The Rotterdam Diabetic Foot Study

A different view on lower extremity neuropathy:
a new hope against the phantom menace?

Willem D. Rinkel

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a new hope against the phantom menace?

De Rotterdamse Diabetische Voet Studie

Een andere kijk op neuropathie in de onderste extremiteit:
een nieuwe hoop tegen de onbekende bedreiging?
(met een samenvatting in het Nederlands)

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To my parents

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Prologue

Consecutive lower extremity amputations as a result of diabetes

A 75-year old man presented to the outpatient clinic with ulceration and necrosis of the hallux of the left foot. The second toe showed a blister with old blood, probably both the result of trauma. He reported pain and a burning sensation on both feet, due to diabetes related neuropathy.

Medical history revealed non-insulin dependent diabetes, hypertension, opticus nerve infarction, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty and percutaneous transluminal angioplasty for chronic leg ischemia (Fontaine stage IV).

Radiographs did not show evidence for osteomyelitis. One month of antibiotic treatment later, the ulcer at the hallux did not heal and subsequently he agreed to have the first toe amputated. The post-operative period was complicated by new occlusions in the fibular and anterior tibial arteries, deteriorating wound healing of the second toe. Despite recanalization and antibiotic treatment, a forefoot amputation was carried out 18 weeks after initial presentation. One month later a trans-tibial amputation had to be performed. Simultaneously, an ulcer under the right hallux developed, followed by an ulcer under the third right toe, which was then followed by an ulcer under the second toe...

This report is exemplary for the common cascade diabetic patients are confronted with during their lifetime.

What if this patient was timely diagnosed with a lower extremity entrapment neuropathy? Might this have given him an option to choose for a treatment?

General introduction

General introduction

1.1 What's the problem?

Current medical practice does not have effective treatments for the tingling, burning, electrical and painful symptoms of diabetes related neuropathy and patients have nowhere to go when seeking treatment for the concomitant numbness in their feet. Refractory to therapies like antidepressants and anticonvulsants, symptoms are not treated to satisfaction and persistent numbness is sadly observed¹. Diabetes related neuropathy lowers quality of life and often precedes diabetic foot disease²⁻⁴. Diabetic foot disease is disabling and deadly. Ulcers underlie eight out of 10 non-traumatic amputations carried out, and the all-cause mortality rate after five years is 39-80% in this patient group⁵⁻⁸! This outranks the mortality rates of lung and colorectal cancers⁹! Patients with sensory deficit at the feet also become at greater risk for falls, which leads to considerable use of healthcare resources, permanent disability and even death¹⁰.

1.2 Is it common?

1.2.1 Prevalence of diabetes mellitus

Most recent estimates indicate that 8.8% of adults (425 million people) worldwide have diabetes and this number will rise to 629 million before the year 2045. A lot of people (30-80%) that are having diabetes today are not even aware of its presence because of asymptomatic early disease. While being undetected/undiagnosed, and therefore untreated, their disease is progressing to more severe stages with complications due to this worrying unawareness. Effective preventive measures are available and key in lowering the chance of complications. Since there is an increasing overweight general population, as a result of fat-rich and high-calorie diets and increased sedentary time, the incidence of diabetes type 2 is on the rise¹¹. Even teenagers and young adults are now diagnosed with this type of diabetes, since age of onset has been falling in recent years¹². With the majority of the total number affected living in low- and middle-income countries, the epidemic is gathering pace at a concerning rate. The figures provide an alarming indication of the future impact of diabetes as a major threat to global development. Globally 727 billion US dollars are spent on diabetes annually, which translates to one for every eight dollars spent on healthcare¹³.

In the Netherlands, approximately 1.2 million people are having diabetes today, of which the diagnosis is made in 1.1 million patients officially (Figure 1). Nine out ten diabetic subjects have type 2 diabetes. The lifetime risk of developing type 2 diabetes is 33%. A significant

number of inhabitants (n=900,000) have impaired glucose tolerance¹, a precursor of overt diabetes. Diabetes is associated with chronic complications that occur in 40 to 56% of patients, as mentioned earlier, often already occurring before diabetes has been officially diagnosed. Examples of these complications include cardiovascular disease (present in 10 to 43% of diabetic subjects), ocular disease (4 to 46%), renal disease (5 to 40%), dementia (8%) and depression (twice as frequent diagnosed compared to the normal population). Diabetes related mortality is difficult to estimate, since death is often the result of the before mentioned related complications, not of the disease itself. In 2015, the costs of diabetes care in the Netherlands approximated 1.6 billion euros, which is 1.8% of the annual healthcare budget. Prevalence numbers of diabetes in the Netherlands are comparable to that of the European Union, with an expected increase in the years to come (34% increase in prevalence in the year 2040 compared to 2015, data from the Netherlands National Institute for Public Health and the Environment [Dutch: Rijksinstituut voor Volksgezondheid en Milieu (RIVM)])¹⁴.

Figure 1 Prevalence of diabetes mellitus in the Netherlands.

Legend: Gender-specific year prevalence of diabetes mellitus (2018) in general practices in the Netherlands (data from the Netherlands Institute for Health Services Research [Dutch: Nederlands Instituut voor onderzoek van de Gezondheidszorg (Nivel)]). X-axis: age categories, Y-axis: number of diabetic patients per 1000 persons.

¹ Impaired glucose tolerance and impaired fasting glucose are both indicators of prediabetes, according to the *American Diabetes Association Classification of Diabetes Mellitus: Standards of Medical Care in Diabetes - 2018*. Diabetes Care, 2018.

Since this thesis is dedicated to lower extremity complications of diabetes, in the following section the adverse effects of diabetes are reviewed in light of the threatened limb.

1.2.2 Prevalence of diabetic neuropathy

Neuropathy in diabetes is a heterogeneous condition that manifests in different forms and at different levels of both the central and peripheral nervous system. In this thesis, a focus is put on the effects of diabetes on the peripheral nervous system.

Peripheral neuropathy includes a large variety of clinical syndromes that are the result of injury to axons and/or the myelin sheaths of peripheral nerves. Patients may be asymptomatic, experience 'positive' symptoms (burning, tingling, pain and other abnormal sensations) or, as the disease progresses, 'negative' symptoms (numbness)². The most common form of peripheral neuropathy is diabetic sensorimotor polyneuropathy (DSP), which is symmetric in nature, starts distally in the feet (dying-back) and is a chronic, nerve-length dependent condition¹⁵. The condition is a common source of morbidity, disability and reduced quality of life². The prevalence of DSP is about 30% in the diabetic population, with up to 50% of patients developing neuropathy during the course of their disease¹⁶. Both type 1 and type 2 diabetes patients are affected. However, important to note is that persons with impaired glucose tolerance are already affected with (early signs of) DSP in about 20% of cases, with reports on neuropathic pain, reduced sweat secretion, a diminished sympathetic skin response and impaired nerve conduction studies¹⁷. The incidence rate of painful DSP in the Dutch general population is 0.72 per 1000 person-years¹⁸.

DSP accounts for about 75% of the diabetic neuropathies^{19,20}. In current clinical practice it remains a diagnosis made often only on the basis of the patient interview and a short physical examination, and by a neurologist frequently complemented with nerve conduction studies²¹. This confounds the possibility of other diabetic neuropathies, especially entrapment neuropathies, that may lie at root of the patient symptoms and are not detected by a general neurological examination and nerve conduction studies; the next sections elaborate on this²². Table 1 summarizes the other neuropathies seen in patients with diabetes.

Chapter I gives an overview of normal skin physiology to introduce the reader to the different pathophysiologies discussed in this thesis.

2 Several terminologies are used for sensory disturbances: hypoesthesia (decreased sensitivity to non-painful stimuli), hypoalgesia (decreased sensitivity to painful stimuli), hyperesthesia (increased sensitivity to non-painful stimuli), hyperalgesia (increased sensitivity to painful stimuli), allodynia (pain following non-painful, often repetitive, stimuli) and 'wind-up' (increasing pain following repetitive light to moderate painful stimuli).

Table 1 Diabetic neuropathies³.**Diffuse neuropathy***Diabetic sensorimotor polyneuropathy*

- Primarily small-fiber neuropathy
- Primarily large-fiber neuropathy
- Mixed small- and large-fiber neuropathy (most prevalent)

Autonomic

- Cardiovascular system
 - o Reduced heart rate variability
 - o Orthostatic hypotension
 - o Resting tachycardia
 - o Malignant arrhythmia (sudden death)
- Gastro-intestinal
 - o Diabetic gastroparesis
 - o Diabetic enteropathy (diarrhea)
 - o Colonic hypomotility (constipation)
- Urogenital
 - o Erectile dysfunction
 - o Female sexual dysfunction
- Sudomotor dysfunction
 - o Anhidrosis or hypohydrosis
 - o Gustatory sweating
- Hypoglycemia unawareness
- Abnormal pupillary function

Mononeuropathy

Isolated cranial (e.g. n. oculomotorius or n. facialis)

Peripheral nerve entrapment (may be isolated, more often multiple (e.g. mononeuritis multiplex or multifocal neuropathy which resembles DSP))

- Upper extremity
 - o n. medianus (proximal forearm or carpal tunnel)
 - o n. ulnaris (cubital tunnel or Guyon's canal)
 - o n. radialis (upper arm or proximal anterolateral forearm (radial tunnel) or mid anterolateral forearm)
- Lower extremity
 - o n. ischiadicus (around m. piriformis)
 - o n. cutaneous femoris lateralis (at l. inguinale)
 - o n. peroneus communis (at fibular head)
 - o n. peroneus superficialis (at crural fascia)
 - o n. peroneus profundus (around m. extensor hallucis brevis)
 - o n. tibialis posterior (at soleal sling or tarsal tunnel)
 - n. plantaris medialis
 - n. plantaris lateralis

3 Adapted from: Pop-Busui et al. *Diabetic Neuropathy: A Position Statement by the American Diabetes Association*. Diabetes Care, 2017. Names of nerves are written in Latin.

Table 1 Diabetic neuropathies. (continued)

Radiculopathy or polyradiculopathy

Thoracic radiculopathy

Radiculoplexus neuropathy (e.g. lumbosacral polyradiculopathy or proximal motor amyotrophy)

Non-diabetic neuropathies common in diabetes

Pressure palsies

Chronic inflammatory demyelinating polyneuropathy

Radiculoplexus neuropathy

Acute painful small-fiber neuropathies (insulin treatment induced)

1.2.3 The double crush hypothesis

In 1973, dr. Adrian R.M. Upton and dr. Alan J. McComas, two neurologists, proposed their 'double crush in nerve entrapment syndromes' hypothesis in the international literature²³. Based on a series of 115 patients with carpal tunnel syndrome and/or cubital tunnel syndrome, associated cervical root lesions in the neck were found in 81 of cases. They did not think this association to be fortuitous, what made them propose the hypothesis that 'neural function is impaired because single axons, having been compressed in one region, become especially susceptible to damage at another site'. They postulated this to be the result of serial constraints of axoplasmic flow in nerve fibers⁴, and not of impulse conduction, which is an all-or-nothing phenomenon. They noted that different types of neural lesions could give rise to denervation, including a generalized (subclinical) neuropathy (e.g. DSP, which involves both the myelin sheath and axons).

It was in the early eighties that dr. A. Lee Dellon, a plastic hand surgeon with great interest in peripheral nerve pathology, started further exploring the relationship between diabetes and entrapment neuropathy in both animal models and clinical studies²⁴⁻²⁶. He found that diabetes and diabetes related neuropathy (i.e. DSP) are often the first crush on the peripheral nerve that causes the nerve to swell, resulting in a second crush (i.e. entrapment) that further decrements peripheral nerve function²⁵. These critical observations have given rise to a whole new field of peripheral nerve research, including basic science and anatomical studies, development of treatment modalities and consequent outcome assessment²⁷.

1.2.4 A model for nerve entrapment

Entrapment of peripheral nerves is common in subjects with diabetes, and is associated with significant morbidity^{28,29}. Carpal tunnel syndrome, an entrapment neuropathy of the median nerve at wrist level (i.e. carpal tunnel) is more prevalent in patients with DSP than in the general population (point estimates: 3.8% in the general population, 14% in diabetic subjects without symptoms of DSP and 30% in those with DSP) and its treatment less

4 Nerve fibers are the axons of the neuron, which usually comes in tens of thousands per peripheral nerve.

successful³⁰⁻³². Since carpal tunnel syndrome is highly prevalent and amongst the most common hand surgeries, it is therefore widely studied³³. To introduce the reader to lower extremity entrapment neuropathy and its treatments, carpal tunnel syndrome and other upper extremity nerve entrapments (since they have been most frequently studied) will be used as an epitome in the following sections.

The second most common upper extremity nerve entrapment is cubital tunnel syndrome, however, few studies reported on diabetes-specific prevalence estimates. A study from Italy showed that 6% of cases with ulnar nerve entrapment, as assessed with nerve conduction studies, had underlying diabetes. Another study from the same country showed that 45% of unselected diabetic patients had evidence of ulnar neuropathy on nerve conduction studies, suggestive of focal entrapment, which increased when patients also had symptoms of DSP³⁴. These numbers are higher than the prevalence rates reported from a general, non-diabetic, population (1.8%-5.9%), although these estimates were assessed using self-reported measures³⁵. Yet, the latter suggests that, similar to the median nerve at the wrist, the ulnar nerve also becomes more susceptible to focal entrapment, if compromised by endoneurial ischemia or metabolic factors that occur in diabetes³⁶. Other sites of upper extremity nerve entrapment include the proximal median nerve (pronator teres syndrome), anterior interosseous nerve (motor branch of median nerve, Kiloh-Nevin syndrome) and ulnar nerve at Guyon's canal. However, these syndromes are already relatively rare in the non-diabetic population, with no robust reports in the literature on prevalence estimates in the diabetic population.

Few studies exist on the epidemiology of lower extremity nerve entrapments in diabetic subjects, which is partially due to the difficulties of diagnosing a super-imposed entrapment neuropathy, in the presence of DSP, with conventional nerve conduction studies³². Therefore, the validity of methods used is a subject of continuing debate³⁷. In the next section, these difficulties are further reviewed, before continuing on the prevalence estimates of lower extremity nerve compression syndromes.

1.2.5 The validity of measures to diagnose a focal entrapment neuropathy in diabetes

Entrapped peripheral nerves, especially early in their course, may evoke symptoms with few, if any, accompanying abnormalities in the classic neuromuscular examination³⁸. Only the patient history can provide evidence on complaints, such as pain and paresthesia, which are often intermittent or transitory in early stages of the disease. These symptoms are induced by ectopic impulses generated in nerve fibers hyper excitable by ischemia and/or pressure, and can often also be elicited when tapping or pressurize the site of entrapment, revealing increased mechanosensitivity³⁸⁻⁴⁰. Electrodiagnostic studies (EDX) are often normal at this stage and not of value in establishing a definitive diagnosis. When compression

persists, endoneurial microvessel integrity is lost, resulting in endoneurial edema²⁴. At this point, the cutaneous perception thresholds for vibration and touch become abnormal³⁸. The latter can be reversed by surgically decompressing the entrapped nerve, however, full remyelination is unlikely⁴¹. With a longer duration of entrapment, axons are being lost, which results in decreased innervation density, which is assessed by static and moving two-point discrimination measurements.

Classic electrophysiological studies are used in current clinical care to provide supportive evidence of the underlying pathophysiology, severity and location of peripheral nerve injury. Indications include, amongst others, the identification of the site of entrapment (e.g. C5/C6 versus superior trunk of brachial plexus, versus forearm compression site, versus carpal tunnel syndrome) and the identification of peripheral neuropathy or myopathy. Local demyelination, from which ready recovery can be expected, is quantified by conduction slowing, while axon loss, from which recovery is slower and less complete, is quantified by loss of amplitude of surface sensory and motor potentials and by denervation changes in innervated muscles (if electromyography (EMG) is used). As the pathophysiology of entrapment on peripheral nerves makes clear, abnormalities may be subtle and undetectable by electrophysiological studies. Yet, other factors also contribute to the questionable validity of these often-used studies, on which will be further elaborated in the following section.

First, experimental models of chronic nerve compression, with histologic evaluation, have shown that large myelinated and small myelinated fibers are affected differently, that the outer layers of a fascicle are likely to be more severely affected than the center of the fascicle and that fascicles within a nerve are not uniformly injured in entrapment neuropathy^{42,43}. As a consequence, the targeted innervated area of interest may be missed by nerve conduction studies. Moreover, few remaining myelinated fibers can continue to conduct normally in the presence of abundant demyelinated fibers in the same fascicle, resulting in a false-negative test result. Secondly, DSP induced axonopathy, with its own demyelination, will impede the demonstration of entrapment induced segmental nerve demyelination and axonal damage^{44,45}. This has been shown in the upper extremity, in which electrophysiological parameters (e.g. conduction velocity (slowing) or conduction block across the site of entrapment) could not demonstrate the presence of median nerve entrapment, in the presence of DSP associated neuropathy³². For the lower extremity, sensitivity and specificity could not be determined in studies on tarsal tunnel syndrome, with the practice advisory of the American Association of Neuromuscular & Electrodiagnostic Medicine revealing significant flaws in current study designs and lack of a reference clinical definition^{22,46}. Thirdly, many (technical) factors may confound the results of electrophysiological studies, such as room temperature, skin temperature, age, sex, body size and height⁴⁷⁻⁴⁹. It is therefore

concluded that nerve conduction studies cannot validly assess super-imposed entrapment neuropathy in diabetic subjects.

How to assess an entrapment neuropathy, in the presence of DSP? In patients with complaints of tingling, burning, prickling or numbness in the hand, carpal tunnel syndrome is often suspected. Surgeons often use the provocative Phalen sign (evoking symptoms by flexing the wrist, which increases pressure) or Tinel sign (evoking symptoms along the distribution of the nerve, by percussing the nerve with a finger) to diagnose median nerve entrapment at the wrist⁵⁰. A positive Tinel sign represents signaling from mechanically sensitive axonal sprouts, at the site of chronic nerve compression and is therefore used as clinical indicator of nerve compression^{38-40,51,52}. Recent research suggests that using Phalen's wrist flexion increases the accuracy of diagnosing median nerve entrapment, while Tinel's sign is more specific to axonal damage that may occur as a result of moderate to severe entrapment⁵³⁻⁵⁵. It may be that in the more advanced stages of nerve entrapment sprouting may have stopped, resulting in a negative sign, suggestive of a point of no return regarding sprouting and reinnervation. This is of critical importance, as the variation in accuracy of tests related to clinical and electrodiagnostic criteria are one of the reasons for controversy in the literature about these tests⁵⁰. One should bear in mind that the sensitivity of provocative tests depends largely on the clinical and electrophysiological severity of the entrapment, with the lowest sensitivity in patients with a severely damaged nerve⁵⁶. There is growing evidence in favor of the use of imaging techniques as complementary to the current diagnostic work-up⁵⁷⁻⁵⁹. Enlargement is often seen just proximal to the site of entrapment, but correlations between physical examination, ultrasonographic and electrodiagnostic findings are not definitively established yet^{60,61}.

It is therefore concluded that the clinical diagnosis of nerve entrapment requires a typical history of complaints, a physical examination with provocative testing and staging of the degree of nerve impairment, by somatosensory testing. The latter may be studied by quantitative sensory testing. This majority of evidence has emerged from the numerous clinical studies on the most frequently studied entrapment neuropathy in the upper extremity: carpal tunnel syndrome. Extrapolation of this evidence to lower extremity entrapment neuropathies is further explored in this thesis.

In **Chapter II** we present normative data for cutaneous threshold and spatial discrimination in the feet. In **Chapter III** the validity and reliability of quantitative sensory testing in the feet is evaluated. In **Chapter VII** we discuss the validity of the Tinel sign in diagnosing tibial nerve entrapment.

1.2.6 Epidemiology of lower extremity nerve entrapments

Diagnosing lower extremity nerve entrapments is of paramount importance, in both the non-diabetic and diabetic population, since entrapment can lie at root in patients suspected of having chronic axonal polyneuropathy or DSP⁶²⁻⁶⁵. Underdetection is likely the cause of an underestimation of the extent of the problem, since physicians are not trained to search for entrapment neuropathies in the lower extremity and diagnostic criteria vary⁶⁶. Unfortunately, only small diagnostic studies exist that investigate diabetes related entrapment, with a large role for electrodiagnostic studies and Tinel's sign⁶⁷. However, these studies often report double-digit prevalence estimates, suggesting a greater extent of the problem⁶⁸. Interventional studies on neurolysis are numerous, but are often of poor quality and have low patient numbers included^{69,70}. As an introduction, the following section focuses on the prevalence estimates of lower extremity peripheral nerve entrapment in diabetic subjects. Not all nerves are reviewed, since elusive entities such as sural and interdigital (Morton's neuroma) nerve entrapment are already rare in the general population (see Table 2 for an overview of lower extremity entrapment sites).

Lateral femoral cutaneous nerve entrapment

Compression injury to the lateral femoral cutaneous nerve results in an entity known as meralgia paresthetica and presents commonly as burning pain, paresthesia, numbness and hypersensitivity to the skin of the anterolateral thigh. It is regarded the most common entrapment neuropathy of the lower extremity, followed by common peroneal nerve entrapment. A population-based study showed the incidence in diabetic subjects was 247 per 100,000 patient years, which was seven times the occurrence of the general population (age- and sex-adjusted incidence: 32.6 per 100,000 patient years). Because of the transient nature of meralgia paresthetica, no prevalence estimations were possible. It was noted that almost 1 out of 5 patients with this entrapment developed diabetes in ten years of follow-up, emphasizing the significant association between diabetes and compression neuropathy⁷¹.

Common peroneal nerve entrapment (fibular tunnel syndrome)

Common peroneal nerve compression is a well-recognized pathology, while entrapments of its branches, the superficial and deep peroneal nerves, are more elusive entities^{69,70}. The common peroneal nerve can become compressed at the neck of the fibula, with symptoms at the anterolateral calf, dorsal foot paresthesia or numbness, leg pain and foot/toe dorsiflexion weakness or foot drop. One study reported diabetes as underlying cause of common peroneal neuropathy in 5% of subjects⁷². A more recent study showed diabetes to be an underlying disease in 30.4% of patients with peroneal nerve palsy, which was significantly higher compared to the general population⁷³. However, entrapment neuropathies may be asymptomatic, and the latter study focused on acute symptomatic

neuropathy diagnosed with EDX or EMG. A study in 81 diabetic subjects, using the Tinel sign as diagnostic maneuver, showed that 55 to 59% of patients with neuropathy symptoms had signs of common peroneal nerve entrapment, compared to 10 to 17% of diabetic subjects without neuropathy symptoms⁶⁸.

Superficial peroneal nerve entrapment

The only study on prevalence estimates of this peripheral nerve entrapment is by Hashemi et al., reporting a Tinel sign in 23 to 31% of diabetic subjects with DSP, compared to 2 to 12% in those without DSP⁶⁸.

Deep peroneal nerve entrapment

Again, only Hashemi et al. reported on deep peroneal nerve entrapment in diabetic subjects, with 36 to 39% of DSP patients having a positive Tinel sign, versus about 5% in subjects without DSP symptoms⁶⁸.

Tibial nerve entrapment

Compression of the posterior tibial nerve is characterized by pain, sensory loss and paresthesias over the medial ankle and heel, sole of the foot and toes. In severe cases, muscle weakness is reported of toe flexors and intrinsic muscles. Entrapment sites include the soleal sling (proximal tibial nerve) and the tarsal tunnel. Several tests exist that aid its diagnosis, including the Tinel test, dorsiflexion-eversion test, Trepman test and the triple-compression test, which combines the Trepman and Tinel tests⁵. The study by Hashemi et al. demonstrated that in diabetic patients with symptoms of DSP, a positive Tinel sign is found at the tarsal tunnel in ± 43 to 59% of patients, compared to ± 5 to 10% in those without symptoms⁶⁸. For the proximal tibial nerve these numbers are $\pm 36\%$ versus ± 5 to 12%, respectively. Branches of the tibial nerve include the calcaneal, medial and lateral plantar nerves that can become entrapped in the fibro-osseous tunnels of the ankle and foot, of which no prevalence estimates are known.

In **Chapter VII** we discuss prevalence estimates of tibial nerve entrapment at the tarsal tunnel.

5 Dorsiflexion-eversion test: passive dorsiflexion and eversion of the ankle for 5 to 10 seconds, resulting in pain or numbness at the ankle or foot sole; Trepman test: passive plantarflexion and inversion, resulting in pain or numbness at the ankle or foot sole.

Table 2 Nerve entrapment neuropathies of the lower limb⁶.

