in the self-management of PDN and its complications.

Table 3. Topics that should be discussed during the medical education session

Aetiology and consequences of diabetes, amongst which DN - Aetiology of diabetes and its complications such as retinopathy, neuropathy, ulcers, risk for amputation. - Discuss why adequate glycaemic control is so important. - Aetiology of DN: explain nerve damage and sensory loss; discuss the results of previously performed medical examinations (e.g. EMG).
Pain in PDN - Aetiology of PDN: nerve damage leads to continuous firing of pain signals. - Discuss acute vs. chronic pain; chronic pain in a damaged nerve is not necessarily a warning sign. - Discuss pain medication: it is not always effective and can have many side effects.
Physical activity - Stress beneficial effects of physical activity on glycaemic control and the reduction of risks for development of secondary complications. - Elaborate on any potential misconceptions regarding limitations and/or risks of physical activity in PDN.

DN: diabetic neuropathy; EMG: electromyography; PDN: Painful Diabetic Neuropathy.

Treatment

After the screening, the actual rehabilitation treatment commences. In this 8 weeks programme, the patient receives one-hour sessions of EXP treatment, twice a week, with a total of 16 sessions. During these sessions, the patient is systematically exposed to the tailored and fear-provoking activities. These fears can be diabetes- or pain related and an elaboration will be done on the cognitions, fears and expectations of the patient regarding the feared activity. After this, the actual exposure to the feared activity will take place. For example, one activity that potentially induces both diabetes and pain related fears could be prolonged walking on uneven grounds. By performing this activity for a longer period of time, it may activate the fear that an episode of hypoglycaemia may set in. The fact that a patient is walking on uneven grounds can reinforce the fear of falling. During each exposure session patients are encouraged to engage in these fearful activities as much as possible until disconfirmation has occurred.

A member of the treatment team checks every activity on safety for patients with PDN, e.g. wearing adequate shoes before walking on uneven ground. Before every session, the patient is asked about current PU's. The treatment session can only start if the patient reports that the skin is in good condition. However, if the patient reports that PU's are present, or he/she is in doubt about the current condition of the skin, the therapist will inspect the feet. In case there are current PU's, the rehabilitation physician will be consulted and the EXP session will be seized. Because this treatment aims to decrease fears and increase self-management skills, we opted not to systematically screen the feet of all patients before and after every session, as we believe this will enhance hypervigilance and fear, rather than decrease it. In all patients who are insulin dependent, glucose levels are measured pre- and post-treatment. In case fear of hypoglycaemia was specified as a limiting factor for physical activity in non-insulin dependent patients, these additional measurements can also be done. In the last session, treatment effects are assessed and recorded using the PHODA-PDN, COPM and PART-Q30©.

Team meetings and aftercare

During the EXP treatment, two team meetings take place (in week 3 and 7). During these meetings, the treatment team discusses the individual treatment goals and progression of the treatment. After each team meeting, the patient has an evaluation session with the physician to discuss progress and answer any questions where needed. After the last session, advices for future follow-up will be provided. Usually, aftercare consists of a meeting with the treatment team 6 weeks post treatment and a final check-up with the physician 3 months after completion of the treatment.

Discussion

This manuscript describes the treatment protocol of our 8 weeks EXP treatment that was specifically designed for patients with PDN that are limited in daily life activities by PDN related fears. To the best of our knowledge, this treatment protocol is the first rehabilitation intervention based on the principles of classical conditioning for patients with PDN. The EXP intervention aims to increase physical ability and QoL by establishing a new positive association between previously expected negative outcomes during a specific activity. This intervention distinguishes itself by the fact that it aims to change behavioural patterns through physical and cognitive exposure of underlying cognitions and fears in specific daily life situations. Furthermore, this treatment protocol is based on a theoretical framework that integrates knowledge from the fields of psychology, behavioural sciences, physical therapy, diabetes care and rehabilitation medicine. Based on this knowledge, customized screening tools were developed and used. The result is a treatment rationale that provides an integrated approach to the individual needs and treatment goals for every single patient. The effectiveness of the EXP treatment protocol for PDN patients has been tested in a repeated measures single case experimental design (SCED) with 6 months follow-up period (ActiFeet study, ClinicalTrials.gov Identifier: NCT03066570).

Clinical Messages

- This innovative 8 weeks EXP treatment protocol has specifically been designed for the risks and needs of patients with PDN.
- It aims to change behavioural patterns through physical and cognitive exposure of underlying cognitions and fears in specific daily life situations, hereby increasing levels of activity and QoL.

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ActiFeet

Chapter 8

Effectiveness of exposure in vivo for patients with painful diabetic neuropathy: a pilot study of effects on physical activity and quality of life

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Abstract

Objective: to evaluate effectiveness of personalized exposure in vivo (EXP) on improving physical activity (PA) and quality of life (QoL) in patients with painful diabetic neuropathy (PDN).

Design: randomized single-case ABC-design.

Subjects: 12 PDN patients, age>18 years, diabetes mellitus type II, Clinical Neurological Examination score>5, Diabetic Neuropathy Symptom Score≥1 and Douleur Neuropathique 4 Questions score≥3.

Methods: The treatment consists of an intensive screening (A), followed by 8-week EXP in vivo (B) specifically adapted to needs/risks of PDN patients, and 6-months follow-up (C). Outcome measures included daily and non-daily measures of PA, QoL, metabolic parameters, disability, depression, general and PDN related anxiety, pain intensity and pain catastrophizing.

Results: Due to high drop-out rates (n=6 during screening, n=2 during EXP, n=1 after EXP), only 3 participants completed the study. Only slight, however non-significant, changes on PA and disability were seen.

Conclusions: Analyses of the reasons for the high drop-out rate indicated that EXP may only have an added value for patients with PDN; 1) whose daily life functioning is mainly impaired by the PDN, 2) the PDN related fears are exaggerated and irrational, 3) specific activities evoke the PDN-related fears, 4) whose spouse and healthcare providers are involved in the treatment and 5) if he/she is willing to change daily behaviour.

Introduction

Diabetic neuropathy (DN) is present 50% of all chronic diabetic patients and is a major cause of morbidity and mortality (1). Up to 25% of the diabetic patients develops painful diabetic neuropathy (PDN), characterized by pain, paraesthesia and sensory loss (1).

PDN is associated with a decrease in the level of physical activity (PA) (2). This is alarming, since reduced mobility can lead to dependence on others, restriction in daily and social activities, depression and decreased quality of life (QoL) (3). Depression on its turn is known to be related to poor glycaemic control and the development of pressure ulcers (PU's) (4). Pain can be enhanced by negative feelings, again leading to less PA and diminished QoL, creating a vicious circle (5). Patients with PDN can suffer from anxiety and fears such as fear of pain, fear of falling and fear of hypoglycaemia, thereby avoiding PA (6, 7). Anxiety is common in patients with diabetes (20%-32%) (8, 9). Anxiety can also play an important role in the maintenance of the consequences of the PDN (5, 6). It seems plausible that the overall QoL of patients with PDN can only be successfully improved when comorbid anxiety and negative emotions are optimally screened, diagnosed and treated (5, 10).

Current care, mostly based on pharmacotherapy and physical training, seems to be insufficient to increase PA and to regain normal daily functioning. Dropout rates in physical exercise programs are high; up to 45%, due to PU's, overuse injuries and lack of motivation (11, 12). Fears may contribute to this dropout. An interdisciplinary therapeutic approach focusing on more than reduction of pain alone, is recommended (13, 14).

In order to restore QoL and improve daily life functioning, it seems beneficial to integrate the knowledge obtained in populations with other pain syndromes into the field of PDN, since patients with chronic pain frequently share the comorbidities depression and fear, and as a consequence disability. Research on the Fear-Avoidance Model (FAM) succeeded to identify the disabling role of specific fears such as fear of movement, fear of pain or fear of (re)injury. This pain related fear can lead to avoidance behaviour and hypervigilance to pain-related stimuli (15). Previous research has confirmed that the FAM may also be applicable in patients with PDN (5, 10, 16). Patients with PDN can suffer from several fears related to diabetes and pain (e.g. kinesiophobia, fear of falling), that might be important predictors of physical and social activities (16). Also, PDN has shown to be associated with catastrophic thinking, which in turn can lead to a perceived decline in physical activity, increased disability and less quality of life (5). Based on the FAM, a cognitive behavioural therapy, Exposure in Vivo treatment (EXP) was developed which appears to be successful in breaking the vicious circle (17).

In this pilot study, we aimed to investigate whether EXP could also be effective in patients with PDN. We hypothesized that, through targeting specific fears, a reduction in the perceived harmfulness of activities would occur, leading to higher level of PA and QoL in patients with PDN.

Methods

Population and procedure

This research was performed at Adelante, location Maastricht University Medical Centre (MUMC+), the Netherlands, where a diversity of chronic pain patients are successfully treated with EXP (18). It was also embedded in the Diabetes Centre and movement laboratories of MUMC+. Here, patients were asked to participate. Furthermore, an invitational letter was sent to patients with PDN who had participated in our previous research (5, 10, 16, 19, 20). An online advertisement was posted on the website of the patient organization (Dutch Diabetes Foundation). The study was approved by the Medical Ethical Committee MUMC+ (reg. no. 163024) and registered in in clinicaltrials.gov (NCT03066570).

Inclusion criteria

Patients were included if they met the following inclusion criteria: age>18 years, diabetes mellitus type II, Diabetic Neuropathy Symptom Score (DNS) ≥1, Douleur Neuropathique 4 Questions (DN4) ≥3, and standardised Clinical Neurological Examination (CNE) >5. Previous research has shown that EMG and CNE score resulted in the same diagnosis of PDN in DM II patients compared to using the abovementioned criteria (21).

Exclusion criteria

Patients with lower limb morbidities other than PDN (e.g. peripheral arterial disease, severe osteoarthritis), other diseases causing pain in the feet and/or damage to the peripheral nervous system (e.g. ulcers), other disease that may cause limitations in PA (e.g. severe cardiopulmonary disease) and/or patients who received cognitive behavioural therapy within the last 6 months were excluded from this study.

Design

A pilot study using a randomized replicated sequential single-case experimental ABC-design (SCED) with multiple measurements was performed (22). T0 represents the first consultation by the rehabilitation physician in which rehabilitation goals were determined and inclusion criteria checked. After this, a baseline measurement period of at least 3 weeks started (period A, T0-T1) in which patients underwent an extensive screening. Then, patients were randomly assigned to the 8-week treatment (period B, T1-T2). After 6-months, there was a follow-up period of 2 weeks (period C, T3-T4). Figure 1 illustrates the study design.

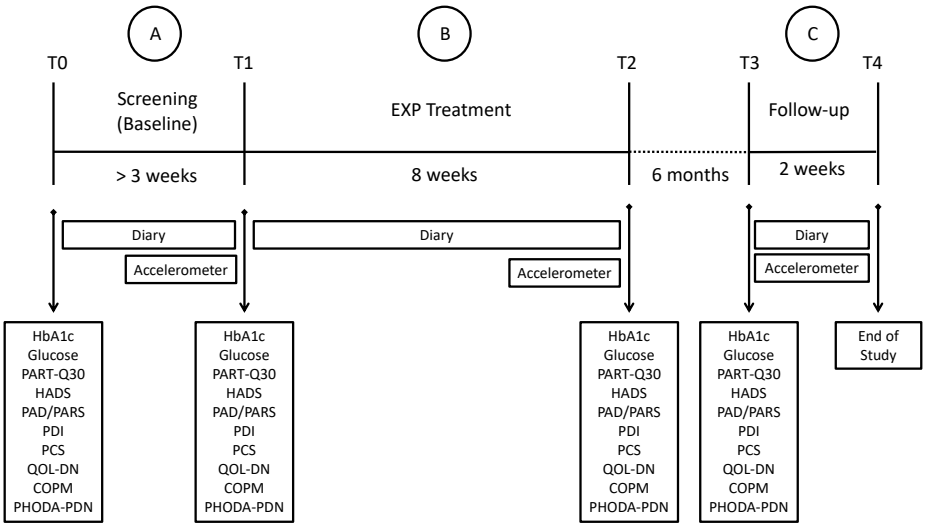

Figure 1: Study Design

PARTQ-30, Painful Diabetic Neuropathy Anxiety Rasch-Transformed Questionnaire; HADS, Hospital Anxiety and Depression Scale; PAD, Perceived Activity Decline; PARS, Physical Activity Rating Scale; PDI, Pain Disability Index; PCS, Pain Catastrophizing Scale; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire-Diabetic Neuropathy, COPM, Canadian Occupational and Performance Scale; PHODA-PDN, Photograph-series Of Daily Activities – Painful Diabetic Neuropathy version.

In this SCED ABC-design, the sequencing of phases is fixed so the randomization cannot be applied to the treatment order. One feature that can be randomly determined without distorting the treatment order, is the moment of phase change, e.g. ABBBC, AABBBC, AAABBBC (23). Therefore, the starting point of the intervention (T1) was determined at random using the waiting list for regular treatments. Repeated measurements (diary and questionnaires) took place in each phase (A, B and C). No blinding was possible for participants or members of the rehabilitation team since all participants received the EXP treatment. Data-analysts were blinded, as they were not involved in the treatment. Subjects who withdrew from the study, received follow-up according to care as usual and were asked to fill in all the questionnaires on the remaining time-points.

Intervention

The EXP in this study was specifically designed for patients with PDN who experienced PDN related fears and wanted to improve their level of activity and QoL. It was adapted to the needs and risks of patients with PDN (potential risks for injury, PU's and/or hypoglycaemia etc.). The treatment was based on results of earlier qualitative and quantitative studies that we performed (5, 10, 16), and PDN specific screening tools, such as the Painful Diabetic

Neuropathy Anxiety Rasch-Transformed Questionnaire, PART-Q30© (19), and Photograph-series of Daily Activities, PDN version (PHODA-PDN) were constructed. Furthermore, blood glucose levels were measured pre- and post-treatment in insulin dependent patients.