Nerve	Site of compression	Symptoms	Surgical treatment (decompression/neurolysis)
N. cutaneous femoralis lateralis	Inguinal ligament / anterior superior iliac spine	Paresthesias, numbness or pain at the anterolateral thigh	Release of inguinal ligament and external/internal oblique/Sartorius fascia next to anterior superior iliac spine
N. peroneus communis	Fibular neck	Paresthesias or numbness at the anterolateral calf, leg pain or foot/toe dorsiflexion weakness or foot drop	Release of deep popliteal fascia and m. peroneus longus myofascial bands at the fibular neck
N. peroneus superficialis	Anterolateral lower limb	Paresthesias, numbness or pain at the dorsal foot, anterolateral calf and dorsum of foot/toes	Release of anterolateral, mid distal calf fascia
N. peroneus profundus	Dorsal foot	Paresthesias, numbness or pain at the first web space or sinus tarsi	Release of m. extensor hallucis brevis tendon/ dorsal foot fascia
N. tibialis	Soleal sling	Paresthesias, numbness or pain at the plantar foot	Release of the soleal sling at the most proximal aspect of the medial m. soleus
N. tibialis posterior	Tarsal tunnel	Paresthesias, numbness or pain at the plantar foot	Release of the flexor retinaculum of the tarsal tunnel
N. calcanei medialis	Tarsal tunnel	Paresthesias, numbness or pain at the medial ankle and/or heel	Release of the flexor retinaculum of the tarsal tunnel
N. plantaris medialis	Tarsal tunnel	Paresthesias, numbness or pain at the medial plantar foot	Release of the septum/fascia of the m. abductor hallucis (medial tarsal tunnel)
N. plantaris lateralis	Tarsal tunnel	Paresthesias, numbness or pain at the lateral plantar foot	Release of the septum/fascia of the m. abductor hallucis (lateral tarsal tunnel)
N. digitalis plantaris communis	Intermetatarsal webspace II to IV	Forefoot pain, paresthesias or numbness of the corresponding interdigital areas	Release of the intermetatarsal ligament

1.2.7 Epidemiology of diabetic foot ulceration and lower extremity amputation

The lifetime risk of developing diabetic foot disease is estimated to be 19-34% among patients with diabetes, with an annual incidence rate of 2 to 11%^{74,75}. The associated burden is high for both patient and the healthcare system⁷⁶⁻⁷⁹. Although healing of the foot is achieved in most patients (65.7 to 67.0% at 1 year follow-up), the recurrence rate is high with 40% at 1 year and 65% within 3 years^{80,81}. Current guidelines distinguish four key risk factors for the development of an ulcer: loss of protective sensation (i.e. the inability to sense the 10 g monofilament), peripheral artery disease, foot deformity and prior ulceration and/or lower extremity amputation⁸². Strategies to prevent these risk factors include rigorous glucose

6 Adapted from: Ducic et al. The role of peripheral nerve surgery in diabetic limb salvage. Plastic and Reconstructive Surgery, 2011.

control together with cardiovascular risk management, early detection of threatening conditions to the foot and education of patients. Foot ulcers are classified as neuropathic, neuro-ischemic or 'purely' ischemic by medical history and clinical examination as they have different outcomes regarding hospitalization, likelihood to heal and amputation⁸³. Infected foot ulcers, for example, have a 56-fold increased risk of hospitalization and 155-fold increased risk of lower extremity amputation compared with diabetic patients without foot infection⁸⁴.

The most burdensome and feared consequence of diabetic foot ulceration is limb amputation, which has an annual incidence of 0.3 to 1.8%^{75,85}. Diabetes underlies eight out of ten non-traumatic amputations, with the majority (85%) preceded by a foot ulcer⁸⁶. Major and minor lower extremity amputations are usually distinguished, with major amputations defined as the surgery carried out above ankle level and with minor amputations below ankle level. Minor amputations occur much more frequently compared to major amputations, with reported rates ranging from 5 to 21%, conditional on the population studied^{81,87,88}. Major amputations are necessary in up to 5% of patients^{81,89}. These interventions are associated with considerable costs, lowering of quality of life, increased risk of re-ulceration, impaired mobility and increased risk of death, with a 5-year survival rate after major amputation as low as 20 to 61%⁸⁶.

In **Chapter XI** the epidemiology of sensory loss in relation to ulceration is presented. In **Chapter XV** the in-hospital costs of diabetic foot ulcers and consequent amputations are explored.

1.2.8 *Epidemiology of falls*

Approximately one third of community-dwelling persons aged over 65 years fall at least once a year which makes accidental falls the most common mechanism of injury. Those injuries are often serious in nature, with 5 to 10% experiencing major head trauma, lacerations or fracture, not uncommonly resulting in hospitalization⁹⁰. The Longitudinal Aging Study Amsterdam established an incidence rate of recurrent falls of 129.7 versus 77.4 per 1000 person-years in patients with and without diabetes, with an adjusted hazard ratio associated with diabetes of 1.63 (1.06-2.52)⁹¹. The associated morbidity and mortality is high⁹².

In **Chapter IX** we discuss the incidence of falls in a population of diabetic patients, in relation to pedal sensory loss.

1.3 How does it start?

1.3.1 *Etiology of diabetes*

Diabetes is due to either the pancreas not producing enough insulin or the cells in the body not responding properly to the produced insulin (i.e. insulin resistance). Type 1 diabetes is caused by selective autoimmune destruction of the beta cell, located in the pancreas, inducing insulin deficiency and predominantly manifests itself in young people. Type 2 diabetes usually begins with insulin resistance and as the disease progresses a relative deficient insulin production is observed. The resulting malabsorption of glucose results in high blood glucose levels and other metabolic derangements, leading to the clinical entity of diabetes, which is characterized by symptoms such as frequent urination, thirst and increased hunger. Acute complications include diabetic ketoacidosis, hyperosmolar hyperglycemic state or death. Long-term complications are often divided in macrovascular complications (peripheral artery disease, coronary artery disease or stroke) and microvascular complications (e.g. diabetic nephropathy, neuropathy and retinopathy)⁹³.

Factors leading to impaired glucose intolerance and type 2 diabetes are captured in the term 'metabolic syndrome', and include insulin resistance, hypertension, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol and obesity. The prevalent metabolic syndrome not only makes patients prone to diabetes but also to cardiovascular disease, which is the major cause of death in approximately 50% of patients with type 2 diabetes⁹⁴.

1.3.2 *Etiology of diabetic sensorimotor polyneuropathy*

Hyperglycemia results in a cascade of metabolic changes that injure the peripheral nerve⁹⁵. The afferent nerves that supply the foot with sensation are the longest nerves in the body, with the small neuronal body residing in the dorsal root ganglia. Therefore, these long axons are more vulnerable most distally, since defective axonal transport, sparse vascular supply and impaired autoregulation firsts start insulting the nerve there. Nonetheless, neuropathy itself has its effects on a variety of tissues throughout the body, of which not all is elucidated yet⁹⁶.

Figure 2 Normal peripheral nerve (above) and nerve with neuropathy (below).

The process of demyelination of nerve fibers already occurs before symptoms may arise, whilst loss of axons is seen in more advance stages of DSP, correlating with most symptoms (Figure 2)⁹⁵. Moreover, precursors of overt diabetes can also be accompanied with painful sensory neuropathy, suggesting that abnormal glucose metabolism underlies a relevant proportion of 'idiopathic' sensory neuropathies. In a study where patients with idiopathic sensory neuropathies were subjected to an oral glucose tolerance test, 56% had abnormal results⁹⁷⁻⁹⁹.

Despite the variety of symptoms and causes of peripheral neuropathies, the pathways leading to neuropathy are now thought to be limited to six mechanisms (Figure 3)¹⁰⁰. Since this basic science is beyond the scope of this thesis, epidemiological evidence of the etiology leading to DSP are further focused on instead.

When risk factors of neuropathy are assessed on the population level, determinants of cardiovascular complications are usually found to be associated with neuropathy. These include level and duration of hyperglycemia and 'classic' factors such as body-mass index, smoking, hypertension and hypertriglyceridemia¹⁰¹⁻¹⁰³.

Figure 3 Summary of mechanisms leading to DSP.

Adapted from Yagihashi et al.. AGE, advanced glycation end-products; RAGE, receptor for AGE; ROS, reactive oxygen species; PARP, poly-Adenosine diphosphate (ADP)-ribose polymerase; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor. Cellular factors from bone marrow may play a role but are not fully elucidated yet⁽¹⁰⁴⁾.

1.3.3 Etiology of compression neuropathy

Two related phenomena are reviewed: 1) peripheral nerve enlargement as seen in diabetes and 2) nerve compression leading to dysfunction of the peripheral nerve.

Peripheral nerves in diabetic patients are frequently diffusely swollen, leading to entrapment at sites of anatomical narrowing⁵⁷. This phenomenon is observed in patients with and without symptoms of neuropathy. Peroperatively, frequently a yellowish discoloring of the nerve is observed, resembling fatty tissue. Places of narrowing are often found near joints, since nerves, amongst tendons and vessels that cross a joint, are held in position by ligaments that make the nerve susceptible to compression when enlarged. It is believed that the impairment of axonal flow in the diabetic nerve causes an accumulation of materials within the axon, leading to the observed increased cross sectional area^{57,105}.

This impairment is facilitated by the activated polyol pathway and takes place in both neurons and Schwann cells. Instead of converting glucose into glucose-6-phosphate by hexokinase, excess glucose is transformed into sorbitol by aldose-reductase. Sorbitol acts as osmotic driver due to its low plasma membrane permeability, causing accumulation of water in the nerve, leading to swelling¹⁰⁵.

In the process of chronic nerve compression, that is when the nerve becomes entrapped at fibro-osseous tunnels, several steps in the pathogenesis are distinguished (Figure 4). Firstly, there are changes in the blood-nerve barrier, followed by edema and fibrosis, focal demyelination, diffuse demyelination and finally axonal degeneration. This cascade leading to the detriment of nerve function is now further discussed.

Several processes lie at root of changes in the blood-nerve barrier, including higher fluid pressures surrounding the peripheral nerve due to edema and edematous synovium that becomes fibrotic, tethering the nerve, limiting nerve gliding and dwindling vascular supply¹⁰⁶. Increased tension on a nerve through positional or postural changes can have an important impact on venous outflow too, which is already at stake when pressure on the nerve is increased to 20 mm Hg. Wrist extension, for example, increases carpal tunnel pressures to 40 mm Hg¹⁰⁷. In the lower extremity, tension on the tibial nerve at the tarsal tunnel is increased when pronating the ankle¹⁰⁸. The impaired venous outflow during prolonged compression leads to venous stasis and causes capillary leakage, intraneural and extraneural edema and further intraneural pressure. Generally, pressures of 35 to 50 mm Hg reduce capillary flow, with 70 mm Hg blocking the microcirculation completely, resulting in ischemia^{109,110}.

Pressure induced endoneurial edema is also caused by inadequate lymphatic drainage, leading to inflammation and fibrin deposition in the early phases of compression. This early response is followed by proliferation of fibroblasts and capillary endothelium, implying the start of angiogenesis^{111,112}. Migrating macrophages, collagen deposition and the development of subperineurial and then intrafascicular fibrosis is then seen at the site of compression, followed by demyelination and remyelination processes, which are late sequelae. Axonal degeneration is thought not yet to occur during these demyelination and remyelination processes, which are Schwann cell mediated¹¹³. Remyelination, however, does not equip the axon with pre-compression quality myelin sheets and is characterized by thinner myelin and decreased intermodal length, resulting in decreased nerve conduction velocity³⁹.

Figure 4 Summary of mechanisms leading to nerve dysfunction due to compression.

Legend: Adapted from Mackinnon and Dellon et al..(27, 42).

During nerve compression, not every fascicle is affected evenly and adjacent fascicles may appear normal. Unmyelinated fibers were observed to be more vulnerable than myelinated fibers in histopathology of radial sensory nerves of patients with this entrapment¹¹⁴. The localized nature of pathology may explain the variability in reported symptoms and translates to the clinic of patients with, for example, proximal tibial nerve compression at the soleal

slings. Some patients may have more weakness of flexor digitorum longus, posterior tibial muscle or flexor hallucis longus than others, depending on the topography of the nerve compression¹¹⁵. Motor functions are generally lost at last, due to the thicker protective myelin sheaths motor fibers are equipped with.

Other conditions that have been associated with nerve compression syndromes are thyroid disease and alcohol abuse^{116,117}. Risk factors for entrapment neuropathy include repetitive stress (e.g. vibration) and are mostly described for the upper extremity^{118,119}. Rapid weight loss and squatting are associated with common peroneal nerve entrapment. Other causes of lower extremity nerve entrapment are trauma or chronic external compression (e.g. habitual leg-crossing, during anesthesia, ganglion cyst, cast or orthosis). The possibility of double-crush lesions in peripheral nerves should always be considered and managed concordantly¹⁰⁶.

1.3.4 *Etiology of diabetic foot ulcers and lower extremity amputations*

Diabetic foot ulcers (DFUs) develop as a result of neuropathy, localized vertical or shear stress leading to callous formation and/or repetitive (minor) trauma⁷⁴. Neuropathy comes in different forms and all have influence on the development of DFUs. Autonomic neuropathy (e.g. small fibers) results in dry skin. DSP and superimposed entrapment neuropathy results in the loss of sensation and motor innervation, the latter leading to joint limitations and foot deformities and thereby localized increased pressures leading to skin breakdown⁸². Although peripheral artery disease (PAD) is a factor in the pathogenesis of DFU formation, it is particularly important in the likelihood of DFUs to heal¹²⁰. PAD among diabetic patients affects more distal calf arteries and causes longer arterial occlusions than PAD among non-diabetic patients¹²¹⁻¹²³. Calcifications are typical tunica media sclerosis, in contrast to atherosclerosis where calcifications are diffusely intimal¹²⁴. It has been suggested that DSP has a role in the development of tunica media sclerosis and acts as an independent risk factor on cardiovascular risk¹²⁵. DFU or DFU related amputations are an important risk factor for re-ulceration and consequent re-amputation due to altered limb biomechanics¹²⁶. Other risk factors for ulceration are visual impairment, diabetic nephropathy, poor glycemic control and smoking^{74,127}.

In general, DFUs are categorized as neuropathic, neuro-ischemic or 'purely' ischemic¹²⁸:

- Neuropathic ulcers: present foot pulses but with elevated vibration thresholds or loss of protective sensation.
- Neuro-ischemic ulcers: a toe pressure of 40-70 mmHg and/or ankle pressure index <90%, but ankle pressure $\geq$ 75 mmHg and elevated vibration thresholds or loss of protective sensation.
- Ischemic ulcers: a toe pressure <40 mmHg and/or ankle pressure <75 mmHg.

As mentioned previously, this categorization is a first step in stratifying the at-risk foot according to its etiology. DFUs are frequently complicated by infection (58% at presentation, 82% during hospitalization), lowering the odds of a favorable outcome¹²⁹. PAD exerts the chances of limb salvage negatively^{83,130}. Other risk factors for lower extremity amputations include concurrent co-morbidities, depth of the ulcer and male gender^{75,80,130}.

The International Working Group on the Diabetic Foot (IWGDF) currently concludes that no existing classification is able to predict the outcome of an individual ulcer, but recommends the Infectious Diseases Society of America/IWGDF classification for infection assessment and the WIfI (Wound, Ischemia, foot infection) classification for perfusion assessment and likelihood of beneficial revascularization. The SINBAD classification is recommended for the audit of DFU outcomes in population studies⁸².

In **Chapter III, IV** and **V** we present methods of grading the most important risk factor for diabetic foot ulceration: sensory loss. In **Chapter VI** and **VIII** data reduction techniques are used to quickly estimate the overall degree of sensory loss at the feet and to predict ulcer-free survival, with a selection of tests. In **Chapter X** the natural history of tarsal tunnel syndrome in diabetic subjects is presented, in light of diabetic foot ulcer development. In **Chapter XI** the long-term outcomes on risk of DFU in light of degree of sensory loss are reported.

1.3.5 *Etiology of falls*

Maintaining balance is achieved by the interplay between sight, proprioception (touch) and the vestibular system. Increasing age and diseases influence the sensory input from the respective organs¹⁰. Risk factors for falls include, amongst others, orthostatic hypotension, visual impairment, impairment of gait or balance, medication use, limitations in basic or instrumental activities of daily living and cognitive impairment. These factors are often intertwined, with risk factors from the medical domain having effects on the functional and mental domains and vice versa¹⁰. In diabetic subjects, for example, diminished sensory perception from the lower limbs due to neuropathy places this group at even higher risk of falling compared to age-matched controls¹³¹.

In **Chapter IX** we address the influence of sensory loss on balance and falls in the diabetic population.

1.4 Can we do anything about it?

1.4.1 Preventing diabetes

Prevention of diabetes itself is key in avoiding the detrimental effects of its complications. Preventing type 1 diabetes is not foreseen in the near future, since (genetic) factors that trigger the onset of the disease are largely unknown¹³². Type 2 diabetes could be partially prevented when physical inactivity, obesity and other underlying causative risk factors for diabetes are addressed. Randomized controlled trials have shown that in individuals at high risk for developing diabetes (i.e. having glucose intolerance) progression to overt diabetes can be stalled with interventions such as oral blood glucose lowering drugs, weight loss, physical activity and diet¹³³⁻¹³⁵. Testing for diabetes in symptomatic patients who are overweight (BMI 25-29 kg/m²) or obese (BMI $\geq$ 30 kg/m²) and have additional risk factors (e.g. high-risk race (e.g. Indo-Surinamese, Latin-Americans), hypertriglyceridemia, physical inactivity, hypertension etcetera) is recommended from age 45 years at 3-year intervals. Monitoring and medical treatments and lifestyle interventions are the cornerstone of modern diabetes care to prevent progression to its complications⁹³. Many of these interventions have proven to be cost-effective¹³⁶.

1.4.2 Preventing diabetic sensorimotor polyneuropathy

The randomized controlled Diabetes Control and Complications Trial (DCCT) and its follow-up, the observational Epidemiology of Diabetes Interventions and Complications (EDIC) studies showed that in type 1 diabetes intensive glucose control to achieve normoglycaemia prevents or delays progression of DSP and cardiovascular autonomic neuropathy¹³⁷. However, the effects are less clear in type 2 diabetes. It was suggested from earlier studies that tight glucose control early in the course of the disease, with patients by then having fewer comorbidities, was advantageous, but this was not confirmed in later studies¹³⁸⁻¹⁴¹. Enhanced glucose control reduces nerve conduction and vibratory threshold abnormalities but is also associated with significantly more periods of hypoglycemia. Interestingly, periodontal treatment benefits glycemic control and reduces the risks of cardiovascular disease¹⁴². Ample pharmaceutical trials have been conducted to study interventions that prevent the onset or modify the natural history of DSP. Unfortunately, virtually none are applied in clinical practice due to conflicting evidence or too small effects observed⁹⁵.

Multiple risk factor-lowering interventions were shown not to be of benefit in preventing DSP, but clear benefits in preventing (microvascular) retinal and kidney complications were observed¹⁴³⁻¹⁴⁵. It may be that the methods used to diagnose and quantify DSP were not sensitive or robust enough to quantify the condition and therefore not able to distinguish differences between study arms.

1.4.3 Preventing lower extremity nerve compression

The prevention of lower extremity nerve compressions is mainly attributed to its main risk factor: diabetes itself. Other risk factors associated with lower extremity nerve entrapments are a history of cisplatin and paclitaxel use, alcohol abuse, colchicine and vitamin B6 deficiency, amongst others¹⁴⁶⁻¹⁴⁸. Since peripheral nerve enlargement is associated with entrapment, nerve compressions should be actively sought-after for in diabetic patients with symptoms of neuropathy. The treatment of choice depends on the patient and is characteristics, but is in general a surgical release of the entrapped nerve²⁸. No clinical studies exist in prophylactically performing neurolysis to prevent symptoms or the detrimental effects of nerve entrapment, other than in the emergency setting (e.g. compartment syndrome)¹⁴⁹.

1.4.3 Preventing diabetic foot ulceration and lower extremity amputation

The cornerstones of DFU prevention are 1) identification of the at-risk foot, 2) educating patient, family and healthcare providers, 3) wearing appropriate footwear and 4) treating risk factors for ulceration. For all patients with diabetes an annual comprehensive foot examination to identify risk factors predictive of DFUs and amputations is recommended. This should include inspection for pre-ulcerative sign and deformities, assessment of pedal pulses and testing for loss of protective sensation. When risk factors are present, timely referral to (members of) a multidisciplinary diabetic foot team is recommended, especially those with a history of prior ulcer or amputation. Treatment of the at-risk foot by a multidisciplinary team has proven to be effective in reducing the incidence of major amputations¹⁵⁰⁻¹⁵². Aggressive treatment of cardiovascular risk factors improved 5-year survival of patients with DFU (52.0% vs. 73.2%), which is otherwise associated with a 5-year mortality of 40%^{153,154}.

Other measures by the patient self to prevent DFUs include daily inspection of the feet and inside of the shoes, appropriate foot care and self-monitoring of foot skin temperature when the foot is in remission from DFU, although only low to moderate quality of evidence is found for these recommendations⁸².

Infection and ischemia should be treated accordingly, with pursuit of at least one tibial artery potent to the foot in avoiding above ankle amputations¹⁵⁵. Limited evidence exists for digital flexor tendon tenotomy, Achilles tendon lengthening, metatarsal head resection, metatarsophalangeal joint arthroplasty or osteotomy to help prevent recurrence of plantar forefoot ulcers⁸². Since the recurrence rate of DFUs is high, it has been postulated that the patients' cured diabetic foot should be regarded as in remission, rather than being healed⁷⁴. The frequency of screening and integrated foot care should be scaled up with increased (recurrent) ulcer risk.

In **Chapter XI** the long-term outcomes of ulceration risk in light of degree of sensory loss are reported. In **Chapter XIV** the opportunities for diabetic limb salvage using plastic and reconstructive techniques are explored.

1.4.4 Preventing falls

Prevention starts with asking the patient about falls that have occurred the last year and if there are difficulties with balance or gait. If so, guidelines recommend a quick test of gait and balance and consequent comprehensive assessment, followed by a multifactorial intervention strategy¹⁵⁶.

Since the etiology of falls is often multifactorial and clinicians are usually more experienced in managing discrete diseases, the implementation of multifactorial healthcare-based strategies is difficult. Moreover, falls prevention requires trade-offs and meticulous reckoning of risks and benefits in, for example, drug prescriptions. Several trials have investigated the effects of interventions to reduce fall risk, targeting the domains that effect the systems that maintain balance (vestibular function, proprioception and sight)¹⁰. Balance, gait and strength exercise programs have proven to reduce risk significantly (estimated risk reduction: 14 to 49%), investigated in both a community and health-care setting. Discontinuation of psychotropic medication reduced the risk with 39% and standardized assessment of home hazards by an occupational therapist along with specific recommendations and follow-up after hospital discharge reduced the risk of falling with 20%¹⁵⁷. However, a meta-analysis of multifactorial interventions for preventing falls in older community-dwelling people brings into question the additional benefit of a multifactorial intervention program¹⁵⁸. Based on observational data, the following assessments are recommended to be able to intervene: circumstances of previous falls, medication use, vision, postural blood pressure, targeted neurologic examination (i.e. proprioception, cognition and muscle strength), targeted cardiovascular examination and home-hazard evaluation.

In **Chapter IX** we discuss screening on sensory loss to assess the risk of balance impairment and future falls in the diabetic population.

1.4.5 A new hope?

In the previous paragraphs measures to prevent lower extremity complications were reviewed. A focus was put on etiology and current medical practices, supplemented with current best evidence for intervention strategies that battle these burdensome conditions. However, there is one common denominator in preventing diabetic foot disease, lower extremity amputations and falls that has not been addressed yet: lower extremity nerve decompression (LEND) surgery.

LEND is the surgical procedure in which entrapped lower extremity nerves are released⁷. First described in a clinical study in 1992, and preceded by laboratory studies, dr. A. Lee Dellon and co-workers showed that in diabetic subjects with symptoms of DSP, neurolysis of the common and deep peroneal and posterior tibial nerves resulted in a significant improvement of symptoms and electro diagnostic parameters^{25,159}. The return of sensory modalities is reported in a majority of subsequent studies, which is reason for true optimism in a population of patients where sensory loss is normally sadly observed⁶⁴! Since sensory loss, and more specifically, loss of protective sensation is the most important driver in the cascade to DFU formation; this type of surgery has the potential to reverse the associated risks. Prospective studies with longer follow-up indeed showed that decompression of the before mentioned nerves resulted in a lower risk of ulceration compared to the normally observed natural history (incident ulceration: 0.25% vs. 15%, re-ulceration: 3.7% vs. 25 to 60%, at three years follow-up), with only one amputation necessary (0.2%)¹⁶¹. Moreover, another study showed that balance is improved after this type of surgery¹⁶². However, published reports on LEND surgery are mainly uncontrolled studies and case series, generating substantial controversies regarding the effects and promises to prevent lower extremity complications and falls¹⁶³⁻¹⁶⁵.

These issues will be further elaborated in this thesis, connecting peripheral nerve neuroscience, diabetic peripheral neuropathy, lower extremity complications and peripheral nerve surgery with each other.

In **Chapter XII** and **XIII** patient selection for LEND surgery is discussed. In **Chapter XVI** a model-based estimate of the cost-saving implications and health effects of LEND surgery is presented.

Chapter XVII is the end as well as the beginning. Although the chapter ends this thesis, it provides the reader with a glimpse in the near future, from which this thesis was just the starting endeavor: the first randomized controlled trial on LEND surgery.

7 Up to five decompressions per extremity are described in LEND surgery (as advocated by dr. A. Lee Dellon). These nerves are the 1) common peroneal nerve, 2) superficial peroneal nerve, 3) deep peroneal nerve, 4) tibial nerve at soleus arch and 5) tibial nerve (and its branches) at the tarsal tunnel.

Scope and outline of the thesis

The aim of this thesis is to extend the knowledge on diabetes related neuropathies, in particular assessment of somatosensory function and the clinical consequences of tibial nerve entrapment at the tarsal tunnel. With the recognition of possible nerve entrapments in the diabetic patient with symptoms of neuropathy, treatment options become available. The diagnosis, epidemiology, grading and natural history of peripheral neuropathy are described, together with its long-term consequences. Additionally, in-hospital costs of diabetic foot disease and amputations are reported, as complication of diabetes related neuropathy. With a focus on diagnosing and grading peripheral nerve pathology, this thesis aims to form a basis of future prediction research regarding adverse events and therapeutic considerations as well as preventive measures. One such therapeutic intervention is LEND surgery, of which the effectiveness and cost-effectiveness is explored using a disease progression model.

The research of most studies included in this thesis originated from the Rotterdam Diabetic Foot (RDF) Study, a large prospective observational cohort study that aims to investigate diabetes related neuropathy, with a special interest in diabetes related lower extremity entrapment neuropathy, and its sequelae (**Part II & III**). The RDF Study started in 2014 and follows a group of 416 diabetic subjects annually at Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands, in close collaboration with the Departments of Internal Medicine/Centre for Diabetes, Endocrinology and Vascular Medicine and Statistics & Education, Franciscus Gasthuis & Vlietland, Rotterdam and the Departments of Plastic, Reconstructive- and Handsurgery, Franciscus Gasthuis & Vlietland, Rotterdam, Erasmus University Medical Center, Rotterdam and University Medical Center Utrecht, Utrecht, the Netherlands. Side projects next to the RDF Study are presented as well in this thesis (**Part I, IV, V and VI**).

The first order

In **Part I** of this thesis, the neurobiology of touch is elucidated, together with a short description of somatosensory testing (**Chapter I**).

Assessing the feet of the diabetic patient

In **Part II** of this thesis, the assessment of the feet is described, in regard to normative sensation, altered sensation and diabetes related consequences. Normative data of spatial discrimination and cutaneous thresholds of the feet are reported (**Chapter II**) and these somatosensory functions are analyzed in diabetic subjects using quantitative sensory testing (**Chapter III**). Using advanced statistical techniques, hierarchical grading scales of lower extremity sensory loss are developed, on both ordinal and continuous outcomes (**Chapters**

IV and V). These scales allow the categorization of patients in their incurred peripheral nerve damage, and the associated medical decision-making in regard to treatments (**Chapter XII**) and risk stratification (**Part III**). Normative sensation is compared to both neuropathic and non-neuropathic diabetic subjects, as validation of the developed grading scales (**Chapter IV and V**). Item reduction techniques were used to curtail the number of tests to arrive at an estimate of overall degree of sensory loss at the feet (**Chapter VI**). The validity of the current physical examination to diagnose tibial nerve entrapment (the Tinel's sign) is investigated, and its prevalence is estimated in both large diabetic and non-diabetic study groups (**Chapter VII**).

Prediction of adverse events

Part III of this thesis is focused on the abilities of the screening test locations to predict ulcer-free survival. This is relevant as it might reveal on the locations where current screening instruments (10 g monofilament and tuning fork) should be placed on the feet to achieve greatest discriminative power (**Chapter VIII**). Furthermore, the relationship between pedal sensory loss, balance impairment, risk of falls and associated morbidity is investigated (**Chapter IX**). The long-term consequences of tibial nerve entrapment in relation to diabetic foot ulcer risk are described, unfolding the natural history of tibial nerve entrapment in diabetes (**Chapter X**). **Part III** concludes with the assessment of ulcer risk in light of the degree of pedal sensory loss (**Chapter XI**).

Treatment

In **Part IV** of this thesis, two treatment modalities are discussed for two different disease entities that are both sequelae of diabetes mellitus. Firstly, candidate selection and determinants of surgical outcome are investigated by a 5-year follow-up of patients participating in a previous study on LEND surgery (**Chapter XII**), together with a discussion on surgical outcomes in LEND surgery (**Chapter XIII**). Secondly, two case reports on the surgical treatment of DFUs using fasciocutaneous free flaps are used as an epitome to investigate the added value of plastic- and reconstructive techniques in the treatment of the diabetic foot (**Chapter XIV**).

Costs and cost-effectiveness

In **Part V** of this thesis, the in-hospital costs of diabetic foot disease are reported from a cohort of patients treated by a multidisciplinary diabetic foot team (**Chapter XV**). The cost-effectiveness of LEND-surgery as treatment option is evaluated by modeling the short-term and long-term consequences of this type of surgery, in selected patients (**Chapter XVI**).

The future

In **Part VI** of this thesis, the study protocol of a new endeavor to scrutinize the (cost-) effectiveness of LEND surgery is presented: the randomized controlled DeCompression (DECO) trial (**Chapter XVII**), is presented. As this trial protocol is the culmination of the research described in this thesis, the DECO trial is designed to give further evidence on the (cost-) effectiveness of LEND surgery in the prevention of falls, DFUs and amputations compared to current (non-surgical) care of the patient suffering from lower extremity neuropathy.

In the **General discussion** findings and implications of this research for future research and clinical practice are discussed. A special emphasis is laid on the **Valorization** of the results from these studies, to warrant societal utilization of its scientific outcomes.

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The first order

PART I

Chapter I

Touch – Normal skin neurosensory physiology

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Abstract

In the animal kingdom, functionally distinct mechanosensory cell types are tuned to selectively transduce diverse mechanical stimuli from the skin to the central nervous system. Examples include stretch, vibration and pressure. These touch modalities are essential in life and range from avoiding bodily harm to emotional exchange between animals, including humans. In this review, an overview of touch modalities is given and correlated with the clinical tests used these days. This serves the reader with a normative background on touch physiology, which is altered as seen in increasing age and different forms of neuropathy.

Introduction

The skin is the largest organ of the human body and the first barrier to our natural surroundings. It gives us protection against hazardous influences from various origins and plays an important role in how we are able to interact with the external environment. Touch enables us to use our extremities in a whole more delicate way, which makes them often the first to reach into the unknown to assess, recognize, manipulate and socially interact with each other.

The skin acts as a sensory organ, by transmitting information on touch stimuli, itch, temperature and pain to the central nervous system (CNS). All these sense modalities have distinct sensory corpuscles or nerve endings, which are innervated by myelinated and unmyelinated nerve fibers of varying thickness. Touch is a plethora of specific combinations of these mechanosensory end organs and the low-threshold mechanoreceptors (LTMRs) by which they are innervated.

Since peripheral nerve surgery is an important part of the work carried out by the plastic or reconstructive surgeon, it is the purpose of this review to give an overview of the structures that convey the different stimuli to the CNS, how it is processed and how their function can be tested, with clinically relevant instruments.

Skin anatomy

Mammalian skin is composed of two main layers; the epidermis, which provides the first barrier to the natural world and the underlying dermis, which serves as isolator and as a location for appendages of skin (Figure 1)¹. The epidermis is subdivided in strata, of which the predominant keratinocyte constitutes 95% of cells. Langerhans cells, melanocytes and Merkel cells form the rest of this layer. Other somatosensory corpuscles reside beneath the innermost layer, the stratum basale or stratum germinativum. Keratinocytes in this layer proliferate and migrate through the various strata to the outermost layer, while undergoing several stages of differentiation. During this process, cellular junctions (desmosomes) and an extracellular matrix consisting of keratin and lipids are formed that provide mechanical strength to the skin. The process of desquamation continuously replaces the outermost layer, the stratum corneum. The epidermis receives its nutrients via diffusion from blood capillaries extending to the upper layer of the dermis.

Figure 1 Glabrous skin anatomy.

Legend: SA, slowly adapting; RA, rapidly adapting; LTMR, low threshold mechanoreceptor. This is a figure from Zimmerman et al., *Science* **346**, 950—954 (2014), with permission to re-use via Copyright Clearance Center.

The stratum basale is made up of type III collagen, forming a thin sheet of reticular connective tissue between the epidermis and dermis. The dermis acts as a cushion from stress and strain and harbors the somatosensory corpuscles responsible for touch; nociceptors, that sense painful stimuli; pruriceptors, which convey itch; thermoreceptors, that register information on temperature; hair follicles, sebaceous glands, apocrine glands and lymphatic and blood vessels. The peripheral nerves near the skin continue into the subepidermal neural plexus, of which myelinated and unmyelinated fibers branch off and terminate in the dermis or continue through the basement membrane into the epidermis (Aδ and C-fiber nerve endings (high threshold mechanoreceptors (HTMRs)))^{2,3}.

The neural coding of touch

Mammals have both hairy and non-hairy, or glabrous, skin. Up to 90% of the body surface is covered with hairy skin. Glabrous skin is specialized in discriminative touch and therefore found on the ventral portion of the hands, soles of feet, lips, labia minora and glans penis of most mammals. Texture and shape can thereby be discriminated and recognized, providing feedback to the CNS with consequent executions like precision grip and locomotion⁴. The glabrous skin is characterized by its epidermal ridges, in which Meissner corpuscles reside in the dermal papillae, with the highest density found in soles of the feet and palm of the hand, especially the fingertips^{5,6}. The creases and ridges creating the finger or palm prints function to improve tactile sensitivity and grip. Compared to glabrous skin, hairy skin has considerable lower spatial acuity, however, it also has discriminative touch properties. Hairy skin has an important role in affective touch, such as stroking and nurturing.

The glabrous portions of skin have distinct somatosensory corpuscles that are innervated by LTMRs. Recent research suggests an important role of surrounding dermis and epidermis in which the LTMRs reside⁴. To comprehend the neurobiology of touch, we give an overview of how LTMRs end organs convey tactile stimulation. The central projections of LTMR subtypes terminate in the dorsal horn of the spinal cord, but also send collaterals to the dorsal column nuclei of the brainstem, at the junction of the spinal cord and medulla oblongata⁷. How this information is received, integrated and processed within the CNS is not discussed in this review.

Glabrous skin LTMRs

LTMRs are a diverse group of sensory neurons that are distinguished by their sensitivity to react to specific stimuli, adaptation pattern to mechanical stimulation and consequent conduction velocities (Table 1). Four fast conducting LTMRs are present in glabrous skin and their response to mechanical stimuli range from slow (SA), intermediate (IA) to rapidly adapting (RA). SA receptors respond to indentation of skin with continuous afferent firing during stimulation. RA receptors respond to movements and fire only at the onset and offset of stimulation. Slowly adapting type I and II responses are differentiated by their firing rates, receptive field sizes, tuning properties and regularity of their static-phase firing rates, with SA I fibers exhibiting a more irregular static-phase firing rate compared to SA II receptors⁸.

Table 1 Somatosensory receptors.

Receptor	Glabrous skin			Mammalian hairy skin					
	Merkel cell-neurite complex / touch dome [#]	Meissner corpuscle	Pacinian corpuscle	Ruffini corpuscle	Free nerve ending [#]	C-touch	Guard hair	Awl-Auchene hair	Zig-zag hair
Location	Basal layer of epidermis / circular to Guard hair follicles	Dermal papillae	Deeper dermis	Dermis	Predominant in epidermis, compared to dermis	Predominant in epidermis, compared to dermis	Epidermis/ dermis	Epidermis/ dermis	Epidermis/ dermis
Associated fiber	Aβ	Aβ	Aβ	Aβ	Aδ, C	C	Aβ	Aβ, Aδ, C-LTMR	Aδ, C-LTMR
Fiber diameter	6-12 μm	6-12 μm	6-12 μm	6-12 μm	1-5 μm, 0.2-1.5 μm	0.2-1.5 μm	6-12 μm	0.2-12 μm	1 to 5 μm, 0.2 μm
Conduction velocity	16-96 m/s	26-91 m/s	30-90 m/s	20-100 m/s	0.5-100 m/s	0.2-2 m/s	26-91 m/s	26-91 m/s	0.2-30 m/s
Afferent response	SA I-LTMR	RA I-LTMR	RA II-LTMR	SA II-LTMR	C-HTMR	IA-LTMR	RA-LTMR	RA-LTMR	IA-LTMR
Stimuli	Indentation depth, tactile discrimination, perception of texture and form / hair motion	Moving touch, handling objects, gnosis, flutter	Moving touch, handling objects, tactile vibration	Skin stretch, direction of movement, finger position	Noxious mechanical	Pleasant touch, social interaction	Hair movement, pleasant touch	Hair movement, pleasant touch	Hair movement, pleasant touch
Receptive field	9 mm ²	22 mm ²	Finger, hand, toe, foot	60 mm ²	1-3 mm ²	1-3 mm ²	Circumferential to hair follicle	Circumferential to hair follicle	Circumferential to hair follicle
Innervation density*	1.07/cm ²	4.62/cm ²	1.42/cm ²	1.42/cm ²	100/cm ² **	Per hair	Per hair	Per hair	Per hair
Clinical tests	S1PD, S2PD	M2PD, vibrations (30 Hz)	M2PD, vibrations (256 Hz)	Pinching	Pin prick	Light brush (hair follicle deflection)	Light brush (hair follicle deflection)	Light brush (hair follicle deflection)	Light brush (hair follicle deflection)
Response to stimuli	+++++++	++	++	++++++	+++++	+++++	+	+	+

Abbreviations: SA, slowly adapting; IA, intermediately adapting; RA, rapidly adapting; LTMR, low-threshold mechanoreceptor; HTMR, high-threshold mechanoreceptor; SI-PD, static one-point discrimination; S2PD, static two-point discrimination; M2PD, moving two-point discrimination; *, hallux; **, fingertip, since data from the hallux is unknown; #, also present in non-glabrous (hairy) skin. Data derived from Abraira, Kelly and Strzalkowski et al. (1-3).

Each cutaneous sensory neuron can be subdivided according to degree of myelination, axon diameter, axonal conduction velocity and cell body size. A β fibers are the largest sensory neurons and terminate in the Merkel cell-neurite complex, Meissner, Pacinian and Ruffini corpuscles LTMRs. A β fibers exhibit conduction velocities ranging from 16-100 m/s due to the thick myelin sheath, which are the fastest amongst sensory neurons. A δ fibers have medium cell body sizes and are lightly myelinated, with intermediate response velocities that vary from 5-30 m/s. C-type sensory neurons are the smallest, are unmyelinated and therefore exhibit slow axonal conduction velocities (0.2 – 2 m/s). C-fibers are most abundant in the skin. Together with A δ fibers, they are called free nerve endings and terminate in the epidermis, without innervating a specific somatosensory corpuscle. Based on their responses to cold, heat and noxious stimuli, thinly myelinated C and A δ fibers are also called nociceptors. However, the majority of C and A δ fibers exhibit responses below the noxious threshold and are therefore called HTMRs.

Slowly adapting receptors

The Merkel cell resides in the basal epidermis and is connected to the CNS via a single A β nerve fiber (Figure 1, 2). Predominantly found in glabrous skin where spatial acuity is needed, clusters of these specialized oval cells form a complex of up to 150 Merkel cells, with a single A β fiber supplying as many as 15 cells. The Merkel cell is anchored within the epidermis by desmosomes and its cytoplasmic protrusions sticking between adjacent keratinocytes⁹. The nested nature of the Merkel cell in its surroundings transduces physical external forces on the skin to its cell body. The terminal A β axon enlarges near the Merkel cell body and makes a synapse like connection to its dermal side. However, no classic neurotransmitters are involved in the transmission of signals. Instead neuropeptides might be responsible, which reside in vesicles near the 'postsynaptic' region. When glabrous skin is not touched, SA I-LTMRs remain silent and are relatively insensitive to skin stretch of adjacent receptive fields⁶. The afferent response to static skin indentation is linearly correlated with its depth and is characterized by a SA I response, with a high-frequency dynamic phase during initial skin indentation and lower frequency, tonic firing during prolonged indentation. Recent research suggests that both Merkel cells and A β SA I-LTMRs respond independently to skin stimulation, with Merkel cells signaling to terminal axons to activate the LTMR¹⁰. The density of Merkel cell-neurite complexes and their related innervation pattern allows us to perceive a highly accurate spatial image of tactile stimuli. Edges, corners and small protrusions are recognized by very low thresholds of skin displacement (less than 15 μ m), which comes into use in, for example, reading braille by the blind¹¹.

Figure 2 Details of Merkel cell, Meissner and Pacinian corpuscles.

Legend: SA, slowly adapting; RA, rapidly adapting; LTMR, low threshold mechanoreceptor. This is a figure from Zimmerman et al., *Science* **346**, 950–954 (2014), with permission to re-use via Copyright Clearance Center.

Sensitivity of spatial discrimination in an area of skin is determined by two factors. First is the size of the mechanoreceptors field, i.e. Pacinian corpuscles have an extremely broad receptive field encompassing the whole finger or palm, whereas those of Meissner corpuscles and Merkel cell complexes are smaller (22 mm² and 9 mm², respectively). Second is the density of receptors in the skin. Very fine tactile discriminations are conveyed by a higher number of receptors, which results in more afferent information to the CNS. For clinical practice it is important to know that the slowly adapting fiber/receptor system conducts information on constant touch and tactile gnosis, which is tested with static-one point discrimination tests (S1PD), such as monofilaments, and the latter with two-point discrimination tests (S2PD). S2PD will evaluate the innervation density of this fiber/receptor system (just as monofilaments tests the threshold of this fiber system)¹².

The Ruffini end organ is found in the dermis and is cylinder shaped, composed of Schwann cell layers, collagen fibers and a core where nerve fibers in terminate (Figure 1). The density of Ruffini endings is lower compared with Merkel cells, and their receptive fields are about five times larger. Aβ SA II-LTMRs innervates them, with one central low-threshold spot for each fiber that terminate in a Ruffini ending. They are very sensitive to skin stretch and changes in skin shape. They are probably most important in detection of object motion and proprioception by skin stretch. No simple clinical tests is available that solely tests the SA II-LTMR.

Rapidly adapting receptors

The Meissner corpuscle resides in the dermal papillae and is elliptical structured with up to three Aβ RA I-LTMR axons coiling between the lamellar cells (Figure 1, 2, 3)¹³. Up to

30-80 corpuscles can be innervated by a single RA I afferent fiber¹⁴. The Meissner corpuscle is formed by discoid shaped, Schwann cell derived, lamellar cells and are encapsulated by a fibroblast capsule, from which collagen fibers connect with the surrounding basal layer. It reacts to low vibrations (flutter) and motion across the skin. During skin indentation the lamellar cells are compressed via the collagen fibers, generating a RA response. When the stimulus is removed the corpuscle regains its shape, which results in the off-response. Due to its unique response properties, RA I-LTMRs are about four times more sensitive, but with less spatial acuity when the stimulus is moved across the receptive fields, compared to SA I-LTMRs. Moreover, the RA I-LTMR responds consistently and with short latencies to movements on skin, making it able to detect 'losing grip' quickly¹⁵. It is concluded that SA I-LTMRs and RA I-LTMRs complement each other like cones and rods do in the retina in acquiring a spatial image⁸. Interestingly, some corpuscles are innervated by up to two unmyelinated C-fiber afferent axons, suggesting nociceptive properties of the Meissner corpuscle¹⁴. The moving two-point discrimination test will evaluate the innervation density of the quickly-adapting fiber/receptor system (just as vibration tests would assess the threshold of this fiber system).

Figure 3 Immunohistochemistry image of Meissner corpuscle.

Legend: afferent axon displayed in yellow/green. Lamellar cells in red.
Figure gently supplied by Therapath Neuropathology LLC, New York, NY, USA.

The Pacinian corpuscle is located deep in the dermis and contains lamellar cells that are shaped in an onion-like layered manner (Figure 1, 2). During surgery, Pacinian corpuscles are observable with the naked eye as small granule-like structures. They are innervated by a single, thick A β -RA II-LTMR and have foot like protrusions of axons (i.e. filopodia) sticking out of the neuron, into the fluid between the lamellar cells. These structures are thought to be the site of mechanical stimulus recognition, generating action potentials. Pacinian corpuscle afferents detect high frequency vibrations. When closely reviewing the anatomy of both the Meissner and Pacinian corpuscles, evidence of the working mechanisms of how vibration and movement across the skin are processed can be found. In the Pacinian corpuscle, for example, the outer-core lamellar cells and fluid act as filter that mutes low-frequency vibrations, letting only high-frequency signals through to the axonal filopodia. In Meissner corpuscles it is however unknown why this signaling is only the result of low frequency vibrations¹⁶. Non-neuronal cells of cutaneous LTMR end organs have probably a more important role than historically has been appreciated, with even the potential to signal directly to the afferent system using chemicals rather than purely mechanical forces¹⁷. RA II-LTMRs are very sensitive to high-frequency vibration, which are transmitted when, for example, someone stands on the foot sole, but ceases quickly. The amplitude thresholds are lower than RA I-LTMRs thresholds, making RA II-LTMRs more sensitive, especially important when moving an object in the hand. Approximately 2,500 corpuscles are found in the hand, with larger densities found in the fingers. They are located deep in the dermis and have large receptive fields, encompassing larger portions of finger, hand or foot (median in the foot sole: 284.2 mm² (range: 41.7-1248)¹⁸. For clinical practice it is important to know that this fiber/receptor system conducts information on moving touch, tactile gnosis and high frequency vibrations, which is tested with M2PD and tuning fork.

Non-glabrous skin LTMRs

Most studies on mechanotransduction by hairs are done in mice or by in vivo recordings in the cat or rabbit and less is known of the structure and function in humans⁸. It is however briefly reviewed, since majority of data is derived from mammalian species. Next to isolation, hairs have a role in emotional touch. Mice fur has four different anatomical types of hair: guard (straight and long in length), awl/auchene (medium length, where the auchene has a bend) and zigzag (short in length with multiple bends) (Figure 4). The latter is the most abundant⁸. In hairy skin, specialized terminals around hair follicles allow touch sensation by movement of hairs. These touch domes are innervated by A β SA I-LTMRs and are positioned above the sebaceous glands of guard hair follicles. Below these glands, collars of LTMR terminals are found, of which the inner lining is composed of so-called lanceolate terminals in line with the direction of the hair shaft¹⁹. Also a circumferential subtype exists, all differing in their sensitivities, adaptation properties and conduction velocities (Table 1).

The lanceolate endings detect hair deflection and light touch of the skin and are innervated by A β RA-LTMRs, A δ -LTMRs and C-LTMRs. A δ -LTMRs are also rapidly adapting similar to the LTMRs associated with Meissner corpuscles in glabrous skin and detect movement and low-frequency vibration.

Figure 4 Innervation of non-glabrous skin.

Legend: SA, slowly adapting; RA, rapidly adapting; LTMR, low threshold mechanoreceptor. This is a figure from Zimmerman et al., *Science* **346**, 950–954 (2014), with permission to re-use via Copyright Clearance Center.

High-threshold mechanoreceptors

HTMRs protect the body against harm and are found in the epidermis of both glabrous and non-glabrous skin. The free nerve endings are divided in A δ - and C-fibers, which differ in sensitivity to thermal stimuli. A δ -fibers mediate mechanical pain and noxious heat or cold stimuli, with C-HTMRs only responding to mechanical stimuli²⁰. HTMRs can be further subdivided according to their expressive profiles of neuropeptides, which is not further reviewed, but results in differences of function and thereby therapeutic options²¹. Accumulating evidence suggest that A β fibers also conduct nociception, which is important in interpreting fast conducting large diameter afferents, as they do not solely seem to innervate low threshold mechanoreceptors²². Free nerve ending function is tested clinically with a pinprick.

In conclusion

As shown in this short review, each LTMR conveys a specific feature of the force that is imposed on skin when touched. The collective interplay between these signals is in the brain recognized as a distinct touch modality. The ultrastructure of LTMRs give clues how forces are coded into electrical signals, of which not all is elucidated. Knowledge of these basic neurophysiologic properties aids the clinician in interpreting somatosensory test results that are altered, due to increasing age or diseases like neuropathies, aiding patient's follow-up or intervention.

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Assessing the feet of the (diabetic) patient

PART II

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Chapter II

Normative data for cutaneous threshold and spatial discrimination of the feet

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Abstract

Introduction

No data are available for normative values of cutaneous threshold and spatial discrimination of the feet. We developed clinically applicable reference values in relation to the nerve distributions of the feet.

Methods

We determined foot sensation in 196 healthy individuals. Cutaneous threshold (1-point static discrimination, S1PD) was tested with monofilaments (0.008 to 300 gram) and spatial discrimination [2-point static and moving discrimination (S2PD, M2PD)] on 5 locations per foot.

Results

There was a significant age-dependent increase in S1PD, S2PD, and M2PD values ($P < 0.05$). No significant differences were found between both feet. S1PD values differed up to 0.8 g between genders. There were no significant differences between genders for S2PD and M2PD measurements. M2PD values were generally lower than S2PD values.

Discussion

This study provides age-related normative values for foot sensation to help clinicians assess sensory deficits in relation to aging and identify patients with underlying nerve problems.

Introduction

Alterations in the sensation of the feet are seen as complications in a variety of diseases, and diabetes mellitus, alcohol misuse, and HIV infection are the most common causes¹. Sensation of the feet is of utmost importance for a proper gait cycle, for maintaining standing balance, and for protection against mechanical, thermal, and chemical injury. Regardless of the cause of diminished sensation, sensory loss above a certain threshold places patients at risk for falls and injury to the feet. In diabetes, sensory loss is often seen in the context of diabetic sensorimotor polyneuropathy, causing a decreased quality of life and an associated increased mortality^{2,3}. Monitoring impairment of nerve function is essential to identify the foot at risk. Monofilaments and spatial discrimination have proven to be sensitive and easily applicable in different settings^{4,5}. International guidelines recommend screening for the loss of protective sensation with a 10 g monofilament to identify diabetics at risk for foot ulceration^{6,7}. However, a cutaneous threshold (static 1-point discrimination, S1PD) above 10 g is an indicator of large-fiber demyelinating neuropathy^{3,8}. The loss of spatial discrimination is related to axonal loss and is less painfully tested with a more easily applicable method compared to nerve conduction studies⁹. However, measurement of spatial discrimination is somewhat subjective^{10,11}.

Skin sensation is inversely related to age^{5,12-14}. Due to physiological changes in peripheral nerves, a combined loss of sensory receptors and nerve fibers may occur, and both contribute to changed cutaneous threshold and innervation density^{15,16}. The cutaneous threshold is the amount of force applied to the skin to elicit a response. Innervation density is the amount of intact sensory receptors and nerve fibers in the skin. Semmes-Weinstein monofilaments [SWMs (S1PD)] and static- and moving 2-point discrimination (S2PD and M2PD) test the cutaneous threshold and spatial discrimination (innervation density), respectively. The latter become abnormal before current recommended screening instruments for the loss of sensation^{5,17}.