The EXP treatment consisted of three parts; intake by rehabilitation physician, an extensive interdisciplinary one-day screening and the 8-week EXP treatment. During the intake session, the rehabilitation physician took a full medical history and assesses the current PDN related complaints, risks and medication. The interdisciplinary screening consisted of a behavioural analysis by the psychologist, an observation during activities and physical examination by the physical therapist, goal identification by the occupational therapist, a team meeting with the physician and all therapists, and a final educational session for the patient by all team members. The 8-week EXP-programme consisted of two one-hour sessions of EXP per week in which thoughts and beliefs about the fears and bodily sensations were challenged. Then, patients were encouraged to increase the level of PA and apply their newly learned associations in new situations. The full protocol of this EXP treatment has been published elsewhere (20).

Data collection

Data on age, gender, duration of complaints, insulin treatment, use of pain medication, pain intensity, metabolic parameters, anxiety, depression, PA and disability were collected. To check whether EXP increased PA by decreasing PDN related fears, daily and non-daily measures (at T0-T4) were used.

Non-daily measures

Primary outcome measures

PA and perceived activity decline (PAD). Self-reported PA was measured using the Physical Activity Rating Scale (PARS), consisting of 20 daily activities (24). On a 5-point Likert scale (0-4), patients scored how often they have performed these activities in the past two weeks. To estimate the PAD, patients indicated whether they would have performed each specific activity of the PARS more often (yes/no) if they would not experience PDN related pain. PAD has shown good internal consistency and reliability (25).

QoL. QoL was measured using the 35-item Norfolk Quality of Life Questionnaire, Diabetic Neuropathy Version (Norfolk-QOL-DN), a self-administered questionnaire designed to capture and quantify the perceived impact of diabetic neuropathy on QoL. Low score indicates good QOL(26). Reliability has shown to be good for most domains (26).

Secondary outcome measures
Metabolic parameters: blood samples were taken to assess insulin, glucose, HbA1c and HbA1c%.

Pain Intensity. Pain intensity was measured using a Visual Analogue Scale (VAS), ranging from 0-10.

Disability. The 7-item Pain Disability Index (PDI) investigated the magnitude of the self-reported disability in different situations, e.g. work, leisure time, activities of daily living and sports (27). PDI has shown to be internally reliable (27).

Anxiety and Depression. These were measured using the Hospital Anxiety and Depression Scale (HADS), a self-report scale that consists of 7 items on depression symptoms (HADS-D) and 7 items on anxiety symptoms (HADS-A)(28). HADS has shown to have adequate reliability and validity (29).

Fear reduction. Overall PDN related fear was measured using Painful Diabetic Neuropathy Anxiety Rasch-Transformed 30-item questionnaire (PART-Q30©), which encompasses various domains of PDN related anxieties and fears. Higher scores indicate more presence of fears (19). The PART-Q30© has shown to explain approximately 1/3 of disability and almost half of QoL reduction as experienced by PDN patients. The personal separation index of the PART-Q30© has shown to be good (19).

Pain Catastrophizing: To measure negative thoughts and beliefs during actual or anticipated painful experiences, the Dutch version of the validated 13-item Pain Catastrophizing Scale (PCS) was used (30). Psychometric properties of the PCS have shown to be adequate (30, 31).

Identification of PDN specific fears and activities: A list of fear-eliciting activities was made using the PHODA-PDN version (20) with 8 additional photographs to assess the following PDN related fears; hypoglycaemia, falling, amputation, pain, exhaustion, injury, social isolation, and loss of identity (10, 16). The PHODA-PDN was used in 2 phases. First, the patient identified which PDN related fear he/she experienced, using the 8 additional pictures. Next, the identified pictures were paired to pictures of activities from the original PHODA (e.g. walking up a slope induces/activates fear of hypoglycaemia). In this way, the team could determine during which activity the PDN related fear occurred (e.g. walking on uneven ground elicited fear of falling).

Rehabilitation goals. The Canadian Occupational Performance Measure (COPM) was used to assess perceived limitations in personally relevant activities and participation, aiding the goal formulation process (32).
A full description of the PHODA-PDN and COPM are published elsewhere (20).

Daily measures
To check whether the intervention modified PDN related fear, pain catastrophizing and/or pain experience, participants filled in 16 questions on an electronic diary. Participants received daily e-mails asking them to fill in the diary. It consisted of one question concerning pain intensity (VAS 1-10), 10 questions derived from the PART-Q30© questionnaire and two personalized questions based on the PHODA-PDN and COPM (highest scores taken at baseline). Here, participants scored how often they had performed the activity (PHODA-PDN and COPM) and how satisfied they were about the way they could perform this activity (COPM). An example of the diary questions is provided in Table 1.

Table 1. Diary questions

1.	How much nerve pain in the feet do you experience at this moment?		1-10	
2.	I am afraid of injuring myself accidentally.	1	2	3
3.	I would not have this much pain if there was not something potentially dangerous going on in my body.	1	2	3
4.	I think that if my pain gets too severe, it will never decrease.	1	2	3
5.	My fatigue has put my body at risk for the rest of my life.	1	2	3
6.	How often have you have worried about not recognizing/realizing I am having a reaction because of low blood sugar?	1	2	3
7.	I try to avoid activities that cause pain.	1	2	3
8.	I will stop any activity as soon as I sense pain is coming.	1	2	3
9.	As soon as pain increases, I take medication to reduce it.	1	2	3
10.	How concerned are you that you will fall, while walking up or down a slope?	1	2	3
11.	How concerned are you that you will fall, while reaching for something above your head or on the ground?	1	2	3
12.	Today, how often have you performed activity X (*fearful activity identified by PHODA-PDN*)?		1-10	
13.	A. Today, how often have you performed activity Y (*desired activity identified by COPM*)?		1-10	
B.	How satisfied are you about the execution of this activity Y (*desired activity identified by COPM*)?		1-10	

COPM: Canadian Occupational and Performance Scale; PHODA-PDN: Photograph-series of Daily Activities – Painful Diabetic Neuropathy version.

Statistical analyses

Baseline characteristics are presented in means (±standard deviation) or percentages. Results of questionnaires for PA, depression, fears and QoL on T0-T4 are displayed in tables. No statistical analyses could be performed on these data due to the small sample size.

Daily measures were first presented graphically and next interpreted for trends, followed by a randomization test for SCEDs based on the random determination of the moments of phase change(23). In SCEDs, the single case experiments (SCEs) are replicated one after another, hereby demonstrating the external validity of the effects. These replicated SCEs may be considered as multiple studies that can be combined using meta-analytical procedures(33). The randomization tests in this study used the difference between means as test statistic. Because EXP (B) was expected to be superior to baseline (A), the null hypothesis that there was no differential effect for any of the measurement times was tested using a randomization test on the differences between B and A. The follow-up period (C) was expected to be superior to A and should not change in relation to B; therefore, differences between C and A were also tested.

The outcome variables of the diaries were combined in themes of which means were calculated; pain intensity (item 1), fear of injury (FOI, items 2-4), fear of exhaustion/ hypoglycaemia (items 5,6), avoidance behaviour (items 7-9), fear of falling (items 10,11), PHODA (item 12), COPM (items 13A and 13B). Next, the themes were measured systematically over time in each phase (A-B and A-C). Because replicated SCEs in this study provided independent tests of the same null hypothesis, the directional p-values of these test were combined by calculating the sum of the p-values and comparing this sum with all other sums that arose under the general null hypothesis; if the null hypothesis is true, the p-value is a random draw from a uniform [0,1] distribution(23). The results of the diaries are visually presented in running medians (batch size 4, averaged by pairs). The analyses were performed using the online Shiny SCDA web app (https://tamalkd.shinyapps.io/scda) by Kumar De and Onghena, KU Leuven, Belgium.

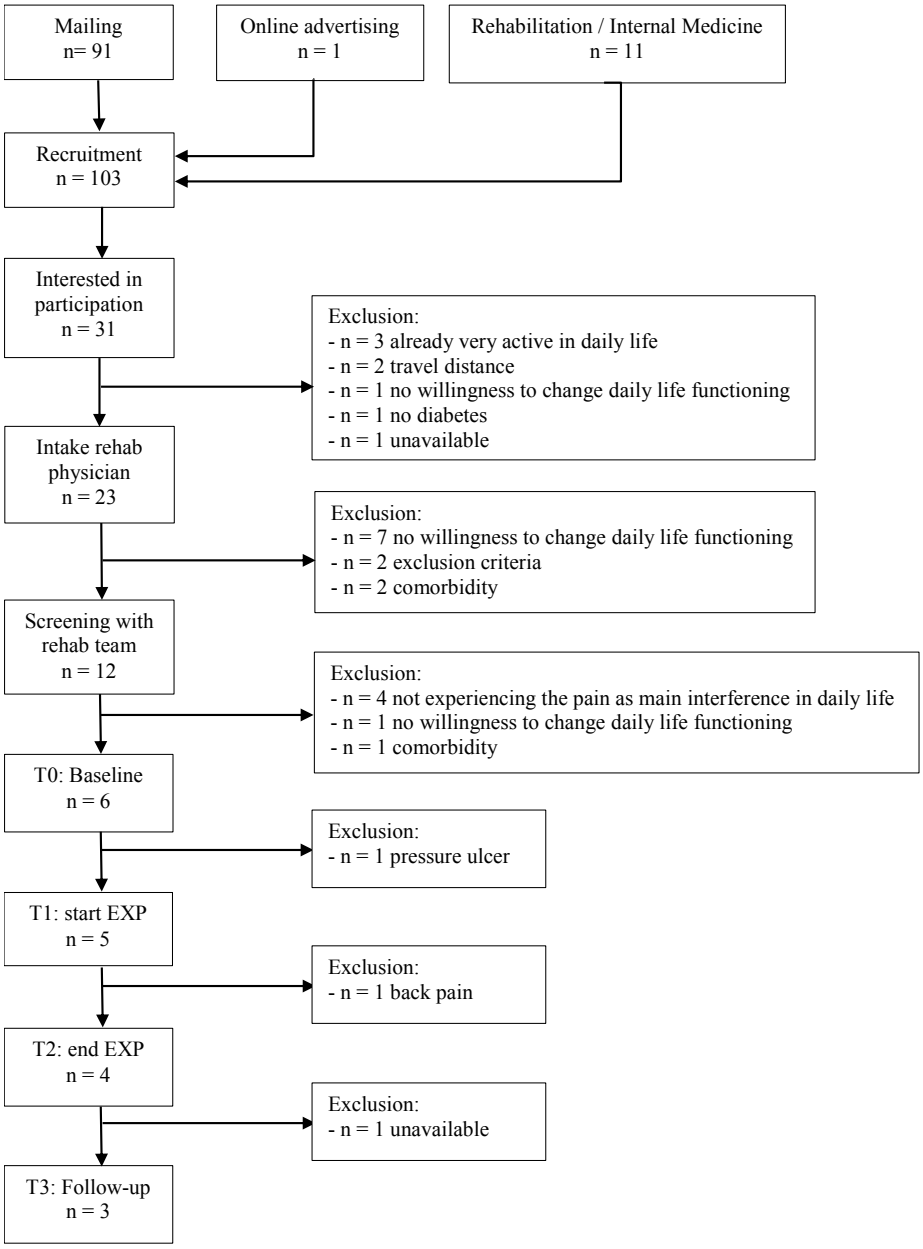

Figure 2: Flow chart of inclusion procedure. EXP: exposure in vivo; T0, T1, T2, T3, T4: timepoints T0-T4.

Results

A total of 103 potential participants were contacted to participate in this study, of which 31 were interested. After an informative phone call by our research team, 23 participants who potentially fulfilled the inclusion criteria, were invited for the intake session with the rehabilitation physician in order to determine final inclusion. Here, exclusion of 11 participants took place due to the unwillingness to change daily life functioning (n=7), exclusion criteria (n=2) and hindering comorbidity (n=2). A total of 12 participants were admitted to the interdisciplinary screening. The screening resulted in a further exclusion of 6 participants due to not experiencing pain as the main interference in daily life functioning (n=4), no willingness to change daily life functioning (n=1) and comorbidity (n=1). A full overview of the inclusion procedure and reasons for exclusion is given in Figure 2.

A total of 6 participants started the baseline period A; 5 started the treatment period B; 4 completed the treatment and a final number of 3 participants completed the follow-up period C. The baseline characteristics of the 6 participants who started the treatment are illustrated in Table 2.

In the next paragraphs, the data of participant 3 (P3), 4 (P4) and 5 (P5) is presented, as these are the only participants who completed the full treatment procedure and all measurements. Participant 1 and 2 dropped out after the intake session. Participant 6 finished the treatment, but did not return questionnaires at T1-T3. Because of the small sample size, mostly descriptive data is presented. For the diaries, p-values are given for the combined items, as described earlier.

Physical activity and QoL

For PA, PAD and QoL, all measures (PARS, PAD and Norfolk-QOL-DN) showed great variability amongst the 3 participants without clear trends. For these measures no cut-off values for a minimal clinically important change (MCIC) are available. All participants deteriorated on disability (PDI) between T0 and T1, followed by an improvement back to baseline after treatment (T2) and a deterioration at follow-up (T3). Here, MCIC (8.5-9.5) was reached in P3 at T2-T3, in P4 at T1-T2, and in P5 at T0-T1 and T1-T2 (34).