No extensive data are available for normative values of S1PD, S2PD, and M2PD of the feet, and there is poor or no information on stratification for age and gender^{18-22,9}. This information is valuable in, for example, bilateral comparisons between the feet or to identify individuals at increasing risk of falls, ulcerations, or amputations. In order to address these shortcomings, we aimed to develop clinically applicable reference values in relation to the nerve distributions of the feet. Validity and sensitivity of 2-point discrimination was investigated in diabetic patients with mild sensory loss.

Materials and methods

Study design and subjects

Between July and December 2015, 196 healthy volunteers were measured at outpatient clinics of the Franciscus Gasthuis and Erasmus MC Medical University Center, Rotterdam, the Netherlands. They were recruited from hospital and university personnel, relatives, and friends of patients. Inclusion criteria were: age >18, no significant cognitive impairment, Dutch or English speaking, and able to provide written informed consent. Exclusion criteria were: active radicular syndrome, neurological disease interfering with sensation of the feet, diabetes, thyroid malfunction, a history of alcohol abuse, HIV, or chemotherapy and inability to give informed consent. A short questionnaire assessed the relevant medical history (history of cancer, foot ulceration, operations, and autoimmune disease). No reimbursement was given. All subjects provided informed consent. The Medical Ethical Committee of Erasmus MC Medical University Center, Rotterdam, the Netherlands approved the studies.

Patients with diabetes and sensory loss

Baseline data from patients (≤ 60 years) with no cutaneous threshold >10 g in at least 3 of 5 test locations and no prior ulcers or amputations included in the Rotterdam Diabetic Foot Study (RDF-study) were used to determine construct validity and sensitivity of S2PD and M2PD measurements at the right hallux. The RDF-study is a prospective cohort of diabetics followed at our institution to investigate the deterioration of sensation of the feet over time.

Sensory tests

Cutaneous threshold (S1PD) was tested on 5 locations [pulp of first and fifth toes, medial heel (above callus), first web, and lateral foot] of each foot with a new set of SWMs (Baseline® Tactile™, USA) ranging from 0.008 to 300 grams. The test sites were chosen in concordance with the nerve distribution of the foot: I, hallux [medial plantar nerve (tibial nerve)]; II, medial heel [calcaneal nerve (tibial nerve)]; III, dorsal first web (deep fibular nerve); IV, lateral foot (sural nerve), and V, fifth toe (lateral plantar nerve) (Figure 1). Areas with excessive callus formation were avoided. Testing started at the first (I) test location (hallux) of the left foot, then the left medial heel (II), etc. Spatial discrimination (S2PD, M2PD) was assessed on the same test locations with the Disk-Criminator™ (US Neurologicals, LCC, WA, USA). A Rydel-Seiffer tuning fork (Martin, Tuttlingen, Germany) tested the vibration threshold at the dorsal interphalangeal joint of the hallux and medial malleolus. Three researches with considerable experience in sensory testing of subjects with diabetes carried out the measurements using the same research protocol and instruments. Sensory testing was done in a quiet soundproof room kept at a constant temperature. For all measurements, participants were asked to close the eyes. The SWMs were applied with the accepted technique of applying

force at right angles to the filament. The monofilament was applied to the skin for 1 to 2 seconds, using 3 trials. The lowest score was noted for which the patient could feel the stimulus, at the correctly answered test site. In the assessment of S2PD and M2PD, the difference between 1- and 2-point (13 to 15mm) stimulation was demonstrated on the index finger. The patients were told that their replies were not judged to be right or wrong. The difference between 1- and 2-point stimulation was again demonstrated on the pulp of the left hallux at the start of the test series. The minimal discriminatory distance was recorded.

Figure 1 Roman capitals indicate test locations: I, hallux; II, medial heel; III, first dorsal web; IV, lateral foot, and V, fifth toe.

Data analysis

Kolmogorov-Smirnov tests were used to assess normality. A logarithmic transformation of the SWMs in grams was used to convert the S1PD measurements to a linear scale. Differences between the feet of the individuals were assessed with a Wilcoxon signed rank test (S1PD, S2PD, M2PD). Differences between genders were assessed with the Mann-

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Whitney U test. Differences between test locations were assessed using a Friedman test (S1PD, S2PD, M2PD). Pairwise comparisons were performed with a Bonferroni correction for multiple comparisons. Estimated effect size was calculated by converting Z-scores with the equation $r = Z / \sqrt{n}$. Spearman rho coefficients (r_s) were used to assess correlations. M2PD measurements of the fifth toe were not taken into account due to a too small area to conduct the test, resulting in unreliable measurements and missing data.

All statistical analysis was carried out using IBM SPSS Statistics 22.0 (IBM, New York, USA) and R (Foundation for Statistical Computing, Vienna, Austria), URL <http://www.R-project.org/>, together with LMS and GAMLSS packages. The GAMLSS method is the method of choice to construct age-related reference ranges for skewed data, when the response variable does not follow an exponential family distribution or exhibit heterogeneity²³⁻²⁵. We accounted for the censored nature of S2PD and M2PD measurements using the method by Stasinopoulos²⁶. We used penalized B-spline to model the location parameter and the linear function of the distribution. In these models the sensory tests are described using parametric distributions, the parameters of which develop smoothly with increasing age. Reference values depending on age were calculated for S1PD, S2PD and M2PD (ninety-fifth percentile values, corresponding to a chosen specificity of 95%). These estimated values were used to assess sensitivity of S2PD and M2PD measurements. Upper 5% values were considered abnormal, for all age categories. Volunteers were categorized according to their age, forming 7 age decade groups. The Spearman rank correlation coefficient was calculated to assess age-related correlations with S1PD, S2PD, and M2PD measurements. Construct validity of S2PD and M2PD measurements by the Disk-Criminator™ were assessed by correlating them with Rydel-Seiffer tuning fork values (Spearman rank test). *P*-values <0.05 (2-sided) were considered statistically significant.

Results

General characteristics

For this cross-sectional study, 196 healthy individuals [mean (SD) age 51.1 y (17.9), range 20.8-89.8] were included. Sixty-six men and 130 women were studied. Significant differences between both feet were present for S1PD on the first dorsal web ($Z=-2.350$, $P=0.019$, $r = -0.17$), S2PD on the hallux ($Z=-3.342$, $P=0.001$, $r = -0.24$), and M2PD on the lateral foot ($Z=-2.636$, $p=0.008$, $r = -0.19$). Due to the fact we only found differences between the feet for 3 of 14 measurements, we used the measurements of both feet to develop reference values for all test locations.

Assessing the cutaneous threshold with static 1-point discrimination

There was a significant age-dependent increase in S1PD measurements at all test locations ($P=0.0001$). Significant differences were also found between men and women for S1PD measurements at the hallux ($U=13749.0$, $P=0.001$, $r = -0.16$), first dorsal web space ($U=14921.0$, $P=0.036$, $r = -0.11$), lateral foot ($U=13845.0$, $P=0.01$, $r = -0.16$), and fifth toe ($U=14776.0$, $p=0.027$, $r = -0.11$). Four of 5 measurements differed between the genders but did not exceed 1 standard error of the mean (1.1 g), as a measure of minimum clinically relevant difference. Therefore, no gender-specific percentile curves were plotted²⁷. Significant differences in S1PD values were found between test locations of the left foot, $\chi^2(4) = 222.708$ ($P<0.0005$), as well as the right foot, $\chi^2(4) = 173.515$ ($P<0.0005$), see Table 1 for pairwise comparisons. Table 2 shows the mean and 95% percentile values per age span, which were calculated as reference values. To illustrate the relationship between age and cutaneous threshold, the LMS method was used to draw the 2.5%, 16%, 50%, 84%, and 97.5% percentile plots (Figure 2).

Assessing spatial discrimination with static 2-point discrimination

There was a significant age-dependent increase in S2PD measurements on 4 test locations ($P<0.05$) except for the medial heel ($r_s=0.071$, $P=0.163$). No significant differences between men and women were found for S2PD measurements. Significant differences were found between the test locations of the left foot, $\chi^2(4) = 13.054$ ($P=0.011$) as well as the right foot, $\chi^2(4) = 25.605$ ($P<0.0005$), see Table 1 for pairwise comparisons. Table 3 shows the mean and 95% percentile values per age span, which were calculated as reference values. The LMS method was used to draw the regression of S2PD to age, together with percentile plots (Figure 3).

Figure 2 Static 1-point discrimination (S1PD) of the foot. A normal distribution was used to fit a GAMLSS. Degrees of freedom were 2.0 (hallux), 3.4 (medial heel), 3.6 (first dorsal web), 2.0 (lateral foot), and 3.0 (fifth toe). Percentile plots: 2.5% (lowest dotted black), 16% (lower dashed red), 50% (middle continuous green), 84% (upper dashed red) and 97.5% (uppermost dotted black).

Figure 3 Static 2-point discrimination (S2PD) of the foot. Generalized Gamma function was used for fitting a GAMLSS. Degrees of freedom were 2.6 (hallux), 3.5 (medial heel), 3.2 (first dorsal web), and 2.0 (fifth toe). Percentile plots: 2.5% (lowest dotted grey), 16% (lower dashed red), 50% (middle continuous green), 84% (upper dashed red) and 97.5% (uppermost dotted grey).

Table 1 Differences between test locations per foot. Median 1-point static and static/moving 2-point discrimination per test location.

	S1PD at hallux	S1PD at medial heel	S1PD at first dorsal web	S1PD at lateral foot	S1PD at fifth toe	Median log 10 (amount of force in gram). Left foot.	Median log 10 (amount of force in gram). Right foot.
S1PD at hallux		0.052	<0.0005*	<0.0005*	<0.0005*	0.1461 (1.4)	0.1461 (1.4)
S1PD at medial heel	<0.0005*		<0.0005*	<0.0005*	0.384	0.0000 (1.0)	0.0000 (1.0)
S1PD at first dorsal web	<0.0005*	<0.0005*		<0.0005*	<0.0005*	-0.3979 (0.4)	-0.2219 (0.6)
S1PD at lateral foot	<0.0005*	<0.0005*	0.017*		0.384	-0.2219 (0.6)	-0.2219 (0.6)
S1PD at fifth toe	<0.0005*	1.000	<0.0005*	0.080		0.0000 (1.0)	0.0000 (1.0)
	S2PD at hallux	S2PD at medial heel	S2PD at first dorsal web	S2PD at lateral foot	S2PD at fifth toe	Median S2PD (mm) left foot.	Median S2PD (mm) right foot.
S2PD at hallux		<0.0005*	0.078	0.004*	1.000	8.0	8.0
S2PD at medial heel	0.619		1.000	1.000	0.039*	10.0	9.5
S2PD at first dorsal web	1.000	1.000		1.000	1.000	9.0	8.0
S2PD at lateral foot	1.000	1.000	1.000		0.204	8.0	10.0
S2PD at fifth toe	1.000	0.008*	0.409	0.740		8.0	8.0
	M2PD at hallux	M2PD at medial heel	M2PD at first dorsal web	M2PD at lateral foot		Median M2PD (mm) left foot.	Median M2PD (mm) right foot.
M2PD at hallux		<0.0005*	0.043*	1.000		7.0	6.0
M2PD at medial heel	0.116		1.000	0.011*		7.0	7.0
M2PD at first dorsal web	0.447	1.000		0.419		8.0	7.0
M2PD at lateral foot	0.053	1.000	1.000			8.0	7.0

P-values are corrected for multiple comparisons using the Bonferroni correction. * significantly different. Left foot: light grey. Right foot: dark grey.

Table 2 Normative values for cutaneous threshold (S1PD) measurements, men and women.

Age category (y)	No. of observations	S1PD at hallux, force (g) (mean (C95%))	S1PD at medial heel, force (g) [mean (C95%)]	S1PD at first dorsal web, force (g) (mean (C95%))	S1PD at lateral foot, force (g) [mean (C95%)]	S1PD at fifth toe, force (g) [mean (C95%)]
20-30	66	0.7 (2.0)	0.4 (1.7)	0.3 (1.1)	0.4 (1.2)	0.4 (1.2)
31-40	58	0.9 (3.2)	0.6 (2.6)	0.3 (1.2)	0.5 (1.6)	0.5 (1.8)
41-50	64	1.2 (5.2)	0.9 (4.4)	0.3 (1.4)	0.7 (2.1)	0.7 (2.8)
51-60	66	1.6 (8.6)	1.4 (7.7)	0.4 (1.8)	0.8 (2.9)	1.1 (4.8)
61-70	62	2.2 (14.7)	2.0 (12.7)	0.6 (2.6)	1.1 (3.9)	1.6 (8.3)
71-80	62	3.0 (25.9)	2.7 (18.9)	0.9 (4.0)	1.4 (5.3)	2.4 (14.4)
80+	14	4.0 (47.5)	3.3 (26.6)	1.3 (6.1)	1.8 (7.2)	3.7 (26.0)

Abbreviations: y, year; mm, millimeter; C, percentile.

Table 3 Normative values for static 2-point discrimination (S2PD) measurements, men and women.

Age category (y)	No. of observations	S2PD at hallux, mm (mean, (C95%))	S2PD at medial heel, mm (mean, (C95%))	S2PD at first dorsal web, mm (mean, (C95%))	S2PD at lateral foot, mm (mean, (C95%))	S2PD at fifth toe, mm (mean, (C95%))
20-30	66	6.6 (10.8)	7.4 (19.1)	6.0 (18.1)	7.5 (19.2)	5.1 (9.5)
31-40	58	6.9 (11.8)	8.5 (22.0)	7.0 (21.1)	7.8 (20.2)	5.9 (11.3)
41-50	64	7.3 (13.0)	9.2 (24.2)	7.7 (23.1)	8.2 (21.1)	6.9 (13.5)
51-60	66	7.7 (14.6)	9.4 (24.8)	8.1 (24.1)	8.6 (22.2)	8.0 (16.1)
61-70	62	8.2 (16.4)	9.3 (24.7)	8.3 (24.8)	9.0 (23.3)	9.2 (19.2)
71-80	62	8.6 (18.5)	9.2 (24.6)	8.4 (25.3)	9.5 (24.4)	10.7 (22.9)
80+	14	9.0 (21.0)	9.3 (25.2)	8.7 (26.0)	9.9 (25.6)	12.3 (27.2)

Abbreviations: y, year; mm, millimeter; C, percentile.

Assessing spatial discrimination with moving 2-point discrimination

There was a significant age-dependent increase in M2PD measurements on 3 test locations ($P < 0.05$), except for the lateral foot ($r_s = 0.067$, $P = 0.192$). No significant differences between men and women were found for M2PD measurements. Significant differences were found between the test locations of the left foot, $\chi^2(3) = 9.188$ ($P = 0.027$) as well as the right foot, $\chi^2(3) = 21.893$ ($P < 0.0005$), see Table 1 for pairwise comparisons. Table 4 shows the mean and 95% percentile per age span, which were calculated as reference values. Threshold values for M2PD turned out to be lower than S2PD values. The LMS method was used to draw the regression of M2PD to age, together with percentile plots (Figure 4).

Figure 4 Moving 2-point discrimination (M2PD) of the foot. A Generalized Gamma function was used for fitting a GAMLSS. Degrees of freedom were 2.0 (hallux), 3.0 (medial heel), 4.8 (first dorsal web), and 2.0 (lateral foot). Percentile plots: 2.5% (lowest dotted grey), 16% (lower dashed red), 50% (middle continuous green), 84% (upper dashed red) and 97.5% (uppermost dotted grey).

Construct validity and sensitivity

One hundred thirty-six patients (65 men, 71 women) who had no major sensory loss from the RDF-study were studied [mean (SD) age 48.9 y (9.3), range 21.6-60.0]. A significant negative correlation was found between 2-point discrimination values and vibration sense tested at the interphalangeal joint of the hallux (S2PD versus vibration sense: $r = -0.247$, $P = 0.004$; M2PD versus vibration sense: $r = -0.195$, $P = 0.025$). The sensitivity (ability to detect diminished vibration sense) of S2PD and M2PD measurements (using 95% percentile normative values) was 33% and 33% for each.

Table 4 Normative values for moving 2-point discrimination (M2PD) measurements, men and women.

Age category (y)	No. of observations	M2PD at hallux, mm (mean, (C95%))	M2PD at medial heel, mm (mean, (C95%))	M2PD at first dorsal web, mm (mean, (C95%))	M2PD at lateral foot, mm (mean (C95%))
20-30	66	5.0 (8.7)	5.2 (15.3)	5.4 (11.4)	5.9 (12.9)
31-40	58	5.4 (10.1)	6.0 (17.8)	6.7 (14.1)	6.1 (13.7)
41-50	64	5.8 (11.7)	6.7 (19.9)	6.9 (14.6)	6.3 (14.7)
51-60	66	6.2 (13.7)	7.2 (21.4)	7.2 (15.1)	6.5 (15.6)
61-70	62	6.5 (15.9)	7.5 (22.3)	7.7 (16.2)	6.7 (16.7)
71-80	62	6.8 (18.6)	7.7 (22.8)	7.6 (16.0)	6.9 (17.8)
80+	14	6.9 (21.7)	7.9 (23.5)	7.6 (16.1)	7.0 (19.0)

Abbreviations: y, year; mm, millimeter; C, percentile.

Discussion

This study provides reference data for sensory measurements at 5 test sites on the foot, together with an assessment of construct validity and sensitivity of S2PD and M2PD measurements for detection of early sensory loss. These data may help in clinical practice to discriminate subjects at risk for, or with sensory loss.

Normative values for the different foot areas are scarce. A study in healthy Nepali volunteers determined the proportional sensation with a 2 g stimulus on the hallux to be 99.3%, and a study in healthy Thais reported a mean S1PD on the hallux of 0.4 – 1.8 g^{18,28}. A study in healthy college-aged volunteers determined the threshold on the hallux to be 0.4 – 0.6 g, in which differences were found between genders¹⁹. A study in healthy Nepali and Indian volunteers reported 97.9% could feel a 4.0 g stimulus on the lateral foot (sural nerve)²². For other test locations, no data were found. In S2PD and M2PD measurements, 1 study reports a value of 6.6 mm (SD: 1.8) for S2PD at the hallux, unfortunately without stratification for age²¹. However, these observations fit the age-stratified percentile curves from our predominantly Caucasian study sample. Our study confirms that across all test locations, there is a gradual decline of sensation during aging, for all measurements. These results are in line with previous studies reporting on cutaneous threshold and spatial discrimination of the feet^{18,28,29}. Our study extends those observations to provide age-related reference values for both cutaneous threshold and spatial discrimination of the feet in relation to the nerve distribution in the feet.

The difference between men and women for all measurements were most profound for S1PD measurements, probably due to differences in callus thickness being more frequent in

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men (data not shown). The difference between men and women averaged between 0.7 and 0.8 g, a difference only detected with monofilaments <2 g due to the logarithmic character of the SWM set. There seems to be no other somatosensory explanation for differences between genders, because studies reporting on the mechanoreceptors in the skin do not show differences between men and women^{16,30}. Test locations were chosen according to the nerve distributions of the lower extremity. Another advantage of these sites is that they show less callus formation compared to, for example, metatarsal heads and heels³¹. We conclude that the cutaneous threshold should not be tested on sites with callus formation, as was suggested earlier³². The threshold differs between the majority of test locations. The dorsal web, for example, had significantly lower thresholds compared to the others, which is explained by differences in callus thickness and skin type. The increasing threshold seen during aging is unlikely the result of possible thicker callus formation, because no relationship between callus and ageing was observed. However, we observed a significant positive correlation between weight and the cutaneous threshold at all test locations. No relation was found between the length of the foot and S2PD or M2PD (data not shown). Other influential factors reported in the literature are types of foot wear, occupation, sitting cross-legged, and prolonged standing, however, other characteristics like skin thickness may be the subject of future studies^{18,22,28,33}.

S1PD measurements have been carried out with a set of SWMs, which are 'steps' on a logarithmic scale. The much advocated use of the 5.07 (10 g) monofilament, for example, only gives information on the cutaneous pressure threshold being either below or above the given marking. The plotted age/force estimated percentiles should therefore be seen in light of the logarithmic force markings. With the provided percentile curves, diabetics, for example, can be evaluated more accurately for the risk of foot ulceration and amputation. It has been suggested that not being able to sense the 10 g monofilament is a relative risk, among others, for foot ulceration of 2.5 [95% confidence interval (CI), 2.0 to 3.2] to 7.9 (95% CI, 4.4 to 14.3) with follow-up between 1 and 4 years. The relative risk for lower extremity amputation, when insensate to the 10 g monofilament, ranges from 1.7 (95% CI, 1.1 to 2.6) to 15.1 (95% CI, 4.3 to 52.6) with follow-up between 1.5 and 3.3 years³⁴. By using a stepping-wise approach with a set of, for example, 3 monofilaments (1 g, 4 g, and 10 g), a more accurate estimate can be given for foot sensation compared to using a 10 g monofilament alone. The validity of the SWM has been established in previous studies and has been shown to be reliable^{18,35-37}.

S2PD tests the slowly-adapting type I afferent A β fiber system in the skin, with the Merkel cell-neurite complex as peripheral receptors. M2PD tests both the quickly-adapting type I afferent A β fiber system, with Meissner corpuscles as mechanoreceptors and the quickly-

adapting type II afferent A β fiber system, with Pacinian corpuscles as mechanoreceptors³⁸. The explanation for lower thresholds observed in M2PD compared to S2PD must be derived from the neurophysiology of the involved nerve fiber/receptor system. The receptive fields of the conducting somatosensory corpuscles differ between S2PD and M2PD. M2PD is mediated by Meissner corpuscles that have a receptive field of 1 to 2 mm. S2PD is mediated by the Merkel cell-neurite complex that has a receptive field of 9 mm. Together with the differences in innervation density between these systems, the lower threshold values in M2PD might be explained³⁹. Our data suggest that the innervation density differs at the test sites on the foot. The increase seen in 2-point discrimination over the life span is attributed to the decline in Meissner corpuscles during aging, degenerative changes of Pacinian corpuscles, abnormalities involving myelinated fibers, fiber loss in peripheral nerves, and degenerative changes in fasciculus gracilis and brain^{12,40}. With increasing age, the Meissner corpuscles become more variable in size and shape, irregular in horizontal distribution, which therefore alters the ability to discriminate 2 points from 1 point touching the skin. The decline in corpuscles conducting spatial discrimination is equal between genders, when accounted for differences in digit size^{16,41}. We suggest that the same principle can be applied to the toes, however, this should be the subject of future studies.

Our data show that the clinimetric properties concerning construct validity are met, and 2-point discrimination can detect altered vibration sense with a sensitivity of 33%. Hallux measurements were chosen to assess construct validity of S2PD and M2PD because of available age-corrected vibration thresholds of the interphalangeal joint⁴². Moreover, S2PD and M2PD measurements at the hallux showed less scatter compared to other test sites. The use of the medial heel, first dorsal web, and lateral foot as test locations for these measurements might be reconsidered, regarding the spread of the data. No information is available on reliability of 2-point discrimination tests at those test sites. A possible explanation for these variances can be found in the fact that it is a difficult test for both patient and operator, in which insensitivity to the varying interprong distance may result in reduced reliability⁴³. A solution might be the use of cut-off values instead of the whole range of measurements. In diabetics, 2-point discrimination seems to be altered before nerve conduction studies become abnormal as indicator of nerve pathology⁹. Although criticized concerning reliability, 2-point discrimination has a place in a more thorough neurological examination as an indicator of early nerve pathology and nerve regeneration in both upper and lower extremities^{4,43-47}.

We studied a population of healthy volunteers who were screened with a questionnaire on disorders interfering with sensation at the feet. A study of polyneuropathy in the general population estimated a prevalence of 1% up to 7% in the elderly. In a substantial proportion

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of cases (20-30%), the cause is idiopathic⁴⁸. Alcohol consumption as a cause might be underestimated, increasing the possible presence of alcohol-induced neuropathy in our population of interest. Symptoms of polyneuropathy are not always observed by patients themselves, which may have led to misclassification in the our healthy volunteers.

The age-related references values have a clinical applicability in a variety of diseases where sensation of the feet is being evaluated, in for example diabetes, HIV, or leprosy. These results can also help the clinician to assess sensory disturbances in bilateral comparisons between affected and non-affected territories in, for example, the tarsal tunnel syndrome. The tests are non-invasive, inexpensive, and quick to perform and can be carried out in a variety of settings in both the developed and developing world. The percentile curves can be used to follow the patient during aging and can identify patients with severely diminished sensation, which is a risk factor for falls, foot ulceration, and amputation.

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Chapter III

Traditional methods versus quantitative sensory testing of the feet at risk. Results from the Rotterdam Diabetic Foot Study

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Abstract

Background

Diabetic sensorimotor polyneuropathy (DSP) is one of the greatest risk factors for foot ulceration. The current study investigated the measurement properties of the Pressure-Specified Sensory Device (PSSD) in comparison to traditional threshold screening instruments, in several categories of sensory loss. Knowledge of these values may help to identify diabetics at risk for ulceration more reliable.

Methods

A partially cross-sectional cohort study was carried out in patients with diabetes. Traditional instruments classified each patient in groups representing severity of DSP. Demographic characteristics, laboratory measures and PSSD measurements were compared between groups. The Bland-Altman method was used to characterize reliability of the PSSD and construct validity was determined by comparing to Semmes-Weinstein monofilaments (SWM).

Results

155 diabetic patients were measured. Fifteen patients had a diabetic ulcer in their medical history, 7 patients were insensate to the 10 g monofilament and had diminished vibration sense (group 1), 34 patients had diminished vibration sense, but no elevated cutaneous threshold (group 2), 99 patients acted as controls (no elevated cutaneous threshold or diminished vibration sense, group 3). The PSSD distinguished these groups with one-point static cutaneous thresholds (1PS) alone. SWM and PSSD measurements were not interchangeable. Spatial discrimination (2PS and 2PM) by the PSSD was more reliable compared to 1PS. SWM (force in g and pressure in g/mm²) correlations with PSSD measurements differed between groups.