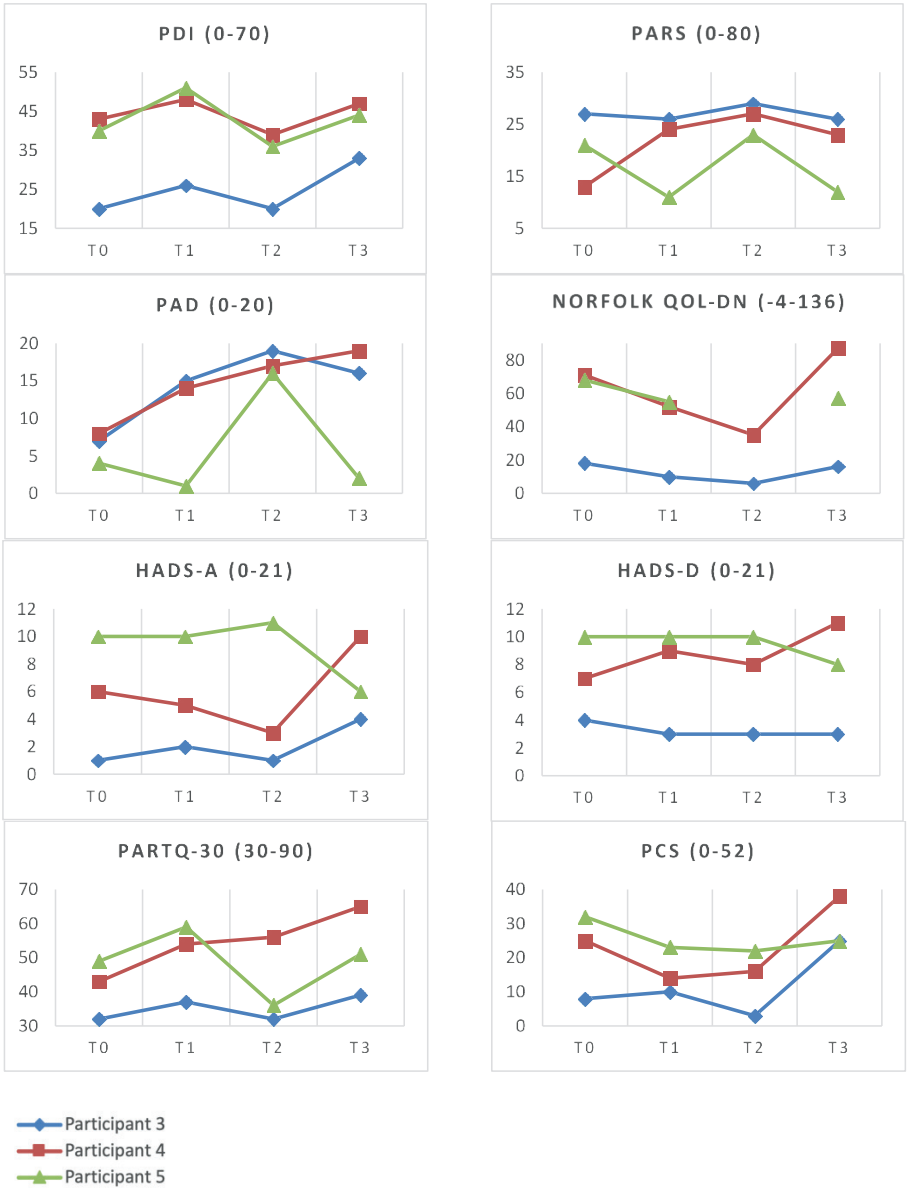

Figure 3: Results of questionnaires Participant 3, 4 and 5. PDI, Pain Disability Index; PARS, Physical Activity Rating Scale; PAD, Perceived Activity Decline; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire-Diabetic Neuropathy, HADS-A, Hospital Anxiety and Depression Scale –Anxiety Subscale; HADS-D, Hospital Anxiety and Depression Scale –Depression Subscale; PARTQ-30, Painful Diabetic Neuropathy Anxiety Rasch-Transformed Questionnaire; PCS, Pain Catastrophizing Scale.

Table 2: Baseline characteristics.

Participant no.	1	2
Age (years)	63.7	51.7
Gender	Male	Female
Duration of neuropathic pain complaints (years)	5	-
Intensity neuropathic pain (min. – max. VAS)	4-8	4-8
Current Pain intensity (VAS)	6	2
Medication use	Pregabalin	Pregabalin
Glucose (mmol/l)	4.7	13.3
Insulin (mU/l)	90	152
HbA1c (mmol/mol)	47	54
HbA1c (%)	6.5	7.1
PDI	-	28
PARS	-	14
PAD	-	6
HADS-A	11	13
HADS-D	8	9
PARTQ-30	47	64
PCS	27	50
Norfolk QOL-DN	57	64

PDI, Pain Disability Index; PARS, Physical Activity Rating Scale; PAD, Perceived Activity Decline; HADS-A, Hospital Anxiety and Depression Scale –Anxiety Subscale; HADS-D, Hospital Anxiety and Depression Scale –Depression Subscale;

Anxiety, depression and catastrophizing

P3 reported no signs of depression or anxiety on all time points (HADS-A and HADS-D <8). P4 only scored mild complaints on the HADS-A (8-10) at T3, and on the HADS-D on all time points (35). P5 scored mild complaints on HADS-A on T1-T2 that had improved on T3, while the mild complaints on HADS-D persisted on all time points. The PARTQ-30 questionnaire showed a great variability amongst all participants without clear trends. For PARTQ-30 no cut-off values/MCIC are available. The presence of catastrophizing is defined as a PCS score of >30 (36). Such score was only observed in P4 on T3 (38) and in P5 on T0 (32). Also, no clear trend could be identified throughout T0-T3. All data of the questionnaires is presented in Figure 3.

3	4	5	6	Mean (±SD)
68.1	56.3	45.6	75.4	60.1 ± 11.0
Male	Male	Male	Female	
3	5	5	5	4.6 ± 0.9
2-7	4-7	7-7	3-7	3-8
3	7	7	1	4.3 ± 2.7
None	None	Amitriptylin	Gabapentin	-
9.1	9.2	10.1	8	9.1 ± 2.8
104	280	152	107	147.5 ± 69.9
56	78	50	48	55.5 ± 11.5
7.3	9.3	6.7	6.6	7.3 ± 1.1
20	43	40	47	35.6 ± 11.2
27	13	21	11	17.2 ± 6.6
7	8	4	8	6.6 ± 1.7
1	6	10	17	10.3 ± 2.7
4	7	10	15	10.5 ± 1.4
32	43	49	67	50.3 ± 13.2
8	25	32	30	28.7 ± 13.5
18	71	68	87	60.8 ± 20.2

PARTQ-30, PCS, Pain Catastrophizing Scale; Painful Diabetic Neuropathy Anxiety Rasch-Transformed Questionnaire; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire-Diabetic Neuropathy.

Glucose regulation

For P3, the glucose and insulin levels were relatively similar in period A (T0-T1) and showed a decrease after the treatment (T2). In the follow-up period C (T3), the glucose levels increased compared to end of period B (T2), whereas the insulin levels remained stable. The HbA1c levels were stable throughout baseline and treatment, however showed an increase at the follow-up measurement. For P4, a different trend was observed. The glucose and insulin levels decreased in period A (T0-T1), and had increased after the treatment (period B, T2) and remained stable after the follow-up period C (T3). The HbA1c levels were stable across all time points. For P5, glucose, insulin levels and HbA1c levels at T1 were not available due to non-compliance. All values showed a decrease between T0 and T2 and an increase in the follow-up period C (T3). The data of the metabolic parameters is presented in Figure 4.

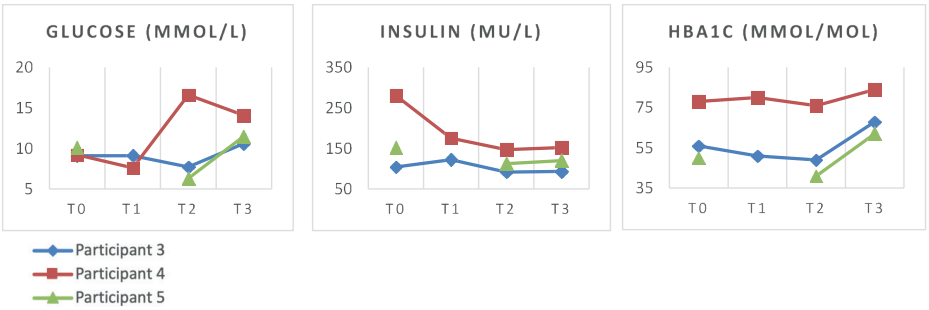

Figure 4. Results of metabolic parameters. Missing values for T1 for participant 5 on all parameters.

Diaries

Visual analyses: Overall, no clear trends could be identified for the individual items in all 3 participants. Only in P3, a decreasing trend was observed for question 1 (pain at this moment) in period A (8-4) and B (6-2), with a higher stable level in period C (4-6). P4 and P5 showed no changes in pain intensity over periods A and B, with scores fluctuating between 6-9 (P4) and stable scores around 7 (P5), respectively. P4 showed a decrease in pain in period C from 6-3, while P5 fluctuated between 5-6. The graphs for question 1 are shown in Figure 5.

For questions 2-11, large floor effects were observed in all participants, with little to no variation. For the personalized questions (questions 12, 13A and 13B), only some variation was observed in P3. Here for question 12, values between 4-8 in period A, 2-6 in period B and 2-8 in period C (PHODA-PDN; walk down the stairs) were observed. Questions 13A and 13B (COPM performance and satisfaction; walk for 1 hour) showed large variability with a decrease during treatment phase (period B) and an increase in the follow-up period (period A 0-6; period B 2-6, period C 4-8 resp.). For the other participants, no variability could be observed in periods A, B and C for the personalized questions (data not shown).

Statistical analyses of daily measures

The changes between baseline and treatment (A-B) and between baseline and follow-up (A-C) of the diary measures were not statistically significant on an individual bases, nor in the combined themes (Table 7).

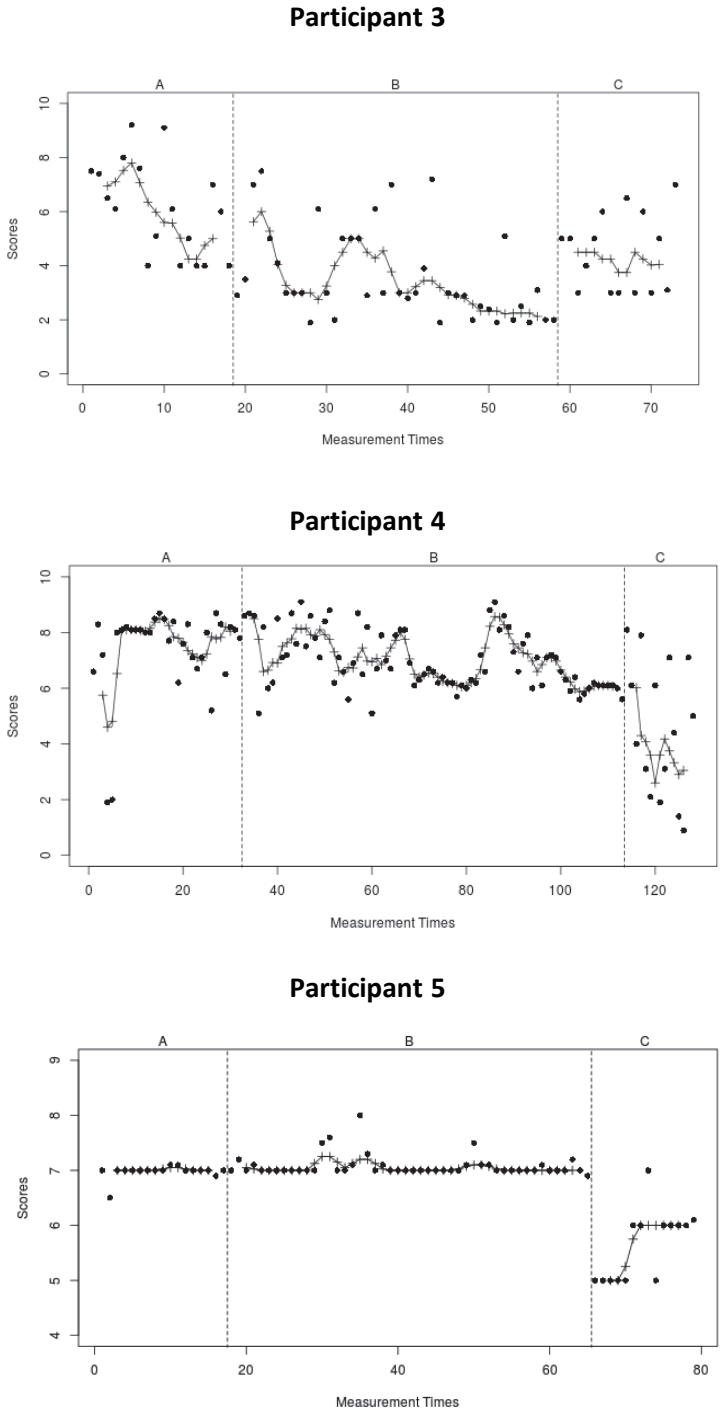

Figure 5. Visual analyses of data on item “Pain at this moment” (VAS 1-10).

	Participant 3	Participant 4	Participant 5
Pain intensity			
Baseline-EXP	0.194	0.945	0.949
Baseline-FU	0.403	0.787	0.795
FOI			
Baseline-EXP	0.222	0.252	0.154
Baseline-FU	0.333	0.252	0.179
FOH/exhaustion			
Baseline-EXP	0.056	1.000	0.333
Baseline-FU	0.056	1.000	0.372
Avoidance			
Baseline-EXP	0.181	1.000	0.128
Baseline-FU	0.528	1.000	0.154
Fear of falling			
Baseline-EXP	0.236	0.323	0.218
Baseline-FU	0.222	0.252	0.218
PHODA-PDN			
Baseline-EXP	0.972	0.472	0.987
Baseline-FU	0.556	0.354	0.564
COPM			
Baseline-EXP	0.662	0.299	0.218
Baseline-FU	0.225	0.441	0.218

Table 7: P-values for each participant on the diary data between baseline – exposure in vivo (EXP) and baseline – follow-up (FU) for the aggregated independent variables of pain intensity, fear of movement (FOI), fear of hypoglycaemia (FOH) /exhaustion, avoidance, fear of falling, Photograph-series Of Daily Activities – Painful Diabetic Neuropathy version (PHODA-PND) and Canadian Occupational Performance Measure (COPM), respectively.

Discussion

In this pilot study, we hypothesized that EXP treatment, through targeting specific fears, would lead to a reduction in the perceived harmfulness of activities, leading to higher level of PA and QoL in patients with PDN. This study describes the results of 3 participants who completed the full study procedure. The results are heterogeneous on most study outcomes such as PA, depression, fears, QoL and metabolic parameters and due to the small sample, it is difficult to determine the effectiveness of EXP treatment. Nonetheless, some valuable lessons can be learned from the findings and drop-out rates in this study.