Conclusions

The PSSD is able to distinguish between categories of sensory loss. The PSSD is valid in measuring cutaneous threshold and can reliable measure spatial discrimination at the feet.

Introduction

Diabetic sensorimotor polyneuropathy (DSP) is one of the most common complications in diabetes, with prevalence ranges from 30% to 50%¹. Foot ulcerations are usually preceded by numbness due to DSP. It has been estimated that at least 15% of diabetics are confronted with a foot ulcer during their life, with eight out of ten non-traumatic amputations being preceded by diabetic ulcers. The 1-year mortality after the development of a diabetic foot ulcer ranges from 13-40%, after 3 and 5 years this is even higher and ranges from 35-65% and 39-80%, respectively. It has been suggested that in these cases, mortality is even higher than most malignancies^{2,3}!

Various strategies have been suggested to decrease the risk to develop diabetic foot ulcers⁴⁻⁶. Current guidelines recommend an annual screening for DSP with a 10 g Semmes-Weinstein monofilament (SWM) or tuning fork^{7,8}. It is still not clear which of these traditional instruments is the most discriminative^{7,9}.

The gradual decline of sensation seen in DSP is caused by physiologic alterations in the peripheral nerves and its nerve endings due to an altered glucose metabolism^{10,11}. As a result, the combined loss of sensory receptors and nerve fibers change both the cutaneous threshold and innervation density. The cutaneous threshold is the amount of force applied to the skin to elicit a response and innervation density is the amount of sensory receptors and nerve fibers in the skin, which both change during DSP. Instruments that assess the functional status of receptors and nerve fibers have proven to be earlier indicators of nerve pathology. Static- and moving two-point discrimination test these thresholds, which become abnormal before the current recommended screening instruments (monofilament or tuning fork) for the loss of sensation^{12,13}.

The PSSD is an instrument that measures the thresholds for both one-point and two-point static and moving touch and has several theoretical advantages, compared to current screening tests^{14,15}. It measures the pressure required to perceive the metal prongs (one or two) that are touching the skin, on a continuous scale. Unlike the SWM-set, which is an ordinal scale. The PSSD may be able to measure a smaller change and therefore measure more accurately the cutaneous threshold. Classic two-point discrimination does not measure the pressure applied. Furthermore, data on clinimetric properties of PSSD measurements in the lower extremity is limited^{13,15-27}.

The purpose of the current study was to compare the PSSD measurements to the SWM measurements, carried out in the feet of diabetics, with varying loss of sensation. Reliability of the PSSD measurements and the validity of the PSSD compared to SWM was assessed.

Materials and methods

Study design and subjects

A partially cross-sectional cohort study was carried out in patients with diabetes to estimate the performance of the PSSD (Sensory Management Services, LLC, Baltimore, Maryland, USA) compared to other sensibility testing instruments. Between January 2014 and August 2014 patients were measured at the outpatient Diabetes Clinic of the Franciscus Gasthuis, Rotterdam, the Netherlands, as part of the Rotterdam Diabetic Foot Study (RDF study). This prospective cohort study was set up to investigate the deterioration of sensation of the feet over time, in patients with diabetes. Diabetics (both type 1 and 2) were consecutively asked to participate. Inclusion criteria were: diabetes mellitus (treated by oral blood glucose lowering drugs and/or insulin), age over 18 years, no mental retardation and speaking Dutch or English. Exclusion criteria were: active radicular syndrome, neurological disease interfering with sensibility of the feet and not being able to give informed consent. Demographic was obtained from the patient records. No reimbursement was given. For current analysis, baseline data from patients included in the RDF study was used. All subjects provided written informed consent. The institutional review board and the Medical Ethical Committee of Erasmus MC Medical University Center, Rotterdam, the Netherlands approved the studies.

Sensory tests

Cutaneous threshold (one-point static discrimination, (S1PD)) was tested on five locations of each foot with SWMs (Baseline® Tactile™, USA) ranging from 0,008 to 300 grams. The test sites were chosen in concordance with the nerve distribution of the foot: I: hallux (medial plantar nerve (tibial nerve)), II: medial heel (calcaneal nerve (tibial nerve)), III: dorsal first web (deep fibular nerve), IV: lateral foot (sural nerve) and V: fifth toe (lateral plantar nerve), Figure 1. Areas with excessive callus formation were avoided. Testing started at the first (I) test location (hallux) of the left foot, then the medial heel (II) etcetera. Innervation density (two-point static and moving discrimination (S2PD, M2PD)) was assessed on the same test locations with the Disk-Criminator™ (US Neurologicals, LCC, WA, USA). A Rydel-Seiffer tuning fork (Martin, Tuttlingen, Germany) tested the vibration threshold at the dorsal interphalangeal joint of the hallux and medial malleolus. Neuropathy complaints were assessed using the Michigan Neuropathy Screening Instrument (MNSI).

Figure 1

Abbreviations: Roman capitals are indicative of test locations: I, hallux; II, medial heel; III, first dorsal web; IV, lateral foot and V, fifth toe.

Sensibility testing was done in a quiet soundproof room kept at a constant temperature. The patients were asked to close the eyes. The SWM were applied with the accepted technique of applying force at right angles to the filament. The monofilament was applied at the skin for 1 to 2 seconds, using three trials. The lowest marking was noted for which monofilament the patient could feel the stimulus, at the correctly answered test site. The pressure in g/mm^2 was retrieved from literature²⁸. Two-point discrimination was assessed using a Disk-Criminator™. Difference between one and two point (13 to 15mm) stimulation was demonstrated at the index finger. The patients were told that their replies were not judged to be right or wrong. The difference between one and two point stimulation was again demonstrated at the pulp of the left hallux, at the start of the test series. The minimal discriminatory distance was recorded.

Consecutively, the PSSD measured one-point static discrimination (1PS), two point static discrimination (2PS) and two point moving discrimination (2PM) on the same sites. When patients receive the stimulus supplied by one or two of the prongs, they pushed a button with their hand, thereby stopping the recording of the increasing pressure (0.1 to 100 g/mm²). S2PD and M2PD values found with the Disk-Criminator™ were used in measuring 2PS and 2PM with the PSSD (g/mm²). If the patient was not able to discriminate a distance of 15 mm with the Disk-Criminator™, 15 mm was used as setting for 2PS and 2PM measurements with the PSSD. Five consecutive measurements were made per test and site.

Hoffman-Tinel sign was used to assess nerve compression and was scored positive when tingling and electrical sparks were elicited when tapping the tibial nerve at the tarsal tunnel. Cold perception was tested by applying a cold piece of metal to the skin of the foot arc. Proprioception was tested with Romberg's test.

Data analysis

Construct validity

For a conversion from force (g) to pressure (g/mm²), the cross-sectional area of the monofilaments was taken into account, making a direct comparison to the PSSD measurements possible²⁸. Differences between (converted) SWM and PSSD tests assessed diagnostic accuracy, using a one sample T-test. Two aspects of construct validity were considered: structural validity and hypothesis testing. Structural validity is defined as the degree to which the scores of measurement instruments are an adequate reflection of the dimensionality of the construct to be measured. Hypothesis testing invests the relationships of measurements on the instrument under study, with scores on other instruments measuring similar constructs or differences in measurements between instruments between patients. Construct validity was determined by defining hypotheses. It examines whether the PSSD score (1PS) represents the construct tested by the SWM-set: the cutaneous threshold. Since the data were not normally distributed, Spearman correlations were used. Only SWM values ≤ 300 g were taken into account. We tested the following hypotheses, based on results from earlier studies^{20,21,29}: 1) there is a positive, significant correlation of force in gram or pressure in g/mm² measured by SWM with PSSD (1PS) measurements, 2) the positive correlation between SWM and PSSD (1PS) is distributed unevenly at the foot, 3) the positive correlation between SWM and PSSD (1PS) measurements is more profound in groups characterized by a more severe form of DSP.

Reliability

To assess reliability of PSSD measurements, the highest and lowest values were compared with mid three values from five consecutive PSSD (1PS, 2PS and 2PM) measurements (right

hallux). A one-sample T-test was used to assess differences. The existence of proportional bias (i.e., significant differences between consecutive tests) indicates that the consecutive tests do not agree equally through the range of measurements. A Bland-Altman plot was used to plot the differences between PSSD tests against their mean value to determine the overall mean difference across all subjects, with 95% limits of agreement. The limits of agreement were determined by calculating two standard deviations around the mean difference.

Statistics

Patients were categorized for the status of their neuropathy as follows. Group 1: a history of ulceration, group 2: diminished vibration sense, no elevated cutaneous threshold (>10 g) in 3 (or more) out of 5 test locations (both feet), group 3: no elevated cutaneous threshold or absent vibration sense (both feet). Statistical comparisons between groups for individual variables were made using Chi-squared and Kruskal-Wallis H tests. Differences between the feet of individuals were assessed with a Wilcoxon signed rank test, for non-normal distributed data (S1PD, S2PD, M2PD, 1PS, 2PS, 2PM). McNemar test was used for dichotomous data (Hoffman-Tinel sign, cold perception). A one-sample T-test was used to assess reliability of PSSD measurements. Estimated effect size was calculated by converting Z-scores with the equation $r = Z / \sqrt{n}$. All statistical analysis was carried out using IBM's SPSS Statistics 22.0 (IBM, New York, USA). P-values below .05 (two-sided) were considered statistically significant.

Results

General characteristics

One hundred fifty five patients were measured with the PSSD (to August 2014). Group 1 consisted of 22 patients (of whom 15 with a previous ulcer), group 2 of 34 patients and group 3 of 99 patients. Groups were comparable regarding gender, ethnicity, weight, BMI, duration of diabetes, type of diabetes, lipid profile, used drugs, medical history (except hypertension) and smoking status. Group 3, acting as controls, were significantly younger compared to group 2 and group 1. Patients with prior ulceration and diminished vibration sense alone had a significantly lower Modification of Diet in Renal Disease (MDRD), compared to group 3. Mean arterial pressure was higher in group 1 and group 2, compared to group 3. Group 1 and 2 compared to group 3 more often reported complaints of DSP (Table 1).

Table 1 Demographic data.

	Group 1 (prior ulcer, MF-, RS-) n = 22	Group 2 (MF+, RS-) n = 34	Group 3 (MF+, RS+) n=99	P value	Results of group comparisons
Gender (M/F)	16/6	22/12	49/50	0.073^a	
Ethnicity (n(%))					
- Caucasian	20 (90.9%)	34 (100%)	76 (76.8%)	0.107^a	
- Indo-Surinamese	1 (4.5%)		13 (13.1%)		
- African	1 (4.5%)		2 (2.0%)		
- Asian	0		1 (1.0%)		
- Other	0		7 (7.1%)		
Age (mean (y), SD)	65.7 ± 9.6	69.4 ± 9.5	58.7 ± 12.7	<0.001^b	1 vs. 2: p=0.256 1 vs. 3: p=0.012 2 vs. 3: p=0.0001
Height (mean (m), SD)	178.1 ± 10.0	174.3 ± 9.8	171.0 ± 9.8	0.004^b	1 vs. 2: p=0.152 1 vs. 3: p=0.004 2 vs. 3: p=0.127
Weight (mean (kg), SD)	92.5 ± 27.5	91.4 ± 17.8	87.4 ± 18.4	0.077^b	
BMI (mean (kg/m²), SD)	29.2 ± 8.2	30.0 ± 4.3	29.9 ± 6.4	0.179^b	
Duration of diabetes (mean (y), SD)	19.8 ± 11.3	19.6 ± 13.2	17.8 ± 10.9	0.705^b	
Type of diabetes (n(%))				0.063^a	
- Type 1	3 (13.6%)	5 (14.7%)	31 (31.3%)		
- Type 2	19 (86.4%)	29 (85.3%)	68 (68.7%)		
Drugs (n(%))					
- Lipid lowering drugs	15 (68.2%)	22 (64.7%)	66 (66.7%)	0.962^a	
- Oral blood glucose lowering drugs	9 (40.9%)	23 (67.6%)	49 (49.5%)	0.097^a	
- Insulin	17 (77.3%)	31 (91.2%)	86 (86.9%)	0.325^a	
HbA1c (mean (mmol/L), SD)	61.4 ± 14.9	62.6 ± 16.2	63.2 ± 14.7	0.832^b	1 vs. 3: p=0.003
MDRD (ml/min/1.73 m)	64.7 ± 29.7	68.6 ± 32.1	82.5 ± 21.6	0.004^b	2 vs. 3: p=0.007
Kreatinine (μmol/L)	122.7 ± 65.6	107.2 ± 46.6	82.7 ± 25.6	<0.001^b	1 vs. 3: p=0.0001
Total cholesterol (mean (mmol/L), SD)	4.2 ± 1.0	4.0 ± 1.0	4.2 ± 1.0	0.695^b	2 vs. 3: p=0.002
LDL-C (mean (mmol/L), SD)	1.8 ± 0.9	1.8 ± 0.9	2.1 ± 0.9	0.247^b	1 vs. 3: p=0.01
HDL-C (mean (mmol/L), SD)	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.3	0.796^b	
Non-HDL-C (mmol/L, SD)	2.7 ± 0.9	2.6 ± 1.0	2.8 ± 0.9	0.697^b	
TG (mean (mmol/L), SD)	1.8 ± 1.5	1.9 ± 1.5	1.7 ± 1.0	0.535^b	
ApoB (g/L, SD)	0.8 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	0.041^b	
Microalbumin (mg/L, SD)	327.4 ± 751.8	152.2 ± 343.5	84.8 ± 273.4	0.031^b	
Mean Arterial Pressure (mean (mmHg), SD)	100.1 ± 16.2	98.0 ± 10.4	93.1 ± 10.3	0.029^b	1 vs. 3: p=0.01 2 vs. 3: p=0.031
Systolic blood pressure (mmHg, SD)	149.4 ± 29.0	140.9 ± 17.2	132.8 ± 17.9	0.005^b	1 vs. 3: p=0.0001 2 vs. 3: p=0.04
Diastolic blood pressure (mmHg, SD)	75.4 ± 13.0	76.6 ± 9.3	73.3 ± 9.0	0.176^b	
Medical history (n(%))					
- Hypertension	17 (77.3%)	23 (67.6%)	41 (41.4%)	0.001^a	
- Myocardial infarction	4 (18.2%)	5 (14.7%)	9 (9.1%)	0.395^a	
- Angina pectoris	2 (9.1%)	5 (14.7%)	11 (11.1%)	0.788^a	
- Coronary artery disease	5 (22.7%)	11 (32.4%)	18 (18.2%)	0.226^a	
- CABG/PCI	4 (18.2%)	11 (32.4%)	15 (15.2%)	0.090^a	
- CVA/TIA	4 (18.2%)	3 (8.8%)	4 (4.0%)	0.059^a	
- Cancer	2 (9.1%)	2 (5.9%)	11 (11.1%)	0.670^a	
- Lung disease	0 (4.5%)	3 (8.8%)	8 (8.1%)	0.824^a	
- Amputation	1 (4.5%)	0	0		
- Ulcer	15 (68.2%)	0	0		

Table 1 Demographic data. (continued)

	Group 1 (prior ulcer, MF-, RS-) n = 22	Group 2 (MF+, RS-) n = 34	Group 3 (MF+, RS+) n=99	P value	Results of group comparisons
Smoking (n(%))					
- Never smoker	8 (36.4%)	18 (52.9%)	67 (67.7%)	0.016^a	
- Past smoker	12 (26.1%)	10 (21.7%)	24 (24.2%)	0.019^a	
- Current smoker	15 (21.4%)	18 (25.7%)	37 (52.9%)	0.019^a	
Diabetic Sensory Polyneuropathy (n(%))					
- MNSI score >4	12 (54.5%)	12 (35.3%)	12 (12.1%)	<0.001^a	
- Positive symptoms	13 (59.1%)	16 (47.1%)	27 (27.3%)	0.006^a	
- Negative symptoms	13 (59.1%)	9 (26.5%)	8 (8.1%)	<0.001^a	
Retinopathy	12 (100%)	8 (30.8%)	13 (17.4%)	<0.001^a	

Abbreviations: MF, monofilaments; RS, Rydel-Seiffer tuning fork; -, insensate; +, sensate; n, number; M, male; F, female; SD, standard deviation; ^a, Chi-square test; ^b, Kruskal-Wallis test; BMI, Body Mass Index; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerids; ApoB, apolipoprotein B; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MNSI, Michigan Neuropathy Screening Instrument.

Results of traditional methods of sensory testing

For S2PD and M2PD measurements, the scale ranged from 2 to 15 mm, with 16 mm being noted when a prong distance of 15 mm was not distinguished as two points. There were no significant differences between the feet for S1PD, S2PD and M2PD tests ($Z=-0.075$, $p=0.940$ to $Z=1.390$, $p=0.164$). There were no statistically significant differences in the proportion of cold perception and Hoffman-Tinel between both feet ($p=0.180$). There were statistically significant differences in S1PD, S2PD, M2PD, Romberg' test and cold perception between groups, on all test locations ($p=0.009$ to $p<0.001$). Group 3 acted as control group, with median cutaneous thresholds ranging from 0.4 to 1.4 g across test sites, increasing in the other groups: 1 to 4 g (group 2) and 8 to 60 g (group 3). Spatial discrimination increased with severity of DSP and already widens when the vibration sense is diminished (group 2). The gradual loss of sensation is also seen in more frequent positive Romberg and negative cold perception tests, in groups characterized by a more severe form of sensory loss. Hoffman-Tinel's sign did not significantly differ between groups, left: $p=0.249$ and right: $p=0.577$ (Table 2).

Table 2 Traditional test characteristics per group.

	Test site	Group 1 (prior ulcer, MF-, RS-) n = 22	Group 2 (MF+, RS-) n = 34	Group 3 (MF+, RS+) n=99	P-value
S1PD left, given force (g) (median (IQR range))	I	60 (26-301)	2 (0.6-7)	1.0 (0.4-1.4)	<0,001^b
	II	26 (10-60)	2 (0.8-9)	1.0 (0.4-4.0)	<0,001^b
	III	10 (3.5-300)	1 (0.4-2)	0.4 (0.14-0.6)	<0,001^b
	IV	8 (2.0-64.5)	1 (0.6-2)	0.5 (0.16-1.0)	<0,001^b
	V	26 (13.8-210)	2 (0.6-7.5)	0.6 (0.4-1.4)	<0,001^b
S1PD right, given force (g) (median (IQR range))	I	60 (15-301)	2 (0.6-7)	1.0 (0.4-1.4)	<0,001^b
	II	15 (7.5-60)	4 (0.8-9)	1.0 (0.4-4.0)	<0,001^b
	III	12.5 (1.9-300.3)	4 (0.8-9)	0.4 (0.16-0.6)	<0,001^b
	IV	8 (1.4-44.5)	1 (0.5-2)	0.6 (0.16-1.0)	<0,001^b
	V	26 (13.8-210.3)	2 (0.4-10)	1.0 (0.4-1.3)	<0,001^b
S2PD left, mm (median (IQR range))	I	16 (15.5-16)	13.5 (7.8-16)	10 (6-15)	0.031^b
	II	16 (15-16)	13.5 (9.8-16)	11 (7-15)	0.006^b
	III	16 (10-16)	15 (8-16)	9 (5-15)	0.001^b
	IV	16 (15-16)	15.5 (10-16)	10 (5-15)	0.032^b
	V	16 (15.5-16)	15 (10-16)	9 (6-15)	0.004^b
S2PD right, mm (median (IQR range))	I	16 (15.5-16)	15 (9-16)	9 (5-15)	0.004^b
	II	16 (14.3-16)	15 (9-16)	11.5 (6-15)	0.103^b
	III	16 (16-16)	15 (7.3-16)	9 (5-15)	0.010^b
	IV	16 (11-16)	13 (7.8-16)	11.5 (6-15)	0.141^b
	V	16 (16-16)	15 (9.5-16)	10 (6-15)	0.004^b
M2PD left, mm (median (IQR range))	I	16 (15.5-16)	8.5 (5-15)	7 (4-12)	0.003^b
	II	16 (7.8-16)	9 (6.3-13.5)	8 (4-12.8)	0.150^b
	III	16 (9-16)	9 (7-14)	7.5 (4-13.3)	0.117^b
	IV	15.5 (9-16)	11 (6-16)	7 (4-12)	0.058^b
	V	16 (10.5-16)	9 (6.5-15)	7.5 (5-10)	0.012^b
M2PD right, mm (median (IQR range))	I	16 (15-16)	9 (5-15)	7 (4-10.3)	0.002^b
	II	16 (9.3-16)	9.5 (6-15)	8 (4-13)	0.349^b
	III	16 (7-16)	12 (6-16)	8 (4-14)	0.369^b
	IV	14.5 (7.3-16)	9 (5.3-13.8)	8 (5-12.5)	0.090^b
	V	16 (11.5-16)	11 (6-16)	8 (5-12)	0.001^b
Romberg positive (n (%))		8 (36.4%)	4 (11.8%)	6 (6.2%)	<0,001^b
Cold perception left (%)		11 (50.0%)	29 (87.9%)	91 (96.8%)	<0,001^b
Cold perception right (%)		14 (63.6%)	30 (90.9%)	91 (97.8%)	<0,001^b
Hoffman-Tinel sign left (%)		11 (50.0%)	14 (41.2%)	32 (32.3%)	0,249^a
Hoffman-Tinel sign right (%)		9 (40.9%)	14 (41.2%)	32 (32.7%)	0,577^a

Abbreviations: Roman capitals are indicatives of test locations: I, hallux; II, medial heel; III, first dorsal web; IV, lateral foot; V, fifth toe. MF, monofilaments; RS, Rydel-Seiffer tuning fork; -, insensate; +, sensate; n, number; IQR, interquartile range; S1PD, static one-point discrimination; S2PD, static two-point discrimination; M2PD, moving two-point discrimination; ^aChi-Square test; ^b, Kruskal Wallis Test.

Results of Pressure Specified Sensory Device testing

Using the PSSD, significant differences were observed between both feet in testing 1PS on the first toe ($Z=-1.970$, $p=0.049$, $r = -0.16$), 2PS at the lateral foot ($Z=-2.341$, $p=0.019$, $r = -0.20$) and 2PM at the first web ($Z=-2.525$, $p=0.012$, $r = -0.24$). No significant differences were found at the other test sites for 1PS, 2PS and 2PM. Degree of sensory loss had a more

profound effect on 1PS, compared to 2PS and 2PM measurements, see Table 3 for in detail comparisons.

Table 3 PSSD test characteristics per group.

	Test site	Group 1 (prior ulcer, MF-, RS-) n = 22	Group 2 (MF+, RS-) n = 34	Group 3 (MF+, RS+) n=99	P-value
1PS left, g/mm², (median (IQR))	I*	100 (75.6-100)	31.8 (10.2-78.0)	11.6 (4.8-26.3)	<0.001^b
	II	80.2 (38-100)	32.3 (13.6-70.7)	15.4 (7.6-32.2)	0.008^b
	III	81.9 (19.5-100)	21.9 (8.8-69.8)	7.4 (4.3-17.0)	0.002^b
	IV	62.7 (39.5-85.3)	26.3 (11.5-58.0)	9.3 (6.0-17.6)	<0.001^b
	V	80.8 (52.8-100)	20.5 (10.3-78.4)	7.7 (3.6-17.8)	<0.001^b
1PS right, g/mm², (median (IQR))	I	100 (70.6-100)	25.0 (12.7-56.4)	10.5 (5.2-19.1)	<0.001^b
	II	74 (45.3-100)	23.6 (12.0-48.6)	14.5 (8.1-26.2)	0.045^b
	III	77.7 (22.7-100)	22.4 (11.0-77.1)	8.9 (4.0-16.5)	<0.001^b
	IV	63.5 (19.0-94.3)	19.8 (12.0-40.6)	9.9 (5.1-19.2)	0.012^b
	V	81.7 (30.2-100)	25.1 (10.3-66.2)	9.0 (6.4-16.2)	0.001^b
2PS left[#], g/mm², (median (IQR)).	I	97.5 (95.1-98.9)	83.8 (39.9-98.1)	30.8 (17.3-55.9)	0.002^b
	II	93.5 (61.1-98.8)	75.5 (33.6-97.6)	51.9 (22.9-84.4)	0.458^b
	III	97.3 (80.7-99.3)	93.4 (34.3-98.5)	43.2 (15.8-75.6)	0.077^b
	IV	89.6 (54.1-97.1)	70.9 (25.6-91.1)	37.2 (15.2-77.7)	0.152^b
	V	88.6 (54.6-97.6)	67.0 (37.8-95.0)	33.8 (15.0-69.9)	0.036^b
2PS right[#], g/mm², (median (IQR)).	I	98.3 (95.6-98.7)	52.0 (31.3-98.0)	31.2 (15.5-55.5)	<0.001^b
	II	97.3 (63.6-99.1)	80.1 (36.6-98.6)	43.7 (19.4-79.5)	0.296^b
	III	88.5 (45.3-97.9)	83.3 (44.7-98.3)	28.1 (13.6-66.9)	0.007^b
	IV*	79.9 (45.5-98.0)	63.7 (34.5-96.0)	28.1 (13.6-64.0)	0.155^b
	V	98.2 (87.8-99.2)	69.5 (47.6-97.6)	25.3 (13.2-62.3)	0.012^b
2PM left[#], g/mm², (median (IQR))	I	93.6 (62.3-97.7)	62.0 (37.1-88.5)	26.4 (16.7-56.7)	<0.001^b
	II	83.1 (57.2-97.6)	66.7 (40.0-92.8)	44.9 (23.5-79.8)	0.278^b
	III	86.7 (49.0-98.9)	49.7 (35.7-75.2)	26.6 (14.0-54.5)	0.021^b
	IV	71.0 (37.6-90.2)	43.4 (23.9-85.5)	34.5 (16.9-55.3)	0.358^b
	V	96.8 (52.1-98.2)	44.6 (20.6-65.0)	26.7 (17.6-52.7)	0.054^b
2PM right[#], g/mm², (median (IQR))	I	97.5 (92.6-98.1)	47.9 (29.4-95.1)	32.5 (17.2-47.1)	0.003^b
	II	79.0 (54.7-97.7)	66.3 (35.6-91.2)	56.3 (28.4-76.4)	0.417^b
	III*	90.0 (62.0-98.4)	56.7 (28.1-84.8)	31.8 (16.6-64.0)	0.087^b
	IV	76.9 (41.3-98.3)	48.1 (32.7-86.0)	34.2 (18.6-56.9)	0.466^b
	V	95.9 (32.9-98.5)	36.2 (19.9-66.5)	32.8 (15.4-58.1)	0.184^b

Abbreviations: Roman capitals are indicatives of test locations: I, hallux; II, medial heel; III, first dorsal web; IV, lateral foot; V, fifth toe. MF, monofilaments; RS, Rydel-Seiffer tuning fork; -, insensate; +, sensate; n, number; 1PS, one-point static discrimination with PSSD; 2PS, two-point static discrimination with PSSD; 2PM, two-point moving discrimination with PSSD; *) significant difference between left and right (p<0.05) (Wilcoxon Signed Ranks test); #, for interprong distance, see other table; ^b, Kruskal-Wallis H test.