Our study was designed around the hypothesis that the FAM is also applicable to a subgroup of patients with PDN, as was supported by the results of our previous studies in which we identified PDN related fears that could be challenged with EXP (5, 10, 16, 19, 20). However, during the study we encountered some unexpected, yet significant, differences compared to experiences of EXP in other pain conditions. These differences can be related to the aetiology and multimodality of the underlying disease (DM) in which many different healthcare providers are involved, the aetiology of the pain itself (neuropathic versus musculoskeletal) and/or the possible underlying cognitive processes in coping with the pain. In the next paragraphs we will elaborate on these topics.

DM is a common multidimensional condition and daily management is burdensome and long-term complications occur frequently. Up to 25% of patients with DM develops PDN, which itself is known for its debilitating effects on daily life, both physical and mental (3, 5). Despite the high prevalence of patients with PDN with anxiety related complaints, we experienced difficulties in recruiting candidates for the study and also observed a large number of drop-outs. The most important reason for dropping out after the screening by the physician or treatment team, was unwillingness to change daily life functioning (38%) or not experiencing pain as main interference in daily life (19%). This was unexpected, as the participants were specifically recruited based on their experienced burden of the pain. There seems to be a discrepancy in how one perceives his/her pain and disability (high burden), versus the willingness/readiness to participate in a rehabilitation programme that addresses these problems. A reason could be that the DM related comorbidity is so predominant, that patients do not allocate PDN first priority, or patients may simply not believe/realize that their perception and burden of the complaints can be altered. Also, other internal or external personal factors (e.g. personality traits, role of health care providers, spouse) may play a role in this. Based on our experiences, we believe that more research should be done on the hierarchical experienced burden of all aspects of DM and its comorbidities (*"what is the most important DM-related problem that limits your daily life functioning at this moment?*"). Ideally, this information should be paired to (qualitative)

data from DM patients on 1) which of these experienced burdens they want to learn to cope with (willingness to change), 2) what they are now lacking in order to be able to tackle these problems (readiness to change/empowerment), c) and in which way or form they feel healthcare could meet their needs in order to achieve their goals.

EXP aims to increase physical ability and QoL by establishing a new, positive association between previously expected negative irrational outcomes during a specific activity. EXP is most powerful when the discrepancy between the real-life situation and the irrational feared consequences is large (15). The difficulty with PDN related fears is that the evaluation of a fear is not always irrational and some level of concern can be considered appropriate and adaptive; e.g. being afraid of falling when having balance impairments, or being (hyper) vigilant to develop PU's when having little to no sensation in the feet and being told to check for PU's etc. (5, 16). At this time point, no tool is available that can help clinicians to identify the difference between a rational and irrational fear. We also believe that EXP can only be effective when the fears are the foremost reason for the experienced disability in daily life. If there are other reasons such as significantly debilitating (co-)morbidity, EXP alone may not succeed to improve physical functioning. In our study, there were five drop-outs due to comorbidity (back pain, cardiopulmonary problems, pressure ulcer).

Furthermore, it is known that DM is a complex condition that requires attention to many more aspects of one's health than pain alone. The patient is encountering many health care providers over short periods of time and almost all of them have a mainly somatic (*bio*) approach to the various DM related issues. There is a continuous focus on glucose regulation, skin care, dietary restrictions, and prevention/treatment of hypertension and/or dyslipidaemia. When multiple health care providers are involved, this could result in non-compatible or even contradicting advices regarding PA, glucose management and/or the management of skin problems. EXP can only be powerful and successful at diminishing pain related fears, if the patient can be convinced that PA is not harmful. Adequate medical counselling about individual possibilities regarding PA is essential to create this awareness. As soon as other healthcare providers, spouses, friends or relatives advise adversely, uncertainty may (re-)occur and the effect of EXP can be diminished. This mechanism could be an explanation for the discrepancies in improved PA levels combined with higher PAD scores during treatment, and the worsening of almost all outcome variables in in the follow-up period in P4.

Next, there seems to be a difference in how patients cope with chronic musculoskeletal pain compared to neuropathic pain. Studies in various chronic musculoskeletal pain conditions have shown that factors such as psychological flexibility (PF) can play an important role in relation to well-being and daily-functioning (37, 38). In PDN however, only low correlations between PF and functional impairment, depression severity and

depression impact were seen, whereas relatively higher correlations between the pain itself and functional impairment were found(39). Pain severity generally appeared to play a more important role in relation to daily functioning in PDN, than psychological factors did (39). These findings confirm our previous work in which pain severity showed to be the main predictor for disability and QoL, rather than various fears (5), and could also be an explanation for the discrepancies found in this study regarding how one perceives the pain and its disability, versus the willingness/readiness to do something about it. Another study demonstrated that, while the neuropathic pain in PDN did contribute to depression, unsteadiness was the symptom with the strongest, cumulative effect on depression. The patients' perception of their unsteadiness appeared to be an adequate indicator of the actual balance impairment (14). Future interventions that aim to improve PA in PDN, should take balance impairments and the patients perception of their unsteadiness into account, in addition to the above mentioned bio-psychological factors.

An issue of this study that should be addressed, is the fact that the PHODA-PDN is different from the PHODA. The original PHODA is designed to identify activities that evoke fear of (additional) injury. In EXP, these activities are challenged and the fears will be diminished when the patient experiences that he/she can perform the activity without the occurrence of the feared consequence. However, in our previous qualitative studies, we discovered that the most frequent PDN related fears (fear of falling, fear of hypoglycaemia etc.) were not associated with specific activities. To overcome this issue, we altered the procedure by using the PHODA-PDN in 2 phases (step 1: identification of type of fear; step 2: pairing this fear to a specific situation or activity). This adaptation of the PHODA may have affected the effectiveness of EXP, as EXP was originally designed to challenge feared activities, rather than fears itself. Therefore, more research on the PHODA-PDN is needed. Another limitation was the way patients were recruited, as most participants were approached by their own physician and did not apply for the study themselves.

In summary, the effectiveness of EXP for restoring QoL and physical wellbeing in patients with PDN was not confirmed by this study. Despite the overlap of concepts within the FAM that were well-established in a variety of other chronic pain conditions, this study revealed that there seem to be some other significant factors involved in patients with PDN. Given the lessons learned, we believe that EXP may only have a potential added value for patients with PDN if; a) daily life functioning is mostly impaired by PDN, and not by other (co-) morbidity, b) the PDN related fears (feared consequences) that cause these impairments are exaggerated and irrational, c) specific activities can be identified that evoke the PDN related fears and d) spouses and other healthcare providers are involved in the treatment and e) there is a willingness to participate in a rehabilitation programme that addresses PDN related fears in daily life situations. Further research is needed to confirm this.

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Chapter 9

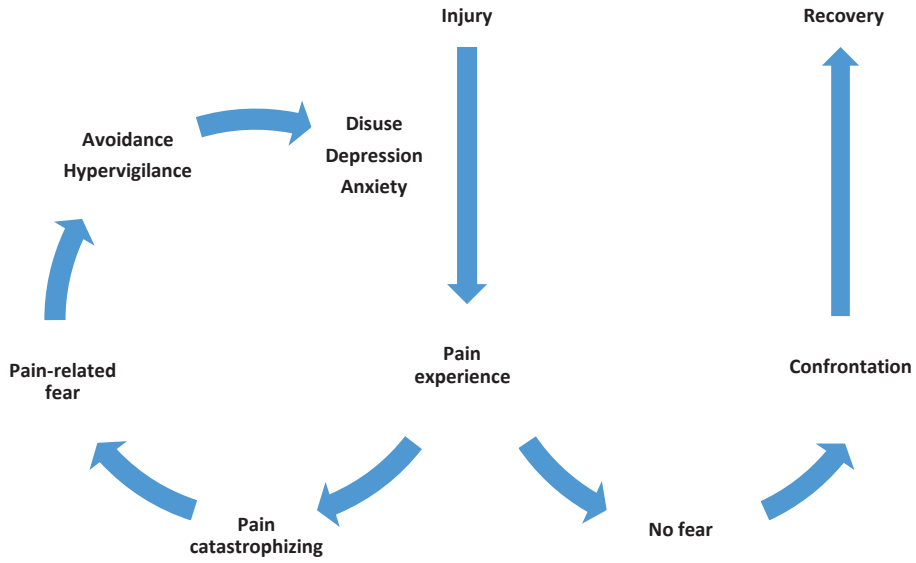
General Discussion

General Discussion

This chapter presents a reflection on our main findings and discussion on potential implications for clinical practice, methodological considerations and directions for future research.

Fear avoidance model in patients with PDN

In Part I we hypothesized that the fear avoidance model (FAM (1)) is applicable to patients with PDN. Findings of the first three studies confirmed the great burden of PDN on daily functioning. The consequences of PDN showed to be physical (weakness, pain, physical restrictions), psychological (feelings of loss, feelings of depression, anger, sadness), and social (social withdrawal, isolation, work limitations, lower career opportunities). Patients reported several fears that were associated with different types of avoidance behaviour. Also, the association between pain catastrophizing with lower quality of life (QoL) and a perceived decline in physical activity (rather than an actual decline in physical activity) was established.



FAM (Vlaeyen 2000)

Based on these results, we designed a new exposure in vivo treatment (EXP) that was adapted to the needs and risks of patients with PDN, including PDN specific screening tools, such as the Painful Diabetic Neuropathy Anxiety Rasch-Transformed Questionnaire, PART-Q30©(2), and Photograph-series of Daily Activities, PDN version (PHODA-PDN) (3-7) (Part II).

The EXP intervention was designed around the hypothesis that the FAM is applicable to a subgroup of patients with PDN who report diabetes mellitus (DM) or pain related fear. However, during the study we encountered some unexpected, yet significant, differences compared to experiences of EXP in other pain conditions. These differences seemed to be related to the assessment of fear in PDN, the possible underlying cognitive processes in coping with the pain and the aetiology and multimodality of the underlying disease (DM). This will be discussed more thoroughly in the next paragraphs.

Assessment of PDN related fear (methodological considerations)

PHODA-PDN

For our study, the PHODA-PDN was adapted from the original PHODA. The PHODA is a tool that identifies activities that evoke fear of (additional) injury (7). In EXP, these activities are challenged and fears will be diminished when the patient experiences that he/she can perform the activity without the occurrence of the feared consequence dysfunctional cognitions are challenged and rejected (8, 9). In our qualitative studies, we discovered that the most frequent PDN related fears (fear of falling, fear of hypoglycaemia etc.) were not associated with specific activities. To overcome this issue, we altered the procedure by using the PHODA-PDN in 2 phases (step 1: identification of type of fear; step 2: pairing this fear to a specific situation or activity). It is not clear whether this adaptation of the PHODA may have affected the effectiveness of EXP, as EXP was originally designed to challenge feared activities, rather than fears itself. More research on the validity of the PHODA-PDN and its applicability in clinical practice is needed.

PART-Q30©

In our study, data obtained from seven generally applied fear scales were stacked (n=88 items) and integrated in Rasch analyses (pre-PART-Q88) to create the 30-item PDN overall Anxiety Questionnaire (PART-Q30©) (10). The development of the questionnaire is an important advance for clinical practice, as it enables the clinician to identify the impact of specific disabling fears for the individual patients based on a relatively simple procedure existing of 30 items to evaluate on an ordinal scale. The actual applicability and clinimetric properties of the PART-Q30© in a larger cohort of patients with PDN still needs to be determined. An important step in doing so, is to examine the validity and reliability of the items' weight and patients' ranking using the new three response options. Future longitudinal studies are needed to investigate the constructed measures of the PART-Q30© in patients with PDN.

PDN related fears; adaptive or maladaptive?

Within the FAM, the main assumption is that pain catastrophizing and fear fuel the vicious circle leading to avoidance, disuse and depression (1). The question arises, whether fears are always dysfunctional in patients who suffer from pain following an underlying medical

disease (secondary chronic pain), such as PDN. In other words, can a certain level of consciousness or fear be helpful and protective in dealing with the risks in diabetes and the prevention of complications? And from this, should all fears be challenged and/or treated? And if yes, to what extent and in what way?

In the case of PDN, being afraid of developing pressure ulcers, falls, or experiencing a period hypoglycaemia during physical activity, could be considered an adequate and adaptive coping mechanism, as having no fear at all will result in increased risks of developing these complications. On the other hand, research has also shown that too much fear of falling can lead to dysfunctional gait with an even higher risk of falling (11, 12), while low, compared to high levels of fear of falling was protective for falling, and that this was even irrespective of the presence of balance impairments (11). In the same way, the evaluation of fear of hypoglycaemia has shown that it is not always irrational and that some level of concern is considered appropriate and adaptive (13).

So, when can fear be considered irrational or exaggerated in persons with PDN? Should there be a defined cut-off point at which a fear itself is considered to lead to additional increased limitations in daily life functioning? On the other hand, can there be individual differences in levels of fear and/or the way in which one copes with his/her complaints, possibly related to the stage or severity of the underlying disease and complications? In other words, can the same level of fear be protective and adaptive for one individual, while it may be hindering in another person? On the contrary, can it be harmful for a patient when there is no fear at all regarding diabetes related risks? Up to now, there is no tool available that can determine the difference between functional and dysfunctional (exaggerated) fear in patients with PDN (or other forms of secondary chronic pain), nor to detect individual differences in the significance of these fears with regard to daily life functioning and QoL. Further elaboration on this topic is needed.

A diagnostic tool should aim to unravel individual differences that can help the clinician to stratify which patients could benefit from which treatment. This tool however, can merely give an indication whether fear is dysfunctional, which can then serve as a starting-point for the interdisciplinary assessment, in which structured interviews create the basis to a patient centred problem analysis and shared decision-making processes.

It should be mentioned that a thorough elaboration of an individuals' pain problem is an interdisciplinary effort, that requires the skills, experience and craftsmanship of all clinicians of the rehabilitation team (physiatrist, physiotherapist, occupational therapist, psychologist), in order to unravel all biopsychosocial factors related to disability in PDN. The interpretation whether fear is dysfunctional in patients with secondary chronic pain

is also dependent on the individual medical (co)morbidities, which makes it essential that a physician (usually a physiatrist) trained in de the underlying disease *and* chronic pain problems is involved in the treatment of these patients.

Coping with PDN

Feeling no need to change and having no request for help; less willingness or ability to change daily life behaviour?

In our intervention study (EXP), the most important reason for dropping out after the screening by the physician or treatment team, was that participants felt no need to change daily life functioning or that they did not experience pain as the main interference in daily life. In other words, there was no request for help for dealing with the pain. This was unexpected, as the participants were specifically recruited based on their experienced burden of the pain and our thorough analyses of the pain problem showed that many aspects of the FAM were present in these patients. However, when they were offered a treatment that could help them challenge the fears and achieve a higher level of functioning despite the pain, the majority declined. Therefore, there seemed to be a discrepancy in how one perceives his/her pain and disability (high burden), versus the willingness/readiness to participate in a rehabilitation programme that aims to improve daily life functioning. It is not clear what caused this discrepancy. One possible explanation could be the fact that up to now, it is difficult to determine whether a present fear is helpful or dysfunctional. Another explanation could be that patients may simply not believe or realize that their perception of the complaints and the level of activity in daily life can be improved. This could be even more true when patients already had an inactive lifestyle before PDN occurred and/or when cognitive impairments are present. In this context, it would be of interest to investigate the treatment credibility and expectancy in patients with PDN, with and without cognitive impairments (14).

Our EXP treatment mainly focussed on pain and disability, and to lesser extent on DM as a whole. To determine potential help requests and treatment targets, more research should be done on the hierarchical contribution of all aspects of DM and its comorbidities on the experienced burden; "*What is the most important DM-related problem that limits your daily life functioning at this moment?*" Ideally, this information should be paired to (qualitative) data from DM patients on 1) which of these experienced burdens they want to learn to cope with (is there a request for help and willingness to change?), 2) what they are now lacking in order to be able to tackle these problems (ability and readiness to change/empowerment), and 3) and in which way or form they feel healthcare could meet their needs in order to achieve their goals.

Self-efficacy and psychological flexibility

Successful management of chronic illnesses like diabetes and rheumatoid arthritis relies on the individual being able to carry out tasks designed to control symptoms and avoid acute, as well as chronic, complications. Successful management of chronic illnesses like diabetes and rheumatoid arthritis relies on the individual being able to carry out tasks designed to control symptoms and avoid acute, as well as chronic, complications. Successful management of chronic illnesses like dia betes and rheumatoid arthritis relies on the individual being able to carry out tasks designed to control symptoms and avoid acute, as well as chronic, complications. Successful management of chronic illnesses like diabetes and rheumatoid arthritis relies on the individual being able to carry out tasks designed to control symptoms and avoid acute, as well as chronic, complications. Successful management of chronic illnesses like DM relies on the individuals' ability to carry out tasks designed to control symptoms and avoid acute, as well as chronic complications (15). Self-efficacy is defined as the perceived confidence in performing behaviours and overcoming barriers related to e.g., pain, and it represents an important mediator in pain-related disability (16). In diabetes research, numerous studies have shown that higher self- efficacy is associated with better diabetes self-management behaviours such as glycaemic control and medication adherence (17-21). Self-efficacy has also shown to play a mediating role in the association between diabetes distress and self-management behaviours (22). Also, self-efficacy is a common facilitator of physical activity. In adults with diabetes, cross-sectional studies support the association between self-efficacy for physical activity and higher physical activity (23, 24). The influence of diabetes management self-efficacy (i.e., confidence in one's ability to engage in behaviours such as managing diet, checking blood glucose and physical activity) on engagement in physical activity is less clear (25). In pain research, self-efficacy has repeatedly shown to be important in explaining coping styles as well as linking pain to decreased functioning and psychological comorbidity (16, 26). There is no literature regarding the role of self-efficacy in PDN, and it was also not included in our studies. Further research is needed on self-efficacy in PDN, as PDN is a disease that requires self-management skills regarding DM, while also having to cope with chronic neuropathic pain.

Psychological flexibility is defined as the ability to contact the present moment more fully as a conscious human being, and to change or persist in behaviour that serves valued ends (27). On the contrary, psychological inflexibility is defined as the inability to act effectively in accordance with a valued life in the presence of unpleasant thoughts, emotions or bodily symptoms (28). Studies in various chronic musculoskeletal pain conditions have shown that psychological flexibility can play an important role in relation to well-being and daily life functioning (29, 30). On the other hand, psychological inflexibility has shown to strongly contribute to disability (31). Self-efficacy and psychological flexibility appear

to be somewhat related, in the way that both constructs involve the perceived ability to perform relevant activities in the presence of interfering private experiences such as pain or distress (31).

There is only scarce literature on psychological flexibility in patients with PDN. Only one study has confirmed the presence of low psychological flexibility in patients with PDN (32). Interestingly however, only low positive correlations between psychological flexibility and functional impairment, depression severity and depression impact were found, while the correlations between the pain itself and functional impairment were relatively higher (32). Our research has also shown that pain severity was the main predictor for disability and QoL, rather than various fears (4). These findings could indicate that pain severity in PDN seems to be the main driver of limitations in daily life, rather than the known psychological aspects from the FAM such as depression, fear, pain catastrophizing and avoidance behaviour (4, 32). We can ask ourselves; are there differences in the way neuropathic pain is experienced in PDN, compared to the way pain is experienced in chronic musculoskeletal pain? In other words; can neuropathic pain in PDN be so predominant, unexpected and overwhelming that psychological processes and coping strategies become less relevant in understanding and treating the consequences of the pain?

Neuropathic pain: expect the unexpected

Research on the differences in functioning and responses to pain between people with neuropathic (post-herpetic neuralgia) and nociceptive pain (low back pain) has suggested that the differences between the two groups were not on the major variables of pain, mood, cognition and physical function, but on the factors that increase pain, people's responses to pain, their beliefs about diagnosis and the cause of pain and the problems they reported as a result of experiencing pain (33). The regular pain treatment was being considered less appropriate for patients with neuropathic pain because these patients associated increases in pain with touch or air movement (allodynia), rather than physical activity (leading to less avoidance compared to patients with low back pain) and because they experienced paroxysmal pain (33). The paroxysmal nature of neuropathic pain could explain why patients with neuropathic pain struggle with pacing daily life activities, as pain grabs attention and interferes with cognitive processes and activity (34). This grabbing of attention may be more urgent and unexpected in paroxysmal neuropathic pain, giving people no other option but to stop activities.

More research should be done on the responses to neuropathic pain and pain increase with regards to physical activity, QoL and daily life functioning in patients with PDN. Also, the role of psychological variables such as psychological flexibility and self-efficacy should be investigated with regard to the paroxysmal nature of neuropathic pain. From

this, rehabilitation treatments for neuropathic pain conditions could include training of patients on how to deal with the fact that neuropathic pain can increase irrespective of daily life activities and/or physical activity. In other words; how to expect the unexpected and deal with it?

Cognitive impairments

DM is associated with decrements of attention and executive functioning, learning and memory deficits, neural slowing (mental and motor), increased cortical atrophy, microstructural abnormalities in white matter tracts and changes in concentrations of brain neuro-metabolites (35). The extent of cognitive dysfunction has shown to be associated most strongly with long disease duration and poor metabolic control (36, 37). Neural slowing on recordings of sensory-evoked potentials, has shown to occur soon after diagnosis and is significantly worse in patients with overt peripheral neuropathy (38, 39). Diminished central nervous system responses have been observed during motor and motor imagery tasks in DM patients with peripheral neuropathy, compared with DM patients without neuropathy (40). Also, verbal, visuospatial, and multitasking measures of executive function can be impaired in adults with peripheral diabetic neuropathy (41). The association between peripheral neuropathy and cognitive impairments has also been established in patients with type I DM (42), and patients with diabetic foot ulcers (43).

Depression, anxiety and mild cognitive impairments in DM seem to be interrelated (44). Especially in elderly patients with DM there is high prevalence of combined depressive symptoms and cognitive impairment, which has shown to be associated with worse self-care behaviours, particularly in the areas of diet and exercise (45).

There is no literature on whether and how cognitive impairments play a role in coping with chronic pain. It seems apparent to integrate factors of cognitive impairment in future research regarding daily life functioning in patients with PDN, as it may affect willingness and ability to change, as well as adherence to treatment (46).

Balance impairments

It is known that the ability to maintain balance is a complex skill that requires the integration of multiple sensorimotor and cognitive processes. Emerging evidence suggests that diabetes-related subtle declines in sensory functions (somatosensory, visual and vestibular), metabolic muscle function and executive functions may also contribute to increased risk of falls in older adults with type 2 DM (47). Sensory deficits, muscle weakness and atrophy can all have implications for motor controlled physical activity (48-50), as it can impact the patient's ability to detect and respond appropriately to ground contact and balance disturbances during walking and other everyday ambulatory activities (25).

Also, cognitive impairments in patients with DM have shown to exacerbate the risk of falls in people with peripheral neuropathy (51). The neuropathic symptoms of pain, combined with unsteadiness and reduced feeling in the feet symptoms, have been associated with depressive symptoms (52). Research has shown that the patients' own perception of their unsteadiness appeared to be an adequate indicator of the actual balance impairment (52). Our studies did not include indices of balance impairment or subjective unsteadiness. Future research on therapeutic interventions that aim to improve physical activity in PDN, should take these factors into account as they should be treated and/or controlled for.

Diabetes and Chronic Pain; bridging the gap

Research and treatment of chronic pain are generally focussed on patients with chronic pain syndromes who have no additional medical risks, hereby concentrating mainly on psychological factors that influence pain and daily life behaviours. Treatment of secondary chronic pain (pain secondary do a medical underlying disease) is slowly emerging and faces some significant challenges as the medical aspects cannot be ignored (53). On the contrary, the approach to treatment and counselling of DM is often very medically oriented, with a lesser focus on psychological aspects. For PDN, it is time to bridge the gap.

Biopsychosocial approach and personalized medicine

The management of PDN asks for an integrated and personalized approach, in which there should be a shift from focussing solely on pain and pain-related factors, towards a focus on DM including *all* of its comorbid problems, of which neuropathic pain is just one. Next, in order to achieve a true holistic perspective on the daily consequences and burden that are caused by PDN, the disease DM – and not PDN only – needs to be analysed from a biopsychosocial perspective. This requires a trained interdisciplinary team consisting of at least a physician (e.g., physiatrist), physiotherapist and/or occupational therapist and a behavioural therapist/ psychologist. Although the biopsychosocial concept has been well-established in the field of rehabilitation medicine and chronic pain, there are no screening tools or treatments available for patients with PDN that address all three domains (54).

Assessment of the *bio* component should not only focus on neuropathic pain and its treatment, but should encompass all biomedical aspects concerning diabetes (sensory deficits, pressure ulcers, retinopathy, nephropathy, occurrence of hypo-/hyperglycaemic episodes, other hindering comorbid cardiovascular problems, medication etc.) and pain (type of pain, previous pharmacological and interventional treatments such as transcutaneous electrical stimulation (55) or epidural spinal electrical stimulation (56, 57) etc.). A thorough medical history should be taken, together with a physical examination. Glycaemic control should be optimised and controlled by the general

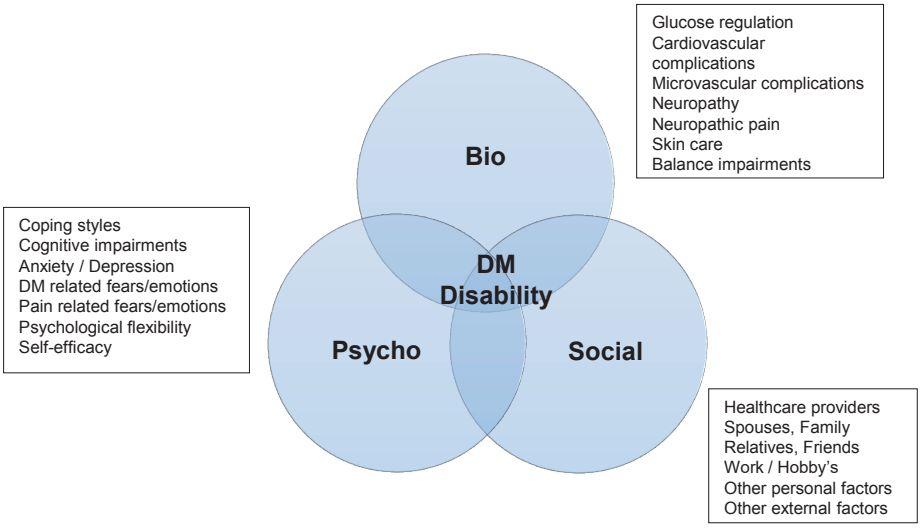
practitioner or a specialist in internal medicine. Peripheral polyneuropathy should be checked and classified based on a standardised clinical neurological examination (CNE) (58). The CNE score is determined by examining the Achilles tendon reflex, vibration awareness, sharp–blunt discrimination, touch sense, position sense at the hallux and manual assessment of extensor muscle strength of the hallux and flexor muscle strength of the foot in which all items are scored as either normal, impaired or absent (0–2 points). In addition, the scoring of light touch sense is related to the anatomical level below which it is impaired (toe, mid-foot, ankle, mid-calf and knee) (0–5 points). The diagnoses of peripheral neuropathy can be confirmed by electromyography (EMG), although research has shown that EMG and CNE scores resulted in the same diagnosis of distal polyneuropathy in DM patients (59-61). All patients should be screened for pressure ulcers on their feet and on whether they are wearing adequate (orthopaedic) shoes. The physiotherapist assesses balance impairments and walking abilities, combined with an observation of the specific body movements during various activities. During this observation special attention should be paid to behavioural responses to specific activities (e.g., fear or avoidance).

The *psycho* component should focus on all psychological issues that are known to be associated with DM, its management and all its potential complications, including pain; e.g., general depression and anxiety, coping styles, personality traits, DM related fears, pain related fears, cognitive impairments, psychological flexibility and self-efficacy. The 30-item PDN overall Anxiety Questionnaire (PART-Q30©) can be used to identify PDN related fears (10). The aim is to complete a behavioural, cognitive and psycho-physiological analysis of the problems associated with DM and PDN. This personalized assessment also includes information about any DM or PDN-related antecedents (situational or internal, episodes of hypoglycaemia, recurrent falls etc.) and its direct and indirect consequences. The psychological analyses should also include other areas of life stress, as they might increase arousal levels and indirectly also fuel diabetes distress.