Reliability and construct validity

For 1PS at the right hallux (t=-2.763, p=0.006) proportional bias was found in the range of measurements (Figure 2). No proportional bias was found for 2PS (t=-0.896, p=0.372) and 2PM measurements (t=-1.179, p=0.241); therefore, Bland-Altman plots were constructed (Figure 3 and 4). Additionally, all other test sites were taken into account to investigate if

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certain locations are more internally consistent. 1PS on the dorsal first web space proved to be reliable ($t=-0,092$, $p=0,927$), as well as 2PS and 2PM for the other test locations, except 2PM measured at the heel ($t=3.008$, $p=0.003$). Significant differences were found for 1PS on the other test locations ($p=0.001$ to $p=0.018$).

Figure 2

1PS by the PSSD of the right hallux. X-axis shows the mean of the measurements, Y-axis shows the difference between the measurements.

Figure 3

Bland-Altman plot of 2PS by the PSSD of the right hallux, comparing limit of agreement between measurements. The middle line shows the mean difference, together with 95% confidence interval lines.

Figure 4

Bland-Altman plot of 2PM by the PSSD of the right hallux, comparing limit of agreement between measurements. The middle line shows the mean difference, together with 95% confidence interval lines.

Construct validity

There were statistically significant differences between SWM and PSSD ($p < 0.0001$) for all test locations. Therefore, we conclude PSSD and SWM (g/mm^2) measurements are not interchangeable. Spearman correlations were calculated between SWM (S1PD) and PSSD (1PS) measurements, presented in Table 4. All hypotheses were confirmed concerning construct validity: 1) a positive, significant correlation of pressure in g/mm^2 measured by SWM with PSSD (1PS) was found ($r_s > .312$), 2) the positive correlation between SWM and PSSD (1PS) is distributed unevenly at the foot (r_s 0.312 to 0.832), and 3) the positive correlation between SWM and PSSD (1PS) measurements is more profound in groups characterized by a more severe form of DSP (group 1: $r_s > .480$ vs. group 3: $r_s > .283$). SWM measurements in pressure (g/mm^2), compared to force (g), did not correlate better with 1PS measurements by the PSSD.

Table 4 Spearman correlations.

	Test site	Group 1 (prior ulcer, MF-, RS-)	Group 2 (MF+, RS-)		Group 3 (MF+, RS+)	
		SWM in gram	SWM in g/mm^2	SWM in gram	SWM in g/mm^2	SWM in g/mm^2
1PS left, g/mm^2	I	0.480*	-0.294	0.428*	0.400*	0.418**
	II	0.773**	0.686**	0.543**	0.553**	0.544**
	III	0.667**	0.039	0.611**	0.613**	0.346**
	IV	0.771**	0.023	0.384*	0.436**	0.312**
	V	0.832**	0.143	0.338	0.260	0.438**
1PS right, g/mm^2	I	0.612**	-0.219	0.489**	0.522**	0.342**
	II	0.599**	0.179	0.587**	0.630**	0.552**
	III	0.644**	-0.196	0.255	0.286	0.283**
	IV	0.706**	-0.232	0.401*	0.430*	0.355**
	V	0.758**	-0.124	0.320	0.370*	0.384**

Abbreviations: Roman capitals are indicatives of test locations: I, hallux; II, medial heel; III, first dorsal web; IV, lateral foot; V, fifth toe. 1PS, one-point static discrimination; SWM: Semmes-Weinstein monofilaments; MF, monofilaments; RS, Rydel-Seiffer tuning fork; -, insensate; +, sensate; n, number; 1PS, one-point static discrimination with PSSD; *) significant at the 0.05 level (2-tailed), **) significant at the 0.01 level (2-tailed).

Discussion

In this study we investigated reliability and validity of PSSD measurements and the ability of the PSSD to discriminate between categories of sensory loss in the feet of diabetics. Reliability was investigated to evaluate consistency of PSSD testing across different categories of sensory loss, at different test locations. By determining validity, sensory tests purporting to measure similar constructs were evaluated (SWMs vs. PSSD).

Currently used screening test for the loss of protective sensation have several disadvantages. The SWM is influenced by temperature and humidity conditions and the cross sectional area of the monofilaments is often not taken into account, resulting in discrepancies between given force and measured pressure^{13,17,28,30,31}. The PSSD measures 0.1 to 100 g/mm² with the same cross-sectional diameter, in contrast to a SWM set, which are 'steps' on a logarithmic scale with increasing cross sectional diameters of consecutive filaments. Both pressure and force did correlate to 1PS tested by the PSSD, which suggests that conversion from force to pressure is not a necessity for interpreting correlations (Table 4). The present study shows that across all test locations, categories of sensory loss were distinguishable using 1PS alone.

The PSSD has been primarily designed for the diagnosis of nerve entrapment. A higher sensitivity is reported in diabetics with superimposed nerve compression, compared to nerve conduction studies^{16,17}. An instrument with five consecutive measurements should not exhibit too much heterogeneity, when used on a single test site, in the same person, in a narrow time frame. We did compare the three measurements to the neglected test results as measure of reliability of PSSD measurements. 2PS and 2PM measurements were reliable, except for the medial heel. However, 1PS testing was only reliable on the first dorsal web. Application speed by the operator, and therefore differences in stimulus recognition, might have been at issue here, which is different from 2PS and 2PM measurements because of the programmed stopped recording when pressure between the prongs differed too much. For all measurements, less severe sensory deficit (a cutaneous threshold <40 g/mm²) showed fewer variations around the mean, compared to higher cutaneous thresholds (Figure 2, 3 and 4). This means an increased sensory deficit results in less reliable results. Increasing age also showed more variability across PSSD measurements (data not shown). This information is especially important for clinicians. More tests on alternating test locations are needed to provide a more confident estimate on the sensory status in patients with more severe sensory loss.

Both SWM and PSSD measure the cutaneous threshold (S1PD, 1PS), which in itself is often increased in diabetics. Our results are consistent with previous studies that assessed the validity of the PSSD, used in the upper extremity^{17,18,32,33}. The most severely affected diabetics, showed the strongest correlations, which is probably due to the severely elevated thresholds, with less deviation seen compared to other groups.

A cutaneous threshold of more than 10 g is an indicator of large fiber neuropathy and a risk for foot ulceration and amputation³⁴, so already quite severe and late in the natural course of DSP. An altered two-point discrimination is proven to be an earlier indicator of nerve pathology^{12,14,35}. Our results suggest that the discriminative distance between two points

increases, before the cutaneous threshold increases in the gradual decline of sensation. Therefore, spatial discrimination is a suitable test to place in a battery of tests to estimate loss of foot sensation at an earlier stage.

Another advantage of the PSSD in measuring spatial discrimination lies in the fact that it measures both prong distance and pressure applied^{16,21,36}. Despite the theoretical advantages, it remains to be seen if these properties result in a better candidate selection for and improved results of, for example, decompression surgery of lower extremity nerves. The ability to detect change over time of the different constructs measured has to be investigated for the lower extremity in more clinimetric sound observational and interventional research³⁶. The clinical applicability of the PSSD not only depends on the scientific evidence of its measurement properties, but also the costs, duration of test and the required user skills have to be taken into account. During our study, we had software issues causing complete data loss of approximately 10% of patients measured. The PSSD is an expensive device, not suitable for a broad application in daily clinical practice. This in contrast to traditional test instruments that are inexpensive and quick to perform in a variety of settings. SWMs have a more limited life cycle, making regular replacements of those sets necessary. Such economic assessments of diagnostic tests have to be taken into account when considering a broader clinical implementation.

Our study investigated certain clinimetric properties of the PSSD, assessed in the lower extremity. The results show that the PSSD can differentiate between categories of sensory loss, with each category having different relative risks for (recurrent) foot ulceration. Not all test locations need to be tested to have a good estimate of overall sensory loss. We suggest assessing static two-point discrimination at the hallux, moving two-point discrimination at first dorsal web and one-point discrimination at the lateral foot to get a quick estimate of where the patient is positioned in the course of sensory loss.

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Chapter IV

Development of grading scales of pedal sensory loss using Mokken Scale Analysis on the Rotterdam Diabetic Foot Study Test Battery data

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Abstract

Introduction

Loss of sensation due to diabetes-related neuropathy often leads to diabetic foot ulceration. Several test instruments are used to assess sensation, such as static- and moving two-point discrimination (S2PD, M2PD), monofilaments, and tuning forks.

Methods

Mokken Scale Analysis was applied to the Rotterdam Diabetic Foot Study data in order to select hierarchies of tests to construct measurement scales.

Results

We developed 39-item and 31-item scales to measure loss of sensation for research purposes and a 13-item scale for clinical practice. All instruments were strongly scalable and reliable. The 39 items can be classified into five hierarchically ordered core clusters: S2PD, M2PD, vibration sense, monofilaments, and prior ulcer or amputation.

Discussion

Guided by the presented scales, clinicians may better classify the grade of sensory loss in diabetic patients' feet. Thus, a more personalized approach concerning individual recommendations, intervention strategies, and patient information may be applied.

Introduction

Diabetic sensorimotor polyneuropathy (DSP) occurs in about 50% of diabetic patients, leading to decreased quality of life and increased mortality.³⁻⁵ Sensory loss due to DSP is one of the most important risk factors for diabetic foot ulceration and amputation.² DSP is frequently accompanied by positive sensory phenomena. Yet, it is the simultaneous process of decreased sensation that places the feet of diabetic patients at risk.¹ Because not every patient with positive sensory symptoms has sensory loss, it is useful to focus on objective measures such as foot sensation to assess large-fiber nerve function.⁶

Loss of sensation can be assessed with several instruments.^{7,8} Current guidelines recommend an annual screening with a 10 g Semmes–Weinstein monofilament (SWM) or a tuning fork.⁹⁻¹¹ These instruments test different somatosensory corpuscles and nerve fibers, functions of which are progressively lost during the natural course of DSP.¹²⁻¹⁴ However, a cutaneous threshold of ≥ 10 g is an indicator of large-fiber demyelination, which becomes informative in a late stage of neuropathy and reflects a high risk for foot ulceration and lower extremity amputation.¹⁵ Other measurements, such as two-point discrimination, have proven to be early indicators of nerve pathology and might be able to detect earlier alterations in foot sensation.^{16,17,6}

Few available studies describe the sequence in which sensory tests become abnormal in the natural course of diabetes-related neuropathy.^{6,18,19} In order to more precisely categorize patients with diabetes according to their degree of sensory loss, we applied the Mokken Scale Analysis (MSA), which is related to nonparametric forms of item response theory (IRT), to the tests used in the Rotterdam Diabetic Foot (RDF) study.⁶ MSA is a scaling method increasingly used in health sciences.²⁰⁻²³ IRT assumes that a latent (not directly observable) trait, denoted as θ (theta), drives the patients' scores on the items. Typically, θ is used as a proxy for the construct being measured (i.e., foot sensation, hence foot sensation determines the item scores). Because θ is latent, a patient's score on θ must be estimated from the observable item scores.^{6,24} MSA is a flexible scaling method, in contrast to other IRT models such as Rasch analysis, so it fits data relatively well and includes a fair amount of items that can be used for ordinal measurement. In the present analysis, we used questionnaire data and the results of sensory tests of the feet as items (Rotterdam Diabetic Foot Study Test Battery).

We investigated if the tests of the Rotterdam Diabetic Foot Study Test Battery were unidimensional, scalable, and reliable in assessing sensation in the feet. Information on the degree of sensory loss may help clinicians to assess the risk of lower extremity complications, resulting in more personalized recommendations regarding intervention strategies and patient information.

Materials and Methods

Study design and subjects

Between January 2014 and June 2015, patients were evaluated at the outpatient Diabetes Clinic of the Franciscus Gasthuis in Rotterdam, the Netherlands as part of the RDF study—a prospective cohort study that investigated the deterioration of sensation in diabetic patients' feet over time. The RDF-study design and methods are described in more detail in previous papers.^{6,25} Inclusion criteria included patients diagnosed with diabetes mellitus (treated by oral blood glucose lowering drugs and/or insulin), who were 18 years or older, spoke Dutch or English, and had no significant cognitive impairment, and had provided written informed consent. Exclusion criteria were assessed at the interview and with a screening questionnaire and included a positive history of active radicular syndrome or a neurological disease that interfered with sensation in the feet. Demographic data were obtained from the patients' files. All subjects provided written informed consent. The institutional review board and the Medical Ethical Committee of Erasmus MC University Center, Rotterdam, Netherlands approved the study (MEC-2009-148).

Comparison with healthy controls without known neuropathy

A total of 196 healthy volunteers were tested with the same measurement instruments and the same protocol as the RDF-study population as part of a separate study to obtain normative test values.²⁶ Volunteers were recruited from hospital and university personnel and relatives and friends of patients visiting the outpatient clinic. Inclusion criteria included patients age ≥ 18 years, with no significant cognitive impairment, who spoke Dutch and provided signed informed consent. Exclusion criteria were a positive history of active radicular syndrome, a neurological disease that interfered with sensation in the feet, diabetes mellitus, thyroid malfunction, alcohol abuse, human immunodeficiency virus, or chemotherapy—all these were established at the interview using a screening questionnaire. Datasets were combined to compare patients to healthy controls.

Measurement instrument

The Rotterdam Diabetic Foot Study Test Battery

Patients and volunteers were screened using monofilaments, static- and moving two-point discrimination tests, a tuning fork, cold sensation tests, the Michigan Neuropathy Screening Instrument (MNSI), and the Romberg test. Information on prior ulceration and amputation, as indicators of severe sensory loss, was retrieved from a patient's file and interview. Cutaneous threshold (one-point static discrimination, S1PD) was tested on five locations of each foot using SWMs (Baseline® Tactile™, USA) ranging from 0.008 to 300 g. The test locations were chosen in concordance with the nerve distribution in the foot: I, plantar hallux

(medial plantar nerve [tibial nerve]); II, medial heel (calcaneal nerve [tibial nerve]); III, dorsal first web (deep fibular nerve); IV, lateral foot (sural nerve); and V, plantar fifth toe (lateral plantar nerve; see Supplementary Figure A). Areas with excessive callus formation were avoided. Innervation density (determined by static- and moving two-point discrimination tests: S2PD, M2PD) was assessed on the same test locations using the Disk-Criminator™ (US Neurologicals, LCC, WA, USA). M2PD was not assessed at the fifth toe because the area is too small. A Rydel-Seiffer tuning fork (Martin, Tuttlingen, Germany) tested the vibration threshold on the medial malleolus and dorsal interphalangeal joint of the hallux. Both feet were examined. Neuropathy complaints were assessed using the MNSI questionnaire, which was administered before the physical examination.

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Using Tinel's sign, we scored localized nerve compression as positive when tingling and electrical sparks were elicited after tapping the tibial nerve at the left and right tarsal tunnel. To test cold perception, a cold piece of metal was bilaterally applied to the skin of the foot arc. Proprioception was tested using Romberg's test.

Data analysis

A cross-sectional analysis of the RDF baseline data was carried out for the MSA. Results of the Rotterdam Diabetic Foot Study Test Battery (both tests of sensation and questionnaire data) were dichotomized because MSA requires that all items have the same number of categories. Individual sensory test items were comprised of both a sensory test and the test location (e.g., S1PD at the hallux is labeled as S1PD I, and S2PD at the medial heel as S2PD II). Based on previously published normative values, the threshold for S2PD and M2PD was set at 8 mm and at 10 g for S1PD.²⁶ Vibration threshold was compared to age-related reference values.²⁷ Positive symptoms (e.g., tingling and burning sensations) and negative symptoms (e.g., numbness) were retrieved from the MNSI questionnaire, resulting in two items. When scoring at or below the threshold (i.e., "could feel the stimulus"), 0 was noted. A score of 1 was noted when a patient scored above the threshold, meaning aberrant (i.e., "could not feel the stimulus"). In total, 42 individual RDF Study Test Battery items were identified per subject. Second and third annual follow-up data are presented and compared to baseline data as a measure of the statistical significance of the change scores.

Mokken scale analysis

In the family of IRT, nonparametric IRT (nIRT) assumes that the relationship between the item score and the latent trait is limited only by order restrictions but is otherwise free.²⁸ MSA, compared to other IRT models used in a previous study, offers more flexible and less restrictive opportunities to select hierarchies of items and is a statistical method used to determine whether hierarchical scales exist in an item bank to construct a measurement

scale (e.g., to measure the level of foot sensation).⁶ Moreover, when the fit criteria are met, a patient's ability may be estimated by simply taking the sum of the test item scores. This is in contrast to parametric IRT, which necessitates the use of software to estimate θ . We used MSA to investigate the scalability and the ordering of the items studied.²⁹ MSA requires that all item scores be directed in the same way so that higher mean scores reflect more severe sensory loss in the feet.

MSA is a set of methods, consisting of three steps, that assesses whether nIRT models fit the data well. The theory behind (n)IRT models has been published in detail.^{6,30-32} In short, IRT assumes that patients with a higher ability ("less impaired") should have a greater chance of obtaining a nonaberrant score on an item. Thus, the probability of a response to an item depends on the differences between the ability of the person and the difficulty of the item.⁶ nIRT models relate patients' item scores to θ .^{33,34} If the item scores fit the nIRT well, a patient's θ value may be estimated simply taking the sum of the item scores. MSA provides information on which items meet the criteria, with well-fitting items selected for a final, optimal scale. In addition, MSA provides information on the strength of the scale (scalability) and the precision of the scale (reliability).³³ In this study, the resulting scale and quality indices may help to classify patients in different stages of sensory loss.

First in MSA, we evaluated the monotone homogeneity model, which allows ordinal scaling of the patients using the sum score of items. We constructed a scale based on a preliminary selection of items for the scale that was conducted using the automated item selection procedure,³⁵ which selects items that pass a marginal test for fitting the monotone homogeneity model and have some discriminatory power between persons located low and persons located high on the attribute scale. In addition, we used the procedure of manifest monotonicity to test for each preliminary selected item whether the probability of obtaining item score 1 increased as θ increased (i.e., does the probability of an aberrant response to a stimulus increase if the patient's foot sensation decreases).^{34,35} Items that passed this test were further analyzed in step two.

Second, we determined the scalability and reliability of the selected items using Mokken's scalability coefficients H_i and H , respectively. Coefficient H_i ($H_i \leq 1$) provides information on the scalability of individual items. Negative values or values around zero indicate poor discriminatory power. In the automated item selection procedures, an H_i value of 0.3 is typically used as a lower limit to include an item in a scale. Higher values indicate more discriminatory power. Very high H_i values ($H_i > 0.8$) are possibly due to linear dependence in the scale and should be mistrusted. Coefficient H provides information on the scalability of the entire scale. Generally, the scalability is weak if $0.30 \leq H < 0.40$, medium if $0.40 \leq H < 0.50$,

and strong if H is ≥ 0.50 . Standard errors of scalability coefficients were also considered when determining scalability. The reliability of the final scale was estimated using the Molenaar-Sijtsma statistic (also known as ρ). In general, ρ values of ≥ 0.90 are recommended for firm conclusions and decisions about individual patients.³⁶

Third, the double monotonicity model was applied using the method of manifest invariant item ordering to investigate which items in the scale had an invariant item ordering (IIO).³⁷ Items that have IIO, that is, items whose item-response functions do not intersect, have the same ordering for each level of θ , which allows ordinal scaling of items using the average item score. An IIO is particularly useful to determine whether the sequence of the variables becomes abnormal and whether this holds true for all patients under study. Manifest invariant item ordering is a three-step procedure consisting of (a) a visual inspection of the nonintersection of estimated item response functions, (b) a backward item-selection procedure removing all items from the scale that do not satisfy an IIO, and (c) the computation of scalability coefficient H^T for the remaining items in the scale. A minimum value of $H^T = 0.30$ is recommended.³⁸

By visually inspecting the estimated item-response functions of invariantly ordered items, we selected a small number of items that were evenly distributed across the scale as a screening instrument, to be used in clinical practice, to determine the loss of sensation in diabetic patients' feet. Items having the strongest scalability and highest reliability were considered and reflected the various types of instruments used.

By following the steps above, the two different nIRT models used in MSA were applied, which allowed us to use a sum score of the selected items for ordinal patient measurement (monotone homogeneity model) and to order items according to mean item scores (double monotonicity model).²⁹

Person-item map

The ordering of the items along the latent trait (θ) was graphically displayed using a person-item map (PIM). A PIM shows the relationship between the estimated item location parameters and the estimated latent trait (i.e., foot sensation) together with a histogram of the estimated latent trait values.³⁹ The map provides useful graphical information on the ordering of items and the relationship between items and persons.

Statistics

MSA was conducted using the R package *mokken*.^{35,40} The PIM was constructed using the R package *eRm*.³⁹ Other statistical analyses were carried out using IBM SPSS Statistics 22.0

(IBM Corp., Armonk, New York, USA). Missing item data were replaced by imputed data using the procedure of expectation maximization, using 25 iterations. Shapiro–Wilk tests were used to assess normality. Because the majority of the variables significantly deviated from a normal distribution, we continued our analyses with nonparametric tests. Correlations were investigated using Spearman coefficients. Using the Mann–Whitney U test, we compared differences between total item scores of RDF-study participants and controls without neuropathy as well as differences in grading scale scores between genders. Differences in grading scale scores of subjects with a second and third follow-up were assessed using a Friedman test. Spearman coefficients were used to study the direction and magnitude of the correlations or differences between these change scores (as a measure of responsiveness), with the null hypothesis that no differences exist in foot sensation during follow-up. We considered p values below 0.05 (two-sided) to be statistically significant.

Results

General characteristics

A total of 416 diabetic patients with varying degrees of complaints and loss of sensation were included in the RDF study. Table 1 shows the general characteristics of patients. Fifty-two patients had a prior ulcer, and 13 patients had a history of lower extremity amputation.

Mokken scale analysis

Under the monotone homogeneity model, the automated item selection procedure selected 39 of the original 42 items (Table 2). Items “Tinel sign left” and “Right” and “MNSI positive symptoms” were not selected, so the 40-point scale ranges from 0 (no aberrant tests) to 39 (all tests aberrant). Scalability coefficients (H_i) ranged from 0.354 to 0.713 (Table 2, third column), with a coefficient of scalability H of 0.538, which indicates a strong scale—except for item “Amputation left,” for which $H_i > 0.8$, probably due to its low prevalence. The Molenaar–Sijtsma statistic equaled $p = 0.964$, suggesting that the 39-item scale (RDF-39) is highly reliable. Of the 39 items, no items showed a violation of monotonicity. The most frequent aberrant items (e.g., on S2PD and M2PD) represent early stages of sensory loss (Table 2, second column). Sensory functions were lost symmetrically, with items representing more distal test sites (e.g., vibration sense at the interphalangeal joint) becoming aberrant before the proximal ones (e.g., vibration sense at the medial malleolus).

Under the double monotonicity model, the manifest invariant item ordering procedure selected 8 items violating IIO, indicated by a double dagger in Table 2. The remaining scale consisted of 31 items (RDF-31) and had a H^T coefficient of .581. Scalability coefficients (H_i)

ranged from 0.431 to 0.836 (Table 2, fifth column) and featured a coefficient of scalability H of 0.550, which indicates a strong scale. The reliability statistic ρ was 0.958.

Table 1 Demographic Data of Diabetic Subjects.

Gender (M/F)	241/175
Ethnicity (n (%))	
- Caucasian	340 (81.7%)
- Indo-Surinamese	35 (8.4%)
- African	15 (3.6%)
- Asian	7 (1.7%)
- Other	19 (4.6%)
Age (median [y], IQR)	64.0 (55.0–70.3)
Length (median [m], IQR)	174.0 (165.0–181.0)
Weight (median [kg], IQR)	88.5 (78.0–103.0)
BMI (median [kg/m²], IQR)	27.2 (23.0–33.6)
Duration of diabetes (median [y], IQR)	16.0 (9.0–25.0)
Type of diabetes (n [%])	
- Type 1	93 (22.4%)
- Type 2	323 (77.6%)
Drugs (n [%])	
- Lipid lowering drugs	267 (64.2%)
- Oral blood glucose lowering drugs	229 (55.0%)
- Insulin	351 (84.4%)
HbA1c (median (mmol/L), IQR)	60.0 (53.0–70.0)
MDRD (ml/min/1.73 m, IQR)	78.9 (60.2–96.6)
Total cholesterol (median (mmol/L), IQR)	4.1 (3.5–4.8)
LDL-C (median (mmol/L), IQR)	1.9 (1.4–2.5)
HDL-C (median (mmol/L), IQR)	1.3 (1.1–1.6)
Non-HDL-C (median mmol/L, IQR)	2.7 (2.1–3.3)
TG (median (mmol/L), IQR)	1.6 (1.0–2.4)
ApoB (median (g/L), IQR)	0.9 (0.8–1.1)
Microalbumin (median (mg/L), IQR)	17.0 (8.0–54.5)
Systolic blood pressure (mmHg, SD)	137.9 ± 19.4
Diastolic blood pressure (mmHg, SD)	76.1 ± 9.9
Diabetic Sensory Polyneuropathy (n (%))	
- MNSI score ≥4	148 (35.6%)
Retinopathy	59 (14.2%)

Legend: M, male; F, female; n, number; SD, standard deviation; IQR, interquartile range; BMI, Body Mass Index; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; LDL, low density lipoprotein; HDL, high density lipoprotein; C, cholesterol; TG, triglycerids; ApoB, apolipoprotein B; MNSI, Michigan Neuropathy Screening Instrument.

Table 2 Mokken Scale Analysis Characteristics.

39-item scale	Mean	Hi (SE)	31-item scale	Hi (SE)	13-item scale	Hi (SE)
S2PD II right	0.762	0.545 (0.036)	S2PD II right	0.550 (0.037)	S2PD II right	0.470 (0.046)
S2PD II left	0.757	0.510 (0.038)	S2PD II left	0.503 (0.040)		
S2PD V right‡	0.738	0.597 (0.025)				
S2PD I left	0.733	0.509 (0.031)	S2PD I left	0.507 (0.033)	S2PD I left	0.461 (0.042)
S2PD V left	0.728	0.544 (0.029)	S2PD V left	0.547 (0.031)		
S2PD IV right	0.728	0.515 (0.033)	S2PD IV right	0.517 (0.034)		
S2PD I right‡	0.724	0.563 (0.026)				
S2PD IV left	0.716	0.542 (0.030)	S2PD IV left	0.538 (0.032)		
S2PD III left‡	0.714	0.479 (0.033)				
S2PD III right	0.709	0.522 (0.032)	S2PD III right	0.520 (0.034)	S2PD III right	0.460 (0.043)
M2PD II left	0.651	0.492 (0.032)	M2PD II left	0.487 (0.034)		
M2PD III left	0.647	0.504 (0.032)	M2PD III left	0.495 (0.034)	M2PD III left	0.404 (0.045)
M2PD III right	0.644	0.529 (0.031)	M2PD III right	0.523 (0.032)		
M2PD II right	0.601	0.546 (0.029)	M2PD II right	0.546 (0.031)		
M2PD IV right	0.594	0.532 (0.030)	M2PD IV right	0.525 (0.032)		
M2PD IV left‡	0.587	0.501 (0.032)				
M2PD I right	0.558	0.575 (0.029)	M2PD I right	0.574 (0.030)		
M2PD I left‡	0.555	0.597 (0.027)				
Vibration sense IP right	0.423	0.483 (0.039)	Vibration sense IP right	0.508 (0.037)	Vibration sense IP right	0.613 (0.032)
Vibration sense IP left	0.423	0.483 (0.039)	Vibration sense IP left	0.508 (0.037)	Vibration sense IP left	0.613 (0.032)
Vibration sense MM right	0.387	0.424 (0.041)	Vibration sense MM right	0.431 (0.041)	Vibration sense MM right	0.512 (0.037)
Vibration sense MM left	0.356	0.460 (0.040)	Vibration sense MM left	0.468 (0.040)	Vibration sense MM left	0.581 (0.034)
MNSI negative symptoms	0.272	0.469 (0.042)	MNSI negative symptoms	0.468 (0.042)		
S1PD I right	0.240	0.614 (0.035)	S1PD I right	0.621 (0.034)	S1PD I right	0.629 (0.039)
S1PD I left	0.236	0.646 (0.033)	S1PD I left	0.647 (0.033)	S1PD I left	0.645 (0.041)
S1PD II right	0.233	0.543 (0.040)	S1PD II right	0.551 (0.039)		
S1PD II left	0.228	0.541 (0.041)	S1PD II left	0.549 (0.041)		
S1PD V right	0.207	0.635 (0.035)	S1PD V right	0.651 (0.035)		
S1PD V left	0.207	0.632 (0.037)	S1PD V left	0.643 (0.039)		
Romberg test positive‡	0.166	0.354 (0.061)				
Cold/warmth left‡	0.142	0.498 (0.057)				
Cold/warmth right‡	0.135	0.483 (0.061)				
S1PD III right	0.135	0.661 (0.039)	S1PD III right	0.693 (0.039)		
S1PD III left	0.130	0.689 (0.041)	S1PD III left	0.713 (0.042)		
Prior ulcer	0.123	0.567 (0.052)	Prior ulcer	0.591 (0.053)	Prior ulcer	0.665 (0.056)
S1PD IV right	0.123	0.626 (0.050)	S1PD IV right	0.651 (0.035)		
S1PD IV left	0.120	0.661 (0.048)	S1PD IV left	0.689 (0.048)		
Amputation right	0.019	0.713 (0.077)	Amputation right	0.744 (0.082)	Amputation right	0.720 (0.094)

Table 2 Mokken Scale Analysis Characteristics. (continued)

39-item scale	Mean	Hi (SE)	31-item scale	Hi (SE)	13-item scale	Hi (SE)
Amputation left	0.014	0.814 (0.033)	Amputation left	0.836 (0.044)	Amputation left	0.736 (0.092)
Coefficient of scalability H*		0.538 (0.022)		0.550 (0.024)		0.551 (0.028)
Coefficient of invariant item ordering HT		0.584		0.581		0.627
Coefficient of reliability p		0.964		0.958		0.910

Legend: Mean, prevalence of aberrant response per item in this group of 416 diabetic subjects; Roman capitals are indicatives of test locations: I, plantar hallux; II, medial heel; III, first dorsal web; IV, lateral foot; V, plantar fifth toe. S2PD, static two-point discrimination; M2PD, moving two-point discrimination; S1PD, static one-point discrimination (10 g Semmes-Weinstein monofilament). IP, interphalangeal joint; MM, medial malleolus; MNSI, Michigan Neuropathy Screening Instrument.

*, *H* for the scale (range, 0-1 under the monotone homogeneity model).

†, items violating IIO.

Person-item map

A PIM showed that the 39 items of the RDF-39 could be classified into five core clusters (Figure 1). The S2PD cluster contained the items that were first becoming aberrant during the natural history of sensory loss, followed by a cluster of all M2PD items, vibration sense items, S1PD items, and items on prior ulceration/lower extremity amputation.

Figure 1 Person-Item Map and Person Parameter Distribution of RDF-study participants.

Legend: Abbreviations: Roman capitals are indicatives of test locations: I, plantar hallux; II, medial heel; III, first dorsal web; IV, lateral foot; V, plantar fifth toe. S2PD, static two-point discrimination; M2PD, moving two-point discrimination; S2PD, static one-point discrimination (10 g Semmes-Weinstein monofilaments); IP, interphalangeal joint; MM, medial malleolus; MNSI, Michigan Neuropathy Screening Instrument; -, negative. The plotted 39 black dots (•) are replaced by black stars (*) as indicator of an item included in the 31-item scale and with white stars (°) when indicating an item included in the 13-item scale. Note that all 13 RDF-13 items are included in the RDF-31 scale.

A clinically applicable screening scale

Table 2, sixth column, shows the item selection that we used to construct a clinically applicable screening scale, based on the 31-item scale. This 13-item scale (RDF-13) examines both extremities; items feature scalability coefficients ranging from 0.404 to 0.736 with $H = 0.551$, which indicates a strong scale. The reliability coefficient being $\rho = 0.910$ suggests that the scale is also reliable. Strong positive correlations have been found between the 39-item scale and the 31-item scale, $r_s = 0.993$, $p < 0.001$, and 31-item scale and 13-item scale, $r_s = 0.966$, $p < 0.001$. The item-response functions for the 13-item scale were plotted (Figure 2), showing their different discriminatory values along the sum score. As the latent trait increases (indicative of more severe sensory loss), so does the chance of obtaining an aberrant item test result. A clinically applicable scoring sheet for the respective scales is available in Supplementary Appendix A.

Figure 2 Item Characteristic Curve of the 13-item Scale.

Legend: Abbreviations: I, plantar hallux; II, medial heel; IP, interphalangeal joint; MM, medial malleolus. Note: ICC curves of items "vibration sense IP left" and "right" are plotted on top of each other.

Comparison to healthy controls

A total of 196 healthy volunteers, whose median age was 50.5 (interquartile range [IQR] = 36.5–65.7), served as the control group—66 men (median age = 50.6 years; IQR = 37.7–64.1) and 130 women (median age = 50.0 years; IQR = 33.3–66.9).²⁶ The median height for this group was 172.0 cm (IQR = 166.3–178.8) and the median weight 72.0 kg (IQR = 63.0–82.0). Diabetic subjects were significantly older and heavier than controls ($p < 0.0005$; see Table 1).

Figure 3 shows the 39-item sum score distribution of diabetic RDF participants compared to the controls. Median total RDF-39 scores (IQR) differed significantly between individuals in the control group (5.5; IQR = 3.0–10.8) and RDF-study subjects with diabetes (17; IQR = 9.0–22.0), $p < 0.0001$.

Figure 3 Sum Score Distribution of the 39-item Scale in Diabetic Patients and Controls Without Known Neuropathy.

Since diabetes-related lower extremity complications (i.e., neuropathy complaints, sensory loss, ulceration, and amputations) are the main drivers of RDF-39 scores in diabetic subjects, correlations between RDF-39 scores and demographic variables such as age, height, and weight were only explored in the control population. Significant positive correlations were found between RDF-39 scores and age, $r_s = 0.405$, $p < 0.0005$, and RDF-39 scores and weight,

$r_s = 0.212$, $p = 0.003$. A nonsignificant positive trend was observed between RDF-39 scores and height, $r_s = 0.135$, $p = 0.059$. Nonsignificant differences in median RDF-39 scores (IQR) were found between males (6.0; IQR = 3.0–12.5) and females (5.0; IQR = 2.8–10.0), $p = 0.563$.

Responsiveness of the RDF-39

We conducted a Friedman test to determine if there were differences within subjects' RDF-39 scores, which were collected at a follow-up RDF study ($n = 135$). RDF-39 scores at baseline (median = 17; IQR = 17–22), at the 1 year follow up (median = 16; IQR = 16–24), and at 2 years follow up (median = 18; IQR = 18–22) did not differ significantly, $\chi^2(2) = 1.536$, $p = 0.464$. There was a strong positive correlation between baseline and first follow up RDF-39 scores, $r_s = 0.698$, $p < 0.0005$, and first and second follow-up scores, $r_s = 0.697$, $p < 0.0005$.

Discussion

This quantitative assessment of the categorical loss of pedal sensation of patients with diabetes showed that the ability to sense S2PD, M2PD, vibration, and S1PD disappears in this order. This study emphasizes the added value of testing static- and moving two-point discrimination and highlights the importance of test locations to the screening of diabetic patients. Furthermore, the instruments (RDF-39, -31, and -13) captured the functional loss that is dictated by the pathophysiology of neuropathy.^{16,18,19}

At present, no data are available on how a tuning fork, monofilament testing, and test locations compare or how these should be interpreted.¹¹ By taking the site of screening into account, we observed that the first dorsal web and the lateral foot are the last of all sensibility tests and locations to become the least sensitive to the 10 g monofilament. This may have predictive value for future lower extremity complications because it suggests substantial deafferentation. Originally, the monofilament was studied as a prognostic indicator of ulceration and amputation.^{41,42} Nowadays, the validity of the monofilament examination to identify the presence of DSP is generally accepted.^{43,44} Because the onset of sensory loss is insidious, its diagnosis may be difficult. Several scoring systems for signs and symptoms of DSP have been developed; however, they can be complex and time consuming.⁴⁵ Electrodiagnostic techniques do not assess all nerve fibers undergoing changes in diabetes; for instance, these test cannot assess the plantar surface of the foot and are not available in all clinical settings.^{46,47} It has been recommended that the diagnosis of DSP requires a test battery, with a high sensitivity, that detects early or mild forms in low-risk populations.⁴⁸ Furthermore, it is important for population studies to possess screening tools that are reproducible, sensitive, and fast to carry out. The simple-to-use instruments

used in the presented scales fulfill these criteria and are already being applied in clinical practice. The presented scales quickly and reliably estimate skin sensation and may be easily implemented by nurses, nurse practitioners, and physicians treating diabetic patients.

MSA is also a flexible scaling method. More restrictive scaling methods, such as Rasch analysis, typically fit the data worse (i.e., the data are not well-described by the Rasch model) and include relatively few items in the scale. However, the scales allow interval measurement.⁶ We believe ordinal measurement is sufficient for our study because the 40 ordinal levels of pedal sensory function produced by the 39-item scale are very informative. Most of the included items are indicators of large fiber function; however, some items assessed small fiber function (items “Cold perception left” and “Right”). We included these items to investigate how they become aberrant in the natural course of sensory loss, compared to large fiber function. Our data show that the ability to detect a cold stimulus decreases at a late stage of sensory loss, just before abnormal monofilament tests on the first dorsal web and lateral foot (Figure 1). However, the exact temporal sequence in which the different nerve fibers lose their functions is not fully understood.^{19,49} MSA may aid this debate in future studies.

The results of our study confirm that a patient most often first loses sensation in the distal extremity, with vibration sense lost at the interphalangeal joint of the hallux before the medial malleolus. The scales also show that a patient loses sensation in both legs symmetrically, which is in line with the definition of DSP being a distal, symmetrical neuropathy.⁴⁸ The item on numbness of the feet has a position after the items on S2PD, M2PD, and vibration sense, which is interesting and suggests that patients seem unaware of the loss of these sensory modalities. At the same time, axonal density decreases, indicating that the feet are likely already at risk.⁵⁰ The 39-item and 31-item scales (RDF-39 and -31) were developed for research purposes; however, they can also be used for patient-level measurements. The short 13-item (RDF-13) scale may help individualized medical decision-making and may serve as a complement to the current prediction models for lower extremity complications.^{51–54}

An automated item selecting procedure ruled out the items “Tinel left” and “Right” and “MNSI positive symptoms,” meaning that they did not pass the marginal test for fitting the monotone homogeneity model. These items do not hold a robust position in the natural course of the disease, as clinicians will recognize from daily practice: patients who have had an ulcer and patients without aberrant large fiber function (e.g., intact S2PD) may still complain of painful neuropathic symptoms. As these results suggest, subjective positive complaints do not necessarily correlate with the degree of sensory loss, which is in contrast to experienced negative symptoms, such as “numbness,” which does have a robust position on the scale.

In our study, 44.9% (95% CI, 40.1 to 49.7%) of diabetic patients exhibited signs of tibial nerve compression, as indicated by a positive Tinel sign at the tarsal tunnel.²⁵ However, this study suggests that this sign has an uncertain place in the natural course of sensory loss; the Tinel sign items were not selected by the models and therefore were not included in the scales. This exclusion may be explained by the pathophysiology behind this diagnostic tool: Demyelination and axonal sprouting elicit a positive sign, but a negative sign is reported when those phenomena have not yet occurred or when the nerve has been irreversibly damaged.⁵⁵ Therefore, sensitivity/specificity calculations are not appropriate because they only can be interpreted when the degree of nerve damage is known.^{56,57}

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The population of the RDF study has a large variety of sensory loss, with and without complaints of DSP, resulting in a low risk of spectrum bias. Therefore, we think that the external validity of our findings is likely to be high. By comparing the distribution of the sum score of diabetic subjects to that of healthy volunteers without known neuropathy, we confirmed our hypothesis that the instruments correctly categorize patients' sensation in the feet. However, due to prior dichotomization of items, with the threshold set at 8 mm for items on static- and moving two-point discrimination, we noted some aberrancy in the first 18 items (S2PD and M2PD) assessed in the healthy controls. Decline in foot sensation due to age was confirmed in our analysis, with age being the most important determinant.⁵⁸ Only nonsignificant differences were observed between genders, which is in line with previous reports.^{7,26,59} The observed association between weight and foot sensation is presumably confounded by (components of) the metabolic syndrome, as it relates to polyneuropathy, and should be investigated in future studies.⁶⁰ The most important risk factors for DSP relate to the duration of diabetes, control of glucose levels, and the existence of cardiovascular risk factors.^{61,62} We retained the null hypothesis that no differences existed in foot sensation in this time frame. A follow up of this cohort will reveal which time frame is applicable on the progressive steps on the scale, as well as the associated risk for (re-) ulceration or amputation, per sum score.¹⁵

In conclusion, MSA revealed new dimensions in the use of current screening instruments in this diverse diabetic population. Based on the presented scales, clinicians may better categorize patients' loss of sensation in their feet. Therefore, an individualized approach with recommendations regarding intervention strategies and patient information may be feasible.^{63–66}

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Supplementary material

Figure A Test locations.

Legend: Abbreviations: Roman capitals are indicatives of test locations: I, hallux; II, medial heel; III, first dorsal web; IV, lateral foot and V, fifth toe.

Appendix A The Rotterdam Diabetic Foot Study Test Battery Scoring Sheet.

Left lower extremity	Test result (0 = nonaberrant, 1 = aberrant)	Right lower extremity	Test result (0 = nonaberrant, 1 = aberrant)
S2PD II *		S2PD II *,*	
S2PD I *,*		S2PD I	
S2PD III		S2PD III *,*	
S2PD V *		S2PD V	
S2PD IV *		S2PD IV *	
M2PD II *		M2PD II *	
M2PD III *,*		M2PD III *	
M2PD IV		M2PD IV *	
M2PD I		M2PD I *	
Vibration sense IP *,*		Vibration sense IP *,*	
Vibration sense MM *,*		Vibration sense MM *,*	
S1PD I *,*		S1PD I *,*	
S1PD V *		S1PD V *	
Numbness *	(derived from the MNSI)		
S1PD II *		S1PD II *	
S1PD III *		S1PD III *	
S1PD IV *		S1PD IV *	
Prior ulcer *,*	(scored for any extremity)		
Cold stimulus		Cold stimulus	
Romberg test			
Amputation *,*		Amputation *,*	
Sub-total		Sub-total	
Total RDF-39 score			
Total RDF-31 score			
Total RDF-13 score			

Legend: Roman capitals are indicatives of test locations: I, plantar hallux; II, medial heel; III, first dorsal web; IV, lateral foot; V, plantar fifth toe. S2PD, static two-point discrimination; M2PD, moving two-point discrimination; S1PD, static one-point discrimination (10 g Semmes-Weinstein monofilament). IP, interphalangeal joint; MM, medial malleolus; MNSI, Michigan Neuropathy Screening Instrument. Black stars (*) are indicators of an item included in the 31-item scale and white stars (°) are items included in the 13-item scale.

Chapter V

Grading the loss of sensation in diabetic patients. A psychometric evaluation of the Rotterdam Diabetic Foot Study Test Battery

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Abstract

Introduction

Static- and moving two-point discrimination (S2PD, M2PD), 10 g monofilaments and tuning fork are validated outcome measures of clinical manifestations of diabetes related neuropathy. No modern statistical techniques have been used to investigate how well these instruments combine to measure sensory loss.

Methods

To grade sensory loss at the feet, we fitted parametric forms of Item Response Theory models to the data of these instruments.

Results

The fit statistics indicate that the loss of sensation is gradable, with readily available instruments. S2PD and M2PD are lost first, followed by vibration sense, the 10g monofilament and the ability to feel a cold stimulus.

Discussion

This test battery appears to provide sound measurement properties in a group of diabetic patients with diverse amounts of sensory loss. This approach may be used in clinical practice to grade sensory loss reliably and quickly, with instruments that are easy to use.

Introduction

Sensory loss due to diabetic sensorimotor polyneuropathy (DSP) can be assessed using non-invasive and readily available screening instruments such as a tuning fork, static- and moving two-point discrimination (S2PD and M2PD) and monofilaments¹⁻⁷.

Each instrument tests different somatosensory functions that are progressively lost during diabetes, in the context of DSP⁸⁻¹¹. S2PD, for example, tests the slowly-adapting type I afferent A β large-fiber system in the skin, with the Merkel cell-neurite complex as peripheral receptors. M2PD tests both the quickly-adapting type I afferent A β fiber system, with Meissner corpuscles as mechanoreceptors, as well as the quickly-adapting type II afferent A β fiber system, with Pacinian corpuscles as somatosensory receptors. The latter system is also tested when performing vibratory testing^{12,13}. Static one-point discrimination (S1PD, e.g. monofilaments) tests the slowly-adapting type I A β system, with the Merkel cell-neurite complex as mechanoreceptors. To establish the exact temporal sequence in which these sensory functions are lost, thereby grading the degree of sensory loss, measurement properties of each instrument need to be clarified in relation to each other.

To investigate how well instruments combine to measure sensory loss, we applied parametric forms of Item Response Theory (IRT) to the tests used in the Rotterdam Diabetic Foot (RDF) study. IRT is a set of mathematical models (e.g. the Rasch model) that describe the relationship between an individual's 'ability' or 'trait' and how they respond to test items¹⁴⁻¹⁶. In short, IRT assumes that patients with a higher ability (less ill) should have a greater chance of obtaining a non-aberrant score on an item. Thus, the probability of a response to an item depends on the differences between the ability of the person and the difficulty of the item. With this information, relative patient disability can be rank ordered on an individual level by measuring patient ability (in this study foot sensation) and comparing this to the ability of each individual test item to differentiate between disability levels. Moreover, parametric IRT models can be used to explore individual ability range, identify fitting and misfitting items to the models and investigate Differential Item Functioning (DIF) between subgroups of patients, which is indicative of item bias.

The purpose of this study was to evaluate the psychometric properties of the 39-item Rotterdam Diabetic Foot Study Test Battery (RDF-39), to explore how test instruments and test locations on the foot compare, to create an outcome measure of foot sensation on a continuous scale and investigate in which areas of the trait (i.e., foot sensation) test information is rich or scarce.

Materials and methods

Study design and subjects

Between January 2014 and June 2015 a total of 416 subjects with type 1 and type 2 diabetes were assessed prospective for the sensory status of their feet at the outpatient Diabetes Clinic of the Franciscus Gasthuis, Rotterdam, the Netherlands as part of the RDF-study to investigate the deterioration of sensation in their feet over time. Baseline RDF-data is used for this cross-sectional analysis. Inclusion criteria were: patients diagnosed with diabetes mellitus (treated by oral blood glucose lowering drugs and/or insulin), age over 18 years, speaking Dutch or English, and no significant cognitive impairment. Exclusion criteria were: active radicular syndrome and neurological disease interfering with sensation of the feet, as assessed in the interview and screening questionnaire. Demographic data were obtained from the patient file. All subjects provided written informed consent. The institutional review board and the Medical Ethical Committee of Erasmus MC Medical University Center, Rotterdam, the Netherlands approved the study (MEC-2009-148).

Measurement instrument

To test the different somatosensory functions at multiple sites of the feet, a battery of tests was used. The RDF-39 includes both instruments and test sites to measure overall foot sensation and consists of 39 individual items that measure the unidimensional construct of foot sensation¹⁷. This scoring system contains dichotomized items on static- and moving two-point discrimination (S2PD and M2PD), static one point discrimination (S1PD), vibration sense, cold stimulus tests, Romberg's test, experienced numbness, prior diabetic foot ulcer and prior amputation. S2PD and M2PD were tested with a Disk-Criminator™ (US Neurologicals, LCC, Poulsbo, Washington, USA), with the threshold set at 8 mm (abnormal >8 mm), based on previously published normative values⁴. S1PD was tested with a 10 g Semmes-Weinstein monofilament (Baseline® Tactile™, USA), based on current international standards of medical care in diabetes^{2,3}. S2PD, M2PD and S1PD test sites were chosen in concordance with the nerve territories of the foot: I, plantar hallux (medial plantar nerve [tibial nerve]); II, medial heel (calcaneal nerve [tibial nerve]); III, first dorsal web (deep peroneal nerve); IV, lateral foot (sural nerve) and V, plantar fifth toe (lateral planter nerve [tibial nerve]), see Supplementary Figure A. M2PD was not tested at the fifth toe due to its small surface area. Vibration sense was tested with a Rydel-Seiffer tuning fork (Martin, Tuttlingen, Germany) at the medial malleolus and dorsal interphalangeal joint of the hallux and compared to normative threshold data⁶. Cold sensation was tested by applying a cold piece of metal to the arch of the foot. Information on numbness was derived from the Michigan Neuropathy Screening Instrument (MNSI), which was administered before the physical examination. Information on prior ulceration and/or amputation, as indicators of severe sensory loss, was derived from

the patient interview. Sensory test items consisted of both a sensory test and test location (e.g. S1PD at the lateral foot (S1PD IV), S2PD at the plantar fifth toe (S2PD V)). All 39 individual items were scored with 1 or 0. A score 1 indicated abnormality on a test item (i.e. could not feel the stimulus). The sum score per patient ranged from 0 to 39. Besides the 39 items on sensory loss, localized tibial nerve compression over the tarsal tunnel was assessed using Tinel's sign¹⁸. Both feet were examined.