Within the *social* component, the team should make an overview of all persons that influence the daily lives of patients, including all healthcare providers that are involved in the treatment of these patients. When a patient is encountering many health care providers over short periods of time, it is essential that all of them speak the same language regarding the individual physical capabilities. Non-compatible or even contradicting advices regarding physical activity, glucose management and/or the management of skin problems can result in feelings of uncertainty and non-adherence to medical treatments and advice. Any physical intervention that aims to improve daily life functioning, can only be powerful and successful when the patient is convinced that the specific activity is not harmful. Adequate medical counselling about individual possibilities regarding physical

activity is essential to create this awareness. Also, communication and collaboration between treatment team members and other involved health care-providers is crucial to create a common approach to DM and pain management and one should be active despite pain.

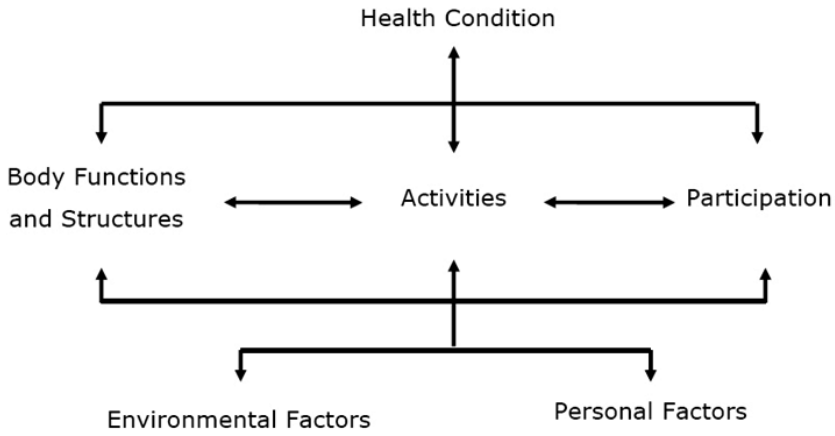
The assessment should also include the role of spouses and other significant family members and/or friends. It is known that DM care needs effective self-management education and support for both patients and family members. Overall, family support has shown to have a positive impact on healthy diet, increased perceived support, higher self-efficacy, improved psychological well-being and better glycaemic control (62). Also in the field of chronic pain management, studies have shown that relationship variables, such as marital satisfaction and spousal support, are associated with pain severity, physical disability, and depression in individuals with chronic pain (63). For this reason, spouses and other significant family members or friends should be educated and engaged in the treatment, so that they can learn to recognize and help patients cope actively with their pain and/or underlying disease (64). An example of a biopsychosocial analyses is given in the figure below.



Biopsychosocial model for DM related disability

ICF Model

Rehabilitation medicine aims to enable people with health conditions experiencing disability to achieve and maintain optimal functioning in interaction with the environment. This is achieved by applying and integrating approaches to optimize a person's capacity, approaches which build on and strengthen the resources of the person, which provide a facilitating environment, and which develop performance in the interaction with the environment (65). From the rehabilitation perspective, patients' functioning and health are associated with, but not merely a consequence of, a condition or disease (66). Furthermore, functioning and health are not only seen in association with a condition but also in association with personal and environmental factors (66). The WHO International Classification of Functioning (ICF) offers a method to systematically describe human functioning from a biological, individual and social perspective.



ICF model

The ICF model can be used as a framework for measuring health and disability at both individual and population levels (67). The ICF model can also be used to establish a personalized holistic analysis of the DM and PDN related disability, which then facilitates the development of a personalized rehabilitation treatment plan, as is shown in the figure below.

Me and my Health			
This is me	My physical & mental condition	What I (can) do	What I want
			
Personal factors Environmental factors	Health condition Body function & structures	Activities Participation	Request for help Willingness to change Treatment goals

Example of personalized patient centred overview of DM disability based on ICF domains

Acceptance and commitment therapy (ACT): the way to go?

Acceptance and commitment therapy (ACT) is a third-wave cognitive behavioural therapy (CBT) that focusses on identifying thoughts, feelings and behaviours that may drive and maintain presenting psychological difficulties (68-70). From an ACT perspective, people's difficulties to persist with, or change, behaviours in order to serve long term values (i.e., psychological inflexibility), strongly contribute to disability. In short, ACT includes a combination of acceptance and mindfulness methods along with activation and behaviour change methods to support individuals to develop psychological flexibility; an individual's ability to respond to changing demands and alterations in emotions (70-72). Within the theory of ACT, psychological flexibility (PF) includes six processes: acceptance, cognitive defusion, awareness of the present moment, self-as-context, committed action, and values-based actions (27). Strategies are focused on learning to live effectively and alongside an unpleasant experience, such as pain, through identifying value-led behaviour change and mindful approaches (70). Therefore, ACT is explicitly not aimed at reducing pain or distress, or at changing the frequency or content of thoughts. Instead, it promotes greater acceptance of negative private experiences in order to increase psychological flexibility (31).

Multidisciplinary treatment based on ACT has shown to be effective in reducing the burden of chronic pain in various chronic pain conditions (73, 74). From this, ACT may also be a good fit to address the multiple impacts of pain and the range of physical and psychosocial comorbidities that people with PDN experience (32). A recent Iranian study in 25 patients with PDN has shown that ACT can be beneficial to improve pain acceptance, pain perception, depression severity and overall sleep quality (75, 76). Another study that investigated an online ACT treatment for patients with PDN, showed clinically meaningful effects on pain intensity and pain distress, depressive symptoms, functional impairment, cognitive fusion, committed action, self-as-context, and pain acceptance (32). It should be noted that this study had a high drop-out rate; only 12 out of 30 participants completed

the study, and it was therefore considered non-feasible. More research should be done on the effects of ACT on improving daily life functioning in patients with PDN. It should also be noted that it is unclear if and how cognitive impairments affected the effectiveness of ACT for patients with PDN.

It seems plausible that ACT may also be useful to help patients cope with DM in general. In adults with type 2 DM, only two studies have examined the effectiveness of ACT, relative to a control group, for improving diabetes self-management behaviours and glycaemic control. In the first study, DM patients who had received ACT were more likely to use ACT-based coping strategies, reported better diabetes self-care (including exercise, diet, and glucose monitoring), and showed a greater mean decrease in glycated haemoglobin (HbA1c) (77). The second study, showed greater improvements in HbA1c and diabetes self-care activities (including exercise, diet, glucose monitoring, medication adherence, cigarette smoking, and foot care) relative to those in the control condition (78). Both studies however, did not address pain. More research is needed to develop treatment modalities that primarily capture *all* DM and PDN related factors that cause disability and diminished QoL, and from which a personalized value-led selection of treatment goals can be made.

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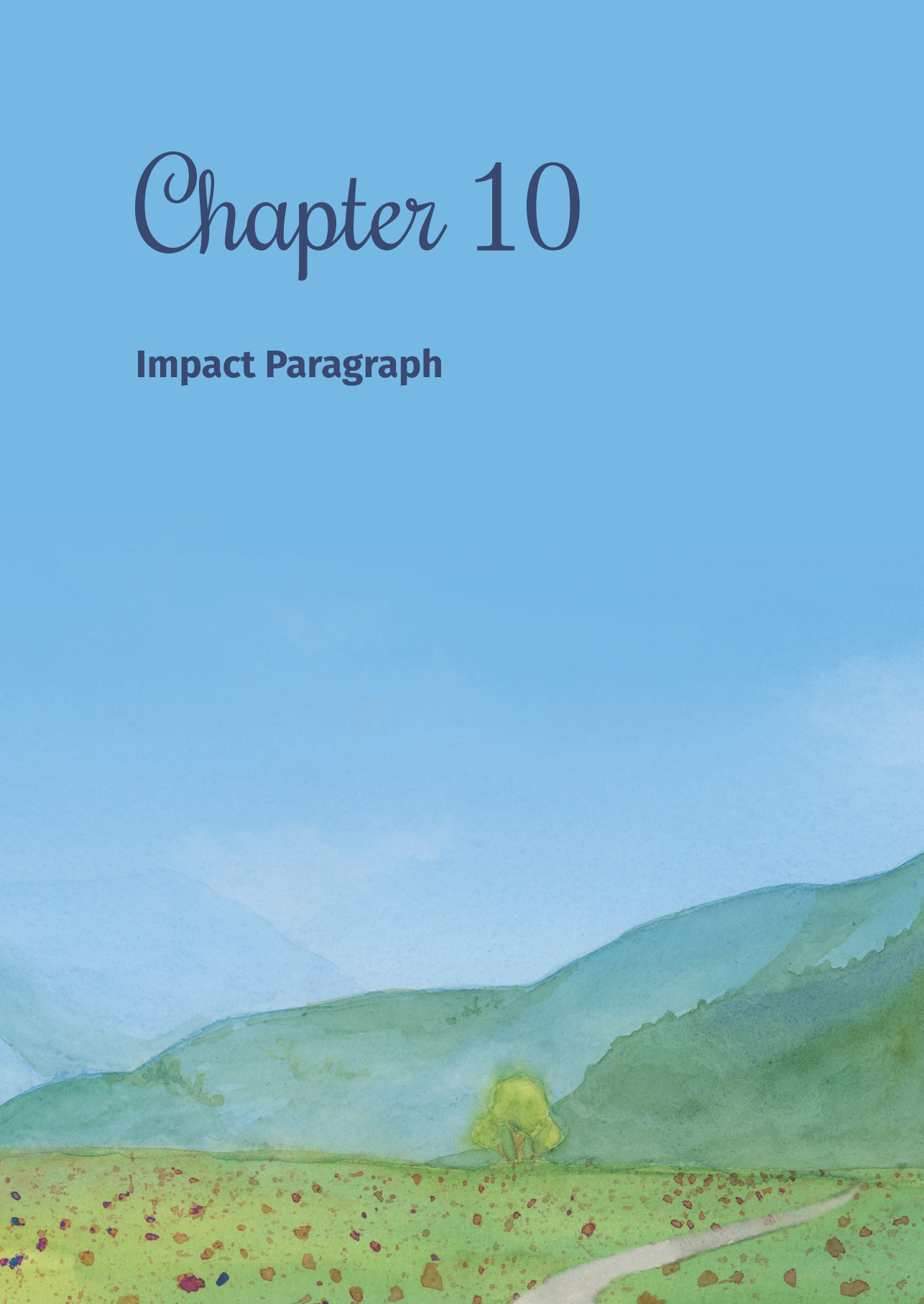
Chapter 10

Impact Paragraph



Impact Paragraph

Besides a contribution to scientific knowledge, the results of this dissertation can have a broader societal impact. This impact paragraph aims to describe the societal impact of the scientific results on the application and implementation in healthcare, to whom our findings are relevant, and it proposes addresses activities for knowledge transfer.

Relevance

DM and its complications, is a burdensome disease that has a huge impact on daily lives and on society. In 2016, there were an estimated 1.1 million DM patients in the Netherlands and the estimated total economic burden of DM was € 6.79 billion (1). On top of this, approximately 25-50% of the patients with DM experiences neuropathic pain (2-4), leading to even more disability and therefore costs for society (5, 6).

When treatment of the underlying disease fails, it is important that healthcare providers help the patient to deal with his/her complaints, to promote physical fitness and to stimulate participation in daily life activities in order to improve QoL, to prevent further complications, and from this, to minimise further societal and healthcare costs. This is also acknowledged by the Dutch Association of Medical Specialists (FMS), who published a vision document for 2025 in which four main priorities are formulated: 1) optimising QoL, 2) patient centred health care, 3) disease prevention & functional maintenance of disease, and,4) self-management, e-health, wearables & big data (7).

This dissertation highlights the high daily life burden for patients with PDN. In line with the modern approach to complex diseases as defined by the FMS, it focusses on improving QoL and daily life functioning in patients with PDN, hereby presenting a holistic personalized interdisciplinary biopsychosocial analyses of PDN-related problems and providing directions for future treatments that aim to help patients cope with PDN-related complaints.

Network medicine

DM is a common multidimensional condition and daily management is burdensome and long-term complications occur frequently. It is known that adequate management of DM and prevention of complications requires attention to many more aspects of one's health than glucose regulation alone. In DM, the patient is encountering many health care providers over short periods of time and there is a continuous focus on glucose regulation, skin care, dietary restrictions, and prevention/treatment of hypertension and/or dyslipidaemia. When PDN is also present, pain specialists and other medical specialist or therapists may get involved. In order to prevent non-compatible or even contradicting advices regarding DM management, pain and being physically active despite pain, it is

essential that healthcare providers work together and speak the same language. For example, all healthcare providers should be aware of the patient's medical concerns regarding DM and PDN. At the same time, these risks should not be magnified and/or exaggerated as this can potentially induce fear of avoidance behaviour. From this point of view, all healthcare providers should also know the actual physical capabilities of the patient, so that good self-care and physical activity can be promoted within the boundaries of what is possible and safe for this individual. This dissertation adds knowledge about how to approach PDN from an interdisciplinary perspective.

The discussion section *Diabetes and Chronic Pain; bridging the gap* provides the outlines of an ICF-based biopsychosocial framework that can be used for the problem analysis and treatment of patients with PDN. Within the field of rehabilitation medicine, this way of thinking and working is already quite common; the physiatrist plays an important role within the rehabilitation team, coordinating the medical and paramedical care around one patient, and seeking help from other healthcare providers where needed. However, in order to achieve true holistic patient centred care, it is important to implement and integrate a biopsychosocial way of thinking in the daily working routines of *all* health care providers. For this, network medicine is key; healthcare providers need to start reaching out to one another, within and beyond the walls of healthcare institutions.

This paradigm shift requires the education and training of medical specialists, paramedics, general practitioners, psychologists and all other involved healthcare givers. Also, healthcare institutions should facilitate network medicine by supporting multidisciplinary team meetings, within and beyond the walls of their own institutions. In addition, electronic patient files should be redesigned to support network medicine, in the way that relevant patient data should be accessible to all involved healthcare providers, while also being adequately protected to ensure data security.

Research should be done on the role of health insurance companies with regard to the reimbursement of network medicine. In the field of rehabilitation medicine in the Netherlands, the current healthcare financing reimburses direct patient contact, while indirect patient related time, such as multidisciplinary consultations, is, with a few exceptions, not reimbursed. This means that it can be more feasible for healthcare providers to treat patients individually, instead of working together with other healthcare providers. It is recommended that the government investigates opportunities on how financial structures can be redesigned so that preventive medicine and network medicine can be facilitated, as increasing evidence shows that personalized medicine that aims to improve QoL and daily life participation results in the prevention of complications of chronic diseases, which may lead to lower health care costs in the long run (8).

E-health

Individuals with DM experience a high burden of disease and they frequently have to consult healthcare providers for glycaemic control, diabetic foot care, medication switches, blood check-ups etc. A pain rehabilitation programme addressing the biopsychosocial components of pain in order to improve daily-life functioning, usually involves multiple weekly sessions with the therapist team for a period of several weeks, causing an additional burden for patients. E-health may be a way to decrease this burden as patients don't need to travel to see a doctor and/or other healthcare provider.

There are different types of e-health. A real-life consultation with a healthcare provider can be replaced by a phone or video call (telemedicine). Mobile telephones with camera technology allow to share images such as photographs of pressure ulcers. In addition, electronic health record systems can be used for electronic administration of measures which can be stored in databases (9). Occasionally, aspects of the physical examination may be undertaken virtually, such as the demonstration of certain movements, which may allow an initial treatment plan to be started (10). E-health can also refer to online treatment modalities, such as diabetes self-care programs or pain rehabilitation programs. In the case of diabetes and diabetic foot management, several digital and online treatment options are available (11, 12). For PDN, an online ACT therapy was developed, which showed to not be feasible in the current form as completion rates did not achieve the pre-specified feasibility target (13). In the field of pain rehabilitation, telemedicine and e-health approaches are gradually being developed and tested, with many studies focusing on lessons learned and barriers to using e-health solutions (10). The COVID-19 pandemic accelerated the development of these e-heath solutions, as treating and supporting people with non-urgent and long-term conditions at a distance from healthcare providers became imperative (10).

Currently, the COVID-19 pandemic has been around for a year, and we have learned that e-health can provide us with more opportunities than we may have imagined before. More specifically, in the field of pain rehabilitation, our team has experienced that it was feasible to provide (parts of) a pain rehabilitation treatments via videoconferencing during the COVID-19 pandemic (14). It is not yet known whether these treatments were equally effective, and more research should be done on this. Given the high burden of medical visits for PDN patients, it seems apparent to further investigate e-health methods for this group of patients.

Knowledge transfer

This dissertation illustrates how complex and multidimensional PDN can be, both physically and mentally, and it underpins the need for a personalized biopsychosocial approach. Especially our lessoned learned are valuable for researchers and clinicians, as they offer

a new starting point for further development of treatments for patients with PDN. New studies using a single-case or randomized controlled trial design, are advised to further investigate and confirm clinical effectiveness of a multidisciplinary rehabilitation treatment for diabetes related disability and/or PDN. In case of proven effectiveness, this treatment can be included in Dutch and international guidelines. To disseminate the scientific results of this dissertation, presentations on national and international conferences were and will be given for researchers and healthcare professionals. The results from all our studies have already been published in international scientific journals.

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Appendix

Summary

The main aim of this dissertation was to gain more knowledge and understanding in the underlying biopsychosocial processes that are involved in coping with PDN (**Part I**), and from this, to design and evaluate a rehabilitation treatment that was specifically adapted to the identified fears, risks and needs of patients with PDN (**Part II**).

In **Part I** of this dissertation, we investigated whether the known principles of the fear avoidance model (FAM) as described in the general chronic musculoskeletal pain population are applicable in patients with PDN. In order to gain more insights into the perceptions, fears and consequences of PDN in daily life, our project started with a qualitative study in which three focus groups with each four patients with PDN were performed (**Chapter 2**). This study showed that patients with PDN can suffer from substantial pain, disability, polyneuropathy and diminished quality of life (QoL). The consequences of PDN showed to be physical (weakness, pain, physical restrictions), psychological (feelings of loss, feelings of depression, anger, sadness), and social (social withdrawal, isolation, work limitations, lower career opportunities). Furthermore, patients reported several fears related to diabetes and pain that could be important predictors of physical and social activities, such as fear of hypoglycaemia, fear of (increased) pain, fear of total exhaustion, fear of physical injury, fear of falling, fear of loss of identity and fear of negative evaluation. Fear seemed to be associated with different types of avoidance behaviour such as the avoidance of or withdrawal from various activities and being less physically active.

To further quantify these fears, we identified available validated questionnaires that matched the earlier mentioned self-reported fears, each measuring one specific element of diabetes related fear or pain related fear. These studies included 154 patients with PDN (62% male).

In the first study, linear regression analyses were performed to assess the association of pain catastrophizing with disability and QoL. Furthermore, we investigated the mediating roles of actual physical activity and a perceived decline in physical activity in these associations. The results showed that PDN was associated with catastrophic thinking, which in turn led to a perceived decline in physical activity (rather than an actual decline in physical activity), increased disability and less QoL (**Chapter 3**). This study emphasized the role of catastrophic thinking about pain and the experienced loss in daily activities due to PDN.

In the same cohort, we illustrated that patients with PDN can suffer from various fears, such as fear of hypoglycemia, kinesiophobia, fear of pain, fear of negative evaluation, fear of falling and fear of fatigue, and that some of these fears are associated with less QoL and increased disability in patients with PDN (**Chapter 4**). Univariate analyses showed that all fears were significantly and negatively associated with QoL and were positively associated with disability. More specifically, multivariate analyses showed that fear of falling, duration of complaints and pain intensity were the most important factors being negatively associated with QoL, while fear of falling, male gender and pain intensity were significantly associated with disability in patients with PDN. Both studies highlighted the great burden of PDN in daily life. Furthermore, the identification of catastrophic thinking and specific fears enabled us to determine potential specific PDN-related psychological targets for the development of a biopsychosocial intervention that aims to improve psychosocial well-being in patients with PDN.

From the data of our quantitative studies, the first interval outcome measure on overall PDN anxiety was developed; the Painful diabetic neuropathy Anxiety Rasch Transformed Questionnaire (PART-Q30©) (**Chapter 5**). After completion by a cohort of 151 patients with PDN, data obtained from seven generally applied anxiety scales were stacked (n=88 items) and subjected to Rasch analyses. The final PART-Q30© questionnaire consists of three items on hypoglycaemia, thirteen items on anxiety, five items on kinesiophobia, six on the fear of falling, one on fear of fatigue and two on the fear of negative evaluation by others. In this way, the PART-Q30© questionnaire covers various domains of PDN related anxieties and fears, while still being unidimensional. Also, the PARTQ-30 showed to have an acceptable internal reliability, and it explained 36% if disability and 63% QoL. The reduction of the items from 88 to 30 with a uniform response option reduces the burden in the assessment of patients and can simplify anxiety assessment in PDN.

Part II of this dissertation focusses on rehabilitation treatment modalities that may help patients with PDN cope with their pain and/or restore physicial activity levels and QoL. A systematic review was performed to provide an overview of the current evidence on the effects of biopsychosocial rehabilitation treatments that combine exercise therapies with psychological therapies (**Chapter 6**). Although studies in the domain of chronic pain have shown that a multidisciplinary therapeutic approach based on the biopsychosocial model may be effective in improving physical activity and QoL in patients with PDN, this systematic review of the literature revealed no studies that described or tested treatments that combined exercise therapy with psychological treatment modalities in patients with PDN. Through a secondary hand search, a total of 3 reviews were identified that described a total of 5 studies regarding either physical *or*

psychological interventions in patients with PDN. This so-called empty review showed that the biopsychosocial approach in the treatment low levels of physical activity and QoL in patients with PDN is a rather unexplored topic.

Based on the results of the studies that are described in Part I, we designed a new, customised exposure in vivo treatment (EXP) for patients with PDN (**Chapter 7**). During EXP, misinterpretations regarding painful stimuli are challenged and corrected, hereby lowering pain-related fear and enabling the patient to reengage in daily life activities. An interdisciplinary team provided EXP in 1-hour sessions twice a week, during 8 weeks in total. The EXP treatment protocol in this dissertation was specifically adapted to the needs and risks of patients with PDN who are limited in the performance of daily life activities due to PDN. The PART-Q30© is used to identiy PDN specific fears. Furthermore, a customized version of the Photograph-series Of Daily Activities (PHODA-PDN) was developed to detect PDN related fear-eliciting activities in each individual patient.

In **Chapter 8**, we elaborated on the effectiveness of the newly developed EXP treatment for PDN patients (ActiFeeT study). In this pilot study in a randomized single-case ABC-design, 12 PDN patients were included. The study consisted of an intensive screening period (A), followed by 8-week EXP treatment (B) that was specifically adapted to needs/risks of PDN patients, and 6-months follow-up period (C). Outcome measures included daily and non-daily measures of physical activity, QoL, metabolic parameters, disability, depression, general and PDN related anxiety, pain intensity and pain catastrophizing. In this pilot study, we hypothesized that EXP treatment, through targeting specific fears, would lead to a reduction in the perceived harmfulness of activities, leading to higher level of physical activity and QoL in patients with PDN. Due to high drop-out rates, only 3 participants completed the full study procedure. From these, the results are heterogeneous on most study outcomes such as physical activity, depression, fears, QoL and metabolic parameters. Therefore, the effectiveness of EXP for restoring QoL and physical wellbeing in patients with PDN was not confirmed by this study. However, the reasons for drop-out gave us some valuable information for future studies. Given the lessons learned, we believe that EXP may only have a potential added value for patients with PDN if; a) daily life functioning is mostly impaired by PDN, and not by other (co-)morbidity, b) the PDN related fears (feared consequences) that cause these impairments are exaggerated and irrational, c) specific activities can be identified that evoke the PDN related fears and d) spouses and other healthcare providers are involved in the treatment and e) there is a willingness to participate in a rehabilitation programme that addresses PDN related fears in daily life situations. Further research is needed to confirm this.

Samenvatting

Suikerziekte (diabetes mellitus, DM) is een stofwisselingsziekte waarbij het lichaam geen of onvoldoende insuline aanmaakt. Insuline is nodig om suikers (glucose) te kunnen verwerken en op te nemen in de cellen. Wanneer dit onvoldoende gebeurt, dan stapelt glucose zich op in het bloed (hyperglykemie). Hyperglykemie kan voor veel medische problemen zorgen in verschillende delen van het lichaam zoals de bloedvaten, het brein, de perifere zenuwen, de ogen, de nieren en de huid (1). Pijnlijke diabetische neuropathie (PDN) is een vorm van zenuwpijn die ontstaat door schade aan de perifere zenuwen bij DM. Voor dit proefschrift is onderzoek gedaan naar de gevolgen van PDN in het dagelijks leven.

DM is een veelvoorkomende aandoening: in 2016 waren er naar schatting in Nederland 1,1 miljoen mensen met deze ziekte (2). Bij ongeveer de helft van de mensen met DM ontstaat schade aan de perifere zenuwen, waardoor ze minder voelen, balansproblemen ervaren, het gevoel hebben op watten te lopen en een verhoogd risico hebben op het ontstaan van wondjes aan de voeten (3). Ongeveer 25-50% van de mensen met DM ontwikkelt daarbij ook zenuwpijn (PDN) (4-6). Zenuwpijn is stekend en prikkend van aard en is niet altijd gerelateerd aan een bepaalde activiteit (7). De pijn kan een grote weerslag hebben op de kwaliteit van leven van mensen, doordat mensen minder actief en angstig of depressief kunnen worden (8, 9). Helaas is PDN moeilijk te behandelen. Er zijn verschillende soorten medicatie beschikbaar, maar deze werken onvoldoende en/of hebben veel bijwerkingen (10).

Wanneer de pijnbehandelingen falen, dan is het belangrijk dat mensen met PDN worden begeleid in het omgaan met hun pijnklachten (11, 12). Binnen de revalidatiegeneeskunde zijn verschillende behandelingen beschikbaar die mensen leren omgaan met chronische pijnklachten. Deze behandelingen zijn gebaseerd op een biopsychosociale benadering. Uitgangspunt van deze benadering is dat de ervaren beperkingen niet alleen worden veroorzaakt door de onderliggende pathologie, maar ook door cognitieve (bijv. het uitvergroten van de klachten; catastroferen), gedragsmatige (bijv. vermijden van activiteiten), emotionele (bijv. somberheid) en sociale factoren (bijv. bepaalde opvattingen over de onderliggende ziekte) (13, 14). Bij deze cognitief-gedragsmatige aanpak wordt stil gestaan bij angsten en niet-helpende (dysfunctionele) gedachten over het bewegen met pijn, zodat deze vervolgens kunnen worden bijgestuurd en/of uitgedaagd. Het doel van de behandeling is dat mensen meer actief worden in het dagelijks leven, ondanks de pijn (13, 14). Deze biopsychosociale principes zijn goed bekend voor verschillende aandoeningen die geen medische risico's met zich mee brengen, zoals chronische lage rugpijn, werk-gerelateerde pijn aan de armen en handen, en chronisch regionaal pijnsyndroom type I (15-19). Deze principes waren echter nog niet onderzocht bij mensen bij PDN.

Het doel van dit proefschrift was om meer inzicht te krijgen in de onderliggende biopsychosociale processen bij PDN en de impact hiervan in dagelijks leven (**Deel I**), en om van hieruit een nieuwe revalidatiebehandeling te ontwikkelen die specifiek is aangepast aan de angsten, risico's en medische aandachtspunten bij mensen met PDN (**Deel II**).

In **Deel I** van dit proefschrift hebben wij onderzocht of de bekende principes van het vrees-vermijdingsmodel zoals we dat kennen bij mensen met chronische pijn aan gewrichten en botten (musculoskeletale pijn), ook toepasbaar zijn bij op mensen met PDN. Dit project startte met een kwalitatieve studie waarbij drie groepen van vier patiënten werden geïnterviewd om meer inzicht te krijgen in de angsten en percepties over PDN en welke consequenties dit kan hebben in het dagelijks leven (**Hoofdstuk 2**). Deze studie toonde aan dat mensen met PDN gebukt kunnen gaan onder aanzienlijke pijnklachten, beperkingen in het dagelijks leven en een verminderde kwaliteit van leven. De consequenties hiervan waren zowel fysiek (algehele zwakte, lichamelijke beperkingen), psychologisch (verlieservaringen, depressie, boosheid, verdriet) en sociaal van aard (isolatie, vermijden van sociale activiteiten, beperkingen in het uitvoeren van werk, verminderde carrièremogelijkheden).

Daarnaast rapporteerden mensen met PDN verschillende angsten, gerelateerd aan DM en/of neuropathische pijn, die mogelijk belangrijke negatieve voorspellers zouden kunnen zijn voor het uitvoeren van dagelijkse fysieke en/of sociale activiteiten. Voorbeelden van deze angsten zijn; angst voor een periode van hypoglykemie (lage bloedsuiker), angst voor (meer) pijn, angst voor uitputting, angst voor letsel, valangst, angst voor verlies van identiteit en angst voor een negatieve benadering door andere mensen. Deze angsten bleken ook gerelateerd te zijn aan verschillende vormen van vermijdingsgedrag, zoals het vermijden van dagelijkse activiteiten of sociale contacten.

In de volgende stap van het onderzoek werden reeds bestaande vragenlijsten gebruikt om de bovengenoemde angsten op een gevalideerde wijze in kaart te brengen (**Hoofdstuk 3**). Deze vragenlijsten hadden betrekking op DM-gerelateerde angsten of pijn-gerelateerde angsten. In het eerste vragenlijstonderzoek werd onderzocht wat de relatie was tussen het catastroferen over pijn (uitvergroten en negatief denken over de pijn) en beperkingen in het dagelijks leven en de kwaliteit van leven. Daarnaast werd de rol van het daadwerkelijke niveau en het ervaren niveau van lichamelijke activiteit in deze relatie onderzocht. De resultaten lieten zien dat mensen met PDN inderdaad kunnen catastroferen over hun pijnklachten. Hoe meer ze dit deden, hoe meer ze hierdoor het gevoel hadden dat ze minder lichamelijk actief waren in het dagelijks leven. Interessant was dat het daadwerkelijke niveau van lichamelijke activiteit gelijk was aan het niveau

bij mensen die niet of minder catastrofeerden over de pijnklachten. Mensen *voelden* zich dus vooral meer beperkt in het dagelijks leven wanneer er sprake was van catastroferen over de pijn en ervaarden hierdoor ook een verminderde kwaliteit van leven. Deze studie benadrukt de beperkende rol van catastroferen over pijn bij mensen met PDN.

In hetzelfde cohort werd bevestigd dat mensen met PDN last kunnen hebben van verschillende angsten zoals angst voor een periode van hypoglykemie, angst om te bewegen (kinesiofobie), angst voor pijn, angst voor een negatieve benadering door andere mensen en angst voor uitputting, en dat sommige van deze angsten ook geassocieerd zijn met een afgenomen kwaliteit van leven en meer beperkingen in het dagelijks leven (**Hoofdstuk 4**). Univariate analyses lieten zien dat alle angsten afzonderlijk significant en negatief geassocieerd waren met kwaliteit van leven en positief geassocieerd waren met beperkingen. Multivariate analyses lieten zien dat valangst, de duur van de klachten en pijnintensiteit de belangrijkste voorspellers waren voor een verminderde kwaliteit van leven. Valangst, mannelijk geslacht en pijnintensiteit waren de belangrijkste voorspellers voor beperkingen in het dagelijks leven bij mensen met PDN. Beide studies benadrukken de grote last van PDN in het dagelijks leven. Op basis van deze resultaten werd een nieuwe behandelvorm ontwikkeld, die erop gericht is om mensen met PDN te leren omgaan met hun klachten, waardoor mogelijk het activiteitenniveau en de kwaliteit van leven kunnen verbeteren.

Vanuit de data uit de hoofdstukken 3 en 4, werd een nieuwe, compactere vragenlijst ontwikkeld; de Painful diabetic neuropathy Anxiety Rasch Transformed Questionnaire (PART-Q30©) (**Hoofdstuk 5**). Deze nieuwe vragenlijst is een samenvoeging van 7 ordinale angstvragenlijsten. In totaal vulden 151 mensen met PDN alle vragenlijsten in (in totaal 88 items). Op deze data werd een Rasch-analyse uitgevoerd, hetgeen uiteindelijk resulteerde in 30 items. Deze items werden getoetst op verschillende statistische waardes, unidimensionaliteit, geordende antwoordopties, het ontbreken van item bias en of er geen items waren die aan elkaar gerelateerd zijn, resulterend in de PART-Q30©. De vragenlijst bevat drie items over angst voor hypoglykemie, vijf items over bewegingsangst, zes over valangst, één over angst voor uitputting en twee items over de angst voor negatieve evaluatie door andere mensen. Hierdoor dekt de PART-Q30© alle bekende domeinen van PDN-gerelateerde angsten. Daarnaast werd de impact van de PART-Q30© op beperkingen en kwaliteit van leven onderzocht, waarbij een acceptabele interne betrouwbaarheid werd gevonden. Het reduceren van de lijst van 88 naar 30 items maakt dat deze vragenlijst gemakkelijk kan worden toegepast in de klinische praktijk.

Deel II van dit proefschrift gaat over het ontwikkelen van een revalidatiebehandeling die mensen met PDN zou kunnen helpen om beter met hun klachten om te gaan, om zo een hoger niveau van functioneren en kwaliteit van leven te kunnen bereiken. Middels

een systematisch literatuuronderzoek werd geprobeerd om een overzicht te krijgen van de publicaties op het gebied van revalidatiebehandelingen met een biopsychosociale benadering die erop gericht zijn om mensen met PDN beter te laten functioneren in het dagelijks leven (**Hoofdstuk 6**). Terwijl vanuit het werkveld van de chronische pijn al veel bekend is over de effectiviteit van dergelijke biopsychosociale revalidatiebehandelingen, bleek bij dit literatuuronderzoek dat er geen enkele studie beschikbaar was die een biopsychosociale benadering beschreef voor mensen met PDN. Middels een tweede handmatige selectie in de gevonden artikelen, werden 3 reviews geïdentificeerd die in totaal 5 revalidatiebehandelingen beschreven die enkel fysiek (bio) óf psychologisch (psycho) ingestoken waren. Dit literatuuronderzoek laat zien dat de biopsychosociale benadering voor mensen met PDN nog erg onderbelicht is.

Op basis van de resultaten uit Deel I, werd een speciale revalidatiebehandeling ontworpen voor mensen met PDN, gebaseerd op de principes van exposure (**Hoofdstuk 7**). Tijdens een exposurebehandeling worden verkeerde aannames (misinterpretaties) over pijnlijke stimuli uitgedaagd en gecorrigeerd, waardoor pijn-gerelateerde angst afneemt, met als gevolg dat mensen in staat worden gesteld om weer meer actief te worden in het dagelijks leven. Een interdisciplinair revalidatieteam bestaande uit revalidatiearts, fysiotherapeut of ergotherapeut en gedragstherapeut (psycholoog), voert deze behandeling uit.

Het protocol voor de exposurebehandeling voor mensen met PDN in dit proefschrift bestond uit twee sessies van 1 uur per week, gedurende in totaal 8 weken. Het protocol bevatte speciale aandacht voor de PDN-gerelateerde angsten die zijn gevonden in de eerdere studies. Ook werd de behandeling zodanig aangepast dat deze geen additionele risico's vormde voor mensen met een diabetische neuropathie, zoals het risico op het oplopen van drukplekken of het ontwikkelen van een lage bloedsuiker. De PART-Q30© werd gebruikt voor het in kaart brengen van de PDN-gerelateerde angsten. Tevens werd gebruik gemaakt van een aangepaste versie van de Photograph-series Of Daily Activities (PHODA-PDN). Dit is een gestructureerde methode van uitvragen van PDN-gerelateerde angsten aan de hand van foto's van activiteiten.

De effectiviteit van de nieuwe exposurebehandeling werd getest in een pilotstudie in single-case-ABC-design (ActiFeeT studie) (**Hoofdstuk 8**). In deze studie werden 12 mensen met PDN geïncludeerd. De studie bestond uit drie fases; intensieve screeningfase (A), 8 weken behandelfase (B), 2 weken follow-up na 6 maanden (C). De uitkomstmaten waren dagelijkse en periodieke metingen over fysieke activiteit, kwaliteit van leven, metabole parameters, beperkingen in het dagelijks functioneren, depressie, pijn-gerelateerde angsten, PDN-gerelateerde angsten, pijnintensiteit en mate van catastroferen. De voornaamste hypothese in deze studie was dat de exposurebehandeling, door middel van

het gericht adresseren van specifieke angsten, zou leiden tot een afname van de ervaren dreiging van activiteiten, hetgeen dan zou leiden tot een hoger niveau van lichamelijke activiteit en kwaliteit van leven bij mensen met PDN.

Door de hoge mate van uitval in de studie, hebben slechts drie deelnemers de gehele studieprocedure doorlopen. Deze drie deelnemers lieten zeer wisselende resultaten zien op de meeste uitkomstmaten zoals fysieke activiteit, depressie, angsten, kwaliteit van leven en metabole parameters. Om deze reden kon er geen uitspraak worden gedaan over de mogelijke effectiviteit van deze exposurebehandeling.

De analyse van de redenen waarom mensen zijn uitgevallen, heeft wel belangrijke informatie opgeleverd. Op basis van deze analyse zijn wij van mening dat exposurebehandeling bij mensen met PDN alleen effectief kan zijn onder een aantal voorwaarden: a) de beperkingen in het dagelijks functioneren worden vooral veroorzaakt door de PDN en niet door andere (co-)morbiditeit, b) de PDN-gerelateerde angsten (en daarmee gevreesde consequenties) die deze beperkingen veroorzaken zijn uitvergroot en irrationeel, c) specifieke activiteiten kunnen worden geïdentificeerd waarbij deze angsten optreden, d) partners en andere zorgverleners worden betrokken bij de behandeling, en e) de hulpvraag ligt op het gebied van het verbeteren van het functioneren, met daarbij aanwezige veranderbereidheid en veranderbaarheid. Toekomstig onderzoek zal moeten uitwijzen of deze aannames kloppen.

Het proefschrift wordt afgesloten met een algemene discussie, met daarin een reflectie op de belangrijkste resultaten uit dit proefschrift en wat deze kunnen betekenen voor de klinische praktijk en toekomstig onderzoek (**Hoofdstuk 9**). Als eerste wordt een beschouwing gegeven op de toepasbaarheid van de meetinstrumenten PARTQ-30© en PHODA-PDN. Daarna wordt dieper in gegaan op de cognitieve processen bij mensen met PDN, waarbij met name specifiek aandacht is voor de (on)mogelijkheden om verschil te maken tussen een helpende rationele angst versus een uitvergrote dysfunctionele angst, het belang van een hulpvraag bij veranderbaarheid/veranderbereidheid, de rol van zelfeffectiviteit en psychologische flexibiliteit, en uiteindelijk de mogelijke beperkingen veroorzaakt door eventuele cognitieve tekorten bij PDN. Ook de fysieke aandachtspunten zoals balansproblemen komen aan de orde.

Het hoofdstuk eindigt met een voorstel voor een biopsychosociale benadering van diabetes-gerelateerde beperkingen, die nog verder gaat dan enkel de focus op PDN-gerelateerde angsten en beperkingen. Er wordt een model aangereikt waarmee de patiënt in kaart kan worden gebracht en kan worden behandeld vanuit het bredere perspectief van DM-gerelateerde beperkingen. Als laatste wordt de mogelijke meerwaarde van een behandeling volgens de principes van de 'acceptance and commitment therapy' (ACT) toegelicht. Vervolgstudies zijn nodig om de bruikbaarheid van dit nieuwe model te toetsen.

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About the author

Charlotte van Laake – Geelen was born on June 25th, 1987, in Heerlen, The Netherlands. As a small child she and her family moved to Munich, Germany, where she lived until the end of high school. At the European School of Munich she obtained her European Baccalaureate cum laude. She moved to Maastricht to study Medicine at Maastricht University in 2005. After this, she spent one year on research in the field of endocrinology at the Maastricht University Medical Center (MUMC+). For this work she received the Prof. dr. J. Terpstra Young Investigator Award 2012 (Nederlandse Vereniging voor Diabetes Onderzoek) and the Endocrine Society Outstanding Abstract Award 2012. In 2013 Charlotte started her residency in rehabilitation medicine at Adelante Zorggroep, where she further pursued her scientific ambitions and started the PhD project that resulted in this dissertation. In 2017 Charlotte started to work as a rehabilitation physician at the department of Spinal Cord Injury at Adelante, location Hoensbroek for two days/week, on location MUMC+ 1day/week, and at Maastricht University (CAPHRI) 1 day/week where she finished her dissertation. Charlottes current clinical work evolves around spinal cord injury and spina bifida, with a special interest in neuropathic pain. Her ambition for the future is to keep combining clinical research with clinical practice, in order to achieve optimal evidence based and patient centred care. In her free time Charlotte enjoys hiking (preferably in the Alps), cooking, dining, being a mum and spending quality time with her family and friends.

About the cover

The cover of this dissertation is a free and artistic representation of what the topic of this dissertation and the work as a rehabilitation physician means to Charlotte. In her opinion, the task of a rehabilitation physician is to guide the patient to explore opportunities that can help him/her to achieve optimal physical and mental health, by pursuing individual meaningful activities. The Alps symbolize a place where physical activity meets quality of life. The hiking boots and walking stick represent the medical walking aids that may be necessary to walk safe and adequately in persons with diabetic neuropathy. The road represents the personal quest and life path of patients, and is also a symbol for the rehabilitation treatment in which the patient can be guided towards the for him/her meaningful end goal. The emblems on the walking stick are symbols of Charlottes own life path (Maastricht and Munich). What will the next emblem be, both for Charlotte and for her patients?

List of publications

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