Parametric Item Response Theory

We examined the psychometric properties of the RDF-39 using parametric IRT models. Supplementary Table A provides definitions of the terms used. A parametric IRT model compares the relative ability of each individual test item to differentiate between patient ability levels. Patients with a lower ability (more ill) have a greater chance of obtaining an aberrant test result, compared to patients with higher ability (less ill). This relationship is visualized by an Item Characteristic Curve (ICC), in which theta (θ) is a variable used to express a patient's underlying ability (or trait) level, measured along the x-axis. The probability of endorsing an item is given along the y-axis and measured from 0 to 1. The location of the item (in log-odd units, logits) on the latent trait (theta, in this study sensation at the feet) represents the estimated difficulty of the item, which is the mean of the threshold location. An example of this relationship is that a patient with a history of diabetic foot ulceration (more ill) is very unlikely to have a non-aberrant S2PD test result at the hallux (less ill). Higher values on theta represent greater levels of loss of foot sensation.

Fit statistics

Fit statistics estimate how well the data match model expectations. By using chi-square statistics, observed data were compared to expected model values. Three parametric IRT models were considered: the one-parameter logistic (standard and extended Rasch) and two-parameter logistic (2PL) models. The standard Rasch model estimates a location parameter for each item and assumes a common discrimination parameter (a) that is fixed at 1. The extended Rasch model, in contrast, estimates the common discrimination parameter (i.e., not fixed at 1). If the assumption of equal discrimination does not hold, the 2PL-model can be used to estimate both location and discrimination parameters for each item. The fitted models were compared with a likelihood ratio test. Once a model appropriate for the data has been selected, further tests of model and item fit are executed.

Item parameters

The most important parameters under IRT are item location, discrimination and trait score. In this study, binary RDF-39 items were considered, so item location (b) (item difficulty) represents the location on the latent trait (theta) where the probability of endorsing an item

is 50% (where the item functions best). Items with higher b values represent more severe sensory loss. Item discrimination (a) reflects the ability of an item to discriminate between patients at different levels of the trait and is defined as the slope of the ICC curve at the item location. A steeper curve is indicative of better discriminatory characteristics, with values closer to zero meaning low discrimination power.

The items of the test battery were analyzed by calculating the negative and positive responses per item. Cronbach's alpha assessed descriptively whether the items measured a common construct (foot sensation, hence foot sensation determines the item scores). To investigate which items fulfill the Rasch assumption (i.e., which items have a discrimination parameter equal to 1), we calculated the 95% confidence intervals for the discrimination parameters and checked for which items the value 1 was included in the interval. The probability of a positive response from the median patient was calculated, i.e. the patient with theta value equal to zero.

Item characteristic curves and item information curves

For all items, ICCs were drawn that describe the relationship between a patient's underlying trait and how that patient responds to a dichotomous item, together with corresponding item information curves. An item information curve can be drawn for each item to see in which range of theta values the specific item provides information (y-axis) and to reveal how precision varies across different levels of the underlying trait (x-axis). The amount of test information per item is defined as $I_i(\theta)$ at an ability level of theta. In IRT, the concept of information reflects how precisely an item or scale can measure the underlying ability (trait). Greater measurement precision is associated with greater information and is inversely related to the standard error of the estimate (theta). Thus, with more information a smaller standard error of the estimated theta score is obtained. Generally, more items provide more information. To quantify the available information from all RDF-39 items, we calculated the area under the total test information curve in specific intervals of theta.

Theta estimates

The trait score can be calculated after a patient has responded to the items of the battery, to estimate their position along the underlying trait (ability). Findings in healthy volunteers without known neuropathy have been published separately and are presented in this study for comparative purposes⁴.

Differential Item Functioning

To investigate whether the items function differently (so called item bias) in patients with respect to gender, type of diabetes, age, duration of diabetes, complaints and signs of

tibial nerve compression at the tarsal tunnel, we tested for DIF using the General Mantel-Haenszel method. This method examines whether the odds of a symptomatic response within each group on the measure is the same across subgroups, after controlling for ability. Assessing DIF is important for valid comparisons between subgroups of patients. Patients were arbitrarily categorized, aiming for a logical and/or approximately equal distribution between the constructed groups. Four age groups were identified by age (18-50 y, 51-60 y, 61-70 y and >70 y); four by duration of diabetes (0-10 y, 11-20 y, 21-30 y, >30 y); and three by the total score on the MNSI questionnaire as an indicator of severity of experienced complaints of DSP (0<4: minor, 4≤7: intermediate, >7 severe).

Statistics

Rasch and 2PL-model analyses were conducted using the R packages 'ltm' and 'difR'^{19,20}. Missing data were handled as part of the modelling process, but were rare (mean per item: 2.0%, range: 0 – 5.8%), resulting in minimal bias. Unidimensionality was assessed through principal components analysis of the residuals. Other statistical analysis was carried out using IBM's SPSS Statistics 22.0 (IBM Corp., New York, USA). Kolmogorov-Smirnov tests were used to assess normality. Differences in continuous variables with skewed distributions (theta) between two independent groups were assessed with Mann-Whitney U tests. P-values < 0.05 (two-sided) were considered statistically significant.

Results

General characteristics

416 RDF-study participants with diabetes were included. Fifty-two patients had a history of diabetic foot ulceration, for which 13 underwent lower extremity amputations. Further baseline characteristics are given in Table 1.

Fit statistics

Excellent internal consistency of the 39 items was observed (Cronbach's alpha >0.938). The likelihood ratio test between the estimated and fixed values of the common discrimination parameter across items was (χ^2 ($df = 1$) = 390.93, $p < .001$), suggesting that the extended Rasch model, which does not fix the discrimination parameter to 1, provides a better fit for the data. However, the likelihood ratio test between the extended Rasch model and the 2PL-model was (χ^2 ($df = 38$) = 267.47, $p < .001$), suggesting that the 2PL-model fitted the data better than the extended Rasch model. Hence, for the remainder of this analysis we continued with the 2PL-model.

Table 1 Demographic data.

Gender (M/F)	241/175
Age (median (y), IQR)	64.0 (15.4)
Height (median (cm), IQR)	173.0 (15.8)
Weight (median (kg), IQR)	87.8 (26.5)
BMI (median (kg/m²), IQR)	29.4 (7.6)
Duration of diabetes (median (y), IQR)	16.0 (16)
Type of diabetes (n (%))	
- Type 1	93 (22.4%)
- Type 2	323 (77.6%)
Drugs (n (%))	
- Lipid lowering drugs	267 (64.2%)
- Oral blood glucose lowering drugs	229 (55.0%)
- Insulin	351 (84.4%)
HbA1c (median (mmol/L), IQR)	60.0 (17.0)
MDRD (median ml/min/1.73 m, IQR)	77.9 (36.0)
Total cholesterol (median (mmol/L), IQR)	4.0 (1.3)
LDL-C (median (mmol/L), IQR)	1.8 (1.1)
HDL-C (median (mmol/L), IQR)	1.3 (0.5)
TG (median (median mmol/L), IQR)	1.6 (1.4)
Systolic blood pressure (median mmHg, IQR)	136.0 (23)
Diastolic blood pressure (median mmHg, IQR)	77.0 (13)
Diabetic Sensory Polyneuropathy (n (%))	
- MNSI score ≥ 4	148 (35.6%)
Retinopathy (n (%))	59 (14.2%)

Legend: M, male; F, female; IQR, inter-quartile range; BMI, Body Mass Index; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; MNSI, Michigan Neuropathy Screening Instrument.

Item parameters (2PL-model)

Estimated difficulty and discrimination parameters from the 2PL-model are given per item in Table 2. In the first column, items are ordered according to the difficulty parameter (from the item with the highest chance of a positive response to the item with the lowest probability of a positive response, as indicated in the second column). Thus, item difficulty ranged from S2PD and M2PD, ordered from those most likely representing milder disease severity to items on severe sensory loss. Specifically, items on S2PD, M2PD, vibration sense and S1PD were clustered, suggesting that for all test sites the loss of S2PD and M2PD precedes the loss of a protective sensation, as assessed with a 10g monofilament. Interestingly, complaints of numbness are reported when S2PD, M2PD, vibration sense and plantar S1PD items are already abnormal, suggesting that the patient is unaware of the loss of these sensory modalities.

Table 2

Items	Difficulty parameter value	P (x=1 z=0)	Discrimination parameter value	95% confidence interval	Differential Item Functioning due to
S2PD II left	-1.076	.893	1.97	1.46 – 2.34	Neuropathy complaints
S2PD II right	-1.040	.916	2.30	1.74 – 2.86	Type of diabetes
S2PD I left	-0.984	.867	2.57	1.93 – 3.21	
S2PD III left	-0.929	.837	1.76	1.35 – 2.17	
S2PD IV right	-0.915	.881	2.18	1.68 – 2.69	
S2PD V left	-0.901	.897	2.40	1.85 – 2.96	
S2PD V right	-0.877	.943	3.21	2.42 – 4.00	
S2PD I right	-0.862	.900	2.55	1.97 – 3.13	
S2PD IV left	-0.844	.894	2.53	1.96 – 3.10	
S2PD III right	-0.839	.859	2.16	1.66 – 2.65	
M2PD II left	-0.657	.760	1.76	1.35 – 2.16	Gender, Tinel
M2PD III left	-0.618	.757	1.84	1.42 – 2.26	Gender, type of diabetes, age
M2PD III right	-0.580	.758	1.97	1.53 – 2.40	Gender
M2PD II right	-0.416	.711	2.16	1.69 – 2.64	
M2PD IV left	-0.392	.665	1.75	1.36 – 2.15	Tinel
M2PD IV right	-0.368	.683	2.09	1.62 – 2.56	Duration of diabetes
M2PD I left	-0.279	.673	2.59	2.01 – 3.17	Gender, type of diabetes, age, neuropathy complaints
M2PD I right	-0.260	.648	2.34	1.81 – 2.87	
Vibration sense IP left‡	0.250	.429	1.14	0.86 – 1.42	Gender, age
Vibration sense IP right‡	0.250	.429	1.14	0.86 – 1.42	Gender, age
Vibration sense MM right‡	0.498	.384	0.95	0.70 – 1.20	Age
Vibration sense MM left‡	0.601	.346	1.06	0.79 – 1.33	Age
S1PD I left	0.781	.094	2.90	2.17 – 3.64	
S1PD I right	0.835	.117	2.43	1.83 – 3.02	Neuropathy complaints
S1PD V left	0.958	.079	2.57	1.93 – 3.21	Neuropathy complaints, Tinel
Numbness‡	0.960	.234	1.24	0.93 – 1.54	Type of diabetes, neuropathy complaints, Tinel
S1PD V right	0.966	.070	2.67	1.99 – 3.36	Age, neuropathy complaints
S1PD II right	1.012	.145	1.75	1.33 – 2.18	

Table 2 (continued)

Items	Difficulty parameter value	P ($x=1$ $z=0$)	Discrimination parameter value	95% confidence interval	Differential Item Functioning due to
S1PD II left	1.018	.144	1.75	1.33 – 2.17	
S1PD III left	1.371	.012	3.23	2.33 – 4.13	Type of diabetes, neuropathy complaints
S1PD III right	1.405	.022	2.71	1.98 – 3.43	
S1PD IV left	1.532	.022	2.46	1.80 – 3.13	
S1PD IV right	1.578	.026	2.29	1.68 – 2.90	Neuropathy complaints
Prior ulcer	1.696	.057	1.65	1.23 – 2.08	Neuropathy complaints
Cold stimulus left‡	1.812	.097	1.23	0.89 – 1.57	Gender
Cold stimulus right‡	1.902	.091	1.21	0.88 – 1.54	Duration of diabetes
Romberg test‡	2.157	.143	0.83	0.56 – 1.10	Gender, type of diabetes, age
Amputation left‡	3.159	.001	2.16	0.79 – 3.53	
Amputation right‡	3.322	.004	1.64	0.79 – 2.49	

Abbreviations: Roman capitals are indicatives of test locations: I, hallux; II, medial heel; III, first dorsal web; IV, lateral foot; V, fifth toe. S2PD, static two-point discrimination; M2PD, moving two-point discrimination; S1PD, static one-point discrimination (10 g Semmes-Weinstein monofilaments). IP, interphalangeal joint; MM, medial malleolus; DIF, differential item functioning; ‡, items included based on discrimination parameter value 1. For details on statistical information on Differential Item Functioning, see Supplementary Table B.

The third column gives the probability of a positive response from the median diabetic patient. Patients experiencing more sensory loss (i.e. having a higher sum score) have a higher chance of scoring positive on items with lower difficulty parameter values (e.g. patients with a history of diabetic foot ulceration or amputation). The fourth column displays the discrimination parameter of each item that quantifies how well the corresponding item can discriminate between patients, together with the 95% confidence interval of the discrimination parameter (fifth column). By checking which items were included based on value 1, we investigated which items fulfilled the Rasch assumption (equal discrimination across items). Ten items met this criterion (Table 2).

Item information curves and theta estimates

The total item information of all 39 items is given in a plot (Figure 1). The area under this curve was divided into specific intervals on theta, to see from which level item information is scarce. High logits indicate more severe sensory loss. From $-4 < \theta < -3$ the available

information was 0.5%, from $-3 < \theta < -2$ 3.1%, from $-2 < \theta < -1$ 15.9%, from $-1 < \theta < 0$ 26.5%, from $0 < \theta < 1$ 21.9%, from $1 < \theta < 2$ 19.4%, from $2 < \theta < 3$ 7.5% and from $3 < \theta < 4$ 3.5%. Most information is provided in the interval of $-2 < \theta < 2$. This may help to determine where information from tests in areas of the trait is scarce.

Figure 1 Total information Curve of all 39 items.

Legend: The total information curve of all items shows the total test information along the trait (with $Y = I_t(\theta)$ * the number of items in the test) and provides data on where test information is scarce.

The patient who scored non-aberrant on all items (equal to zero) had a theta estimate of -2.17, whereas the patient who scored all items aberrant had a theta estimate of 3.21. Most patients fell in the ability range of theta where much of items are situated, indicating that the risk of floor and ceiling effects is low (Figure 2).

Figure 3 shows the theta distribution of diabetic RDF-study participants compared to controls without known neuropathy.

Differential item functioning

Minimal DIF was found in the items of the RDF-39 (Table 2). Eight out of 39 items showed DIF due to gender. Six items showed DIF due to type of diabetes, eight due to age, two due to a longer duration of diabetes, nine due to increasing symptoms as indicated by the total MNSI score and four due to signs of tibial nerve compression at the tarsal tunnel (Supplementary Table B). By investigating residual principal component loadings, the RDF-39 was found to be unidimensional (proportion of variance of first principal component: 94.63%).

Figure 2 Kernel Density Estimation for Ability Estimates.

Legend: The distribution of patients along theta (in logits).

Figure 3 Comparison between diabetic subjects and controls.

Legend: Histograms of theta estimates in both groups show that median theta scores (inter quartile range) differed significantly between individuals without known neuropathy (-0.924 (0.94)) and subjects with diabetes (-0.088 (1.37)), $p < 0.0005$. Control subjects may experience some aberrancy in S2PD and M2PD items, but generally do have intact vibration sensation and protective sensation, compared to diabetic subjects.

Discussion

In this study, we investigated the measurement properties of the RDF-39 by fitting parametric IRT models to the data. Our analysis showed that it is possible to grade sensory loss of the feet more precisely with a set of simple to use instruments on specific test locations. This grading presumably allows for a more precise risk stratification regarding, for example, foot ulceration, amputation and falls.

The effects of hyperglycemia and cardiovascular risk factors produce morphological changes in the structures of the peripheral and central nervous system, resulting in dysfunction of the involved tissues²¹⁻²³. Connective tissue and vascular structures undergo changes as well, contributing to the common clinical entity of neuropathy.

Axonal loss occurs along the whole course of the peripheral nerve but is most severe distally. Both myelinated and unmyelinated fibers undergo changes^{24,9}. Since the nerve fibers innervating low-threshold mechanoreceptors (LTMRs) are terminal parts of sensory nerves, the skin of the foot is presumably the best site to assess the functional status of both LTMRs and its afferent fibers, which degenerate more marked distally. Due to neuropathy, a combined loss of sensory receptors and nerve fibers may occur, that both contribute to changed cutaneous threshold and innervation density¹¹. The results of the current study suggest that as a result of this process the ability to discriminate two static points is lost first, followed by the loss of moving two-point discrimination, vibration sense, S1PD as assessed with a 10 g monofilament and cold sensation.

A strength of the RDF-study is the broad range of patients with varying degrees of sensory loss, including patients with prior ulcerations and amputations. The RDF-39 can be used to consecutively assess patient sensory status and measure the incremental sensory loss. Moreover, relative risks of adverse events can also be estimated per consecutive item on the scale, so that patients with absent vibration thresholds have lower odds for ulceration than do patients with prior ulcers or amputations²⁵. The distribution of patients at the upper and lower ends of the trait makes floor and ceiling effects less likely, as the total information curve suggests.

In many clinical situations, the assumptions of the Rasch model do not hold due to its strict criteria, while more complex models, like 2PL, fit the data better by estimation of item parameters. Our study showed that 10 out of 39 RDF items fulfill the requirements for good fit of the Rasch-model and are indicators of more severe sensory disability in the feet, positioned on the right side of theta. In the 2PL-model we used, items investigating

the loss of S2PD, M2PD and 10 g monofilament testing were included. These items provide information on areas of the trait where Rasch model fit items were not present and therefore provide information on earlier stages of sensory loss. Several checks, as part of the 2PL-modelling process, found that no significant deviations between abilities and difficulties were present, resulting in a model fit of all 39 items.

Minimal DIF was found in the 39 items, which allows us to make valid comparisons between subgroups. However, DIF indicates that comparisons between subgroups should be made cautiously. Items showing DIF due to age were most profound in vibration sense items, which is explained by the prior dichotomization of these items using normative values for age⁶. The type of diabetes resulted in differences observed, among others, in abnormal Romberg's test and reported negative symptoms, mainly attributable to the higher prevalence of type 2 diabetes at an older age. Only two non-clinical significant differences were observed in items related to the duration of diabetes ('M2PD IV right' and 'Cold stimulus right'). Patients with Tinel's sign at the tarsal tunnel more frequently report signs of numbness at the feet, a more frequent loss of protective sensation at the left fifth toe and more abnormal scoring of M2PD at the left heel and M2PD at the left lateral foot. While it is ideal to only retain non-DIF-items, it is possible to account and model for items with DIF to preserve those items in a questionnaire or test battery. Further research on the predictive value of the included items on conditions such as falls and ulcerations will probably show that item reduction is possible, because items on S2PD and M2PD are clustered and highly correlated.

Nerve entrapment is frequently observed in patients with diabetes, in both the upper and lower extremity, and might be partially responsible for sensory disturbances, on top of the metabolic DSP²⁶⁻²⁸. In our cohort, 44.5% of patients have a Tinel's sign at either the left or right tarsal tunnel. However, nerve entrapment is difficult to diagnose with nerve conduction studies in patients with symptoms of DSP^{18,28,29}. The fact that RDF-39 sensory tests in patients with and without signs of nerve compression at the tarsal tunnel do not exhibit abundant DIF suggests that the loss of sensation due to DSP and concomitant compression neuropathy is virtually the same. Sensitivity to touch is an effective psychophysical measure of peripheral nerve function and impairment. The instruments used in the RDF-39 might be able to detect earlier nerve dysfunction and complement nerve conduction studies, which may be of importance in candidate selection for decompression of entrapped tibial nerves at the tarsal tunnel^{18,30,31}. Presumably, patients without axonal loss have a better chance of a beneficial surgical outcome^{18,28,32,33}. However, further clinimetric properties of the RDF-39, such as responsiveness after this type of surgery, should be the subject of future studies.

An abundance of tests have been proposed in the literature as early indicators of sensory loss^{9,34,35}. There is an increasing interest in the quantitative assessment of small fiber damage as an early diagnostic test and for monitoring progression of DSP³⁶. However, the exact temporal sequence of small and large fiber damage is not fully understood. IRT can help determine the place of tests in the progression of the disease and categorize the consecutive loss accordingly. In scale development, forms of IRT can also be used to develop new unidimensional outcome measures that are free from bias, because of the ideal item response pattern^{37,38}. Furthermore, item banks can be constructed so the measurement properties of existing instruments, like nerve conduction studies, can be investigated and compared^{14,16,37}.

This study aids clinicians in the wider interdisciplinary field of diabetic foot care in choosing an appropriate instrument to assess loss of sensation in the feet more precisely than by the use of a monofilament alone. By using these quick and simple instruments, a more reliable estimation can be made of the location of the patient in the natural history of loss of sensation. Limitations are that we developed the RDF-39 from a single-center population. Therefore, external validity of our findings should be investigated in other settings, such as general practices, academic hospitals and nursing homes. Furthermore, test-retest reliability should be investigated in a group of diabetic subjects with varying degrees of sensory loss, and responsiveness of the RDF-39 should be assessed during follow-up of the cohort.

This study establishes how current screening instruments compare and where to apply them on the feet, together with an outcome measure at the interval level¹⁶. Based on this information, a more precise risk stratification may be possible, with subsequent recommendations regarding interventions to prevent complications such as foot ulcers and neurogenic arthropathy³⁹.

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Supplementary material

Supplementary table A

Term	Description
Item Response Theory (IRT)	Item Response Theory is a set of mathematical models (e.g. the Rasch model) that describe the relationship between an individual's 'ability' or 'trait' and how they respond to test items.
Two-parameter logistic model (2PL)	A form of IRT that estimates both item discrimination (a) and item location (b) parameters for each item.
Differential Item Functioning (DIF)	Measurement bias that occurs when the odds of a symptomatic response within each group on the measure is not the same across subgroups, after controlling for ability (trait level).
Theta (θ)	<p>A variable used to express a patient underlying ability (or trait) level (in this study: ability to feel at the feet).</p> <p>Items also do have a position on theta, representing the relative 'difficulty' of the item, which is the mean of the threshold location.</p>
Trait level (or score)	A value on theta, based on the response on an individual item or set of items.
Item characteristic curve (ICC)	The behavior of individual items in a scale relative to the trait is described by an ICC, in which the probability of an individual's score on an item is determined by the trait level. The curve is continuously increasing as the trait level increases, or monotonic, when the item is dichotomous.
Item information curve	A curve that visualizes how well each ability level is being estimated. A total information curve visualizes this for all items involved in the test.
Item discrimination parameter (a)	The slope of the ICC at the location parameter b , on theta. Describes how well an item can differentiate between different trait levels.
Item location parameter (b)	Item difficulty: point on the trait level (theta) where the probability of endorsing an item is 50%.
Unidimensionality assumption	A requirement that all the items measure a single construct (in this study foot sensation).
Local independence assumption	A requirement that all items on the measure are statistically independent of responses to all other items on the measure, conditional upon the latent trait.

Supplementary table B

Differential Item Functioning due to												
Items	Gender	Type of diabetes		Age		Duration of diabetes		Neuropathy complaints		Tinel sign		
	MH stat.	Effect size	MH stat.	Effect size	MH stat.	Effect size	MH stat.	Effect size	MH stat.	Effect size	MH stat.	Effect size
S2PD II left	0.0022	-0.1759 ^A	0.0358	-0.1021 ^A	0.0355	0.0621 ^A	0.1270	-0.2942 ^A	5.8052*	2.3153^C	2.7038	-1.1844 ^B
S2PD II right	0.0647	-0.0733 ^A	0.4822	0.4005 ^A	0.0030	0.2218 ^A	0.0394	-0.1340 ^A	0.0341	0.1627 ^A	0.1626	0.3393 ^A
S2PD I left	1.5079	-0.9283 ^A	1.3740	0.8692 ^A	0.0407	0.2704 ^A	0.3454	0.3369 ^A	0.1293	0.1046 ^A	0.0356	0.1140 ^A
S2PD III left	0.1816	-0.2516 ^A	0.5911	-1.0106 ^B	2.8141	1.8102 ^C	0.0306	0.0183 ^A	0.1834	0.6587 ^A	0.6166	0.6878 ^A
S2PD IV right	1.9673	-0.8354 ^A	3.4936	-1.9291 ^C	3.1834	1.8680 ^C	0.0044	-0.0252 ^A	0.0956	0.5473 ^A	1.0473	-0.8736 ^A
S2PD V left	0.0677	0.0127 ^A	2.6359	1.6372 ^C	0.0983	-0.3130 ^A	0.5755	0.5869 ^A	1.4790	-0.4057 ^A	0.0136	0.1184 ^A
S2PD V right	0.1127	0.4251 ^A	0.0122	-0.1147 ^A	0.0977	0.1711 ^A	0.8964	-0.2564 ^A	1.6946	-0.0928 ^A	0.6867	0.5324 ^A
S2PD I right	0.0366	0.0338 ^A	0.0033	0.0100 ^A	1.0155	-0.6810 ^A	0.0210	0.0543 ^A	0.0089	0.4732 ^A	1.5238	1.2717 ^B
S2PD IV left	0.3794	-0.4976 ^A	1.0282	-1.1052 ^B	0.1257	0.6201 ^A	0.0050	0.0666 ^A	0.0020	0.3829 ^A	2.2725	-1.1647 ^B
S2PD III right	0.0475	0.1047 ^A	0.1162	-0.3198 ^A	1.4925	1.2279 ^B	0.2193	0.4844 ^A	0.0451	0.2941 ^A	0.0208	0.3897 ^A
M2PD II left	7.7340**	-1.8294^C	0.0252	-0.2794 ^A	1.1934	1.3436 ^B	3.0551	-0.9362 ^A	0.1005	0.1301 ^A	4.1625*	-1.1536^B
M2PD III left	7.5790**	-1.9384^C	4.7082*	-2.0853^C	7.9927**	2.7879^C	1.3078	1.0955 ^B	0.0045	0.3700 ^A	1.7460	-0.8495 ^A
M2PD III right	4.8220*	-1.4357^B	1.0451	-0.7311 ^A	1.5008	1.0994 ^B	0.1490	-0.0716 ^A	0.2180	0.1888 ^A	3.1447	-1.2576 ^B
M2PD II right	3.4987	-1.3230 ^B	0.2090	0.0777 ^A	0.2265	-0.0662 ^A	0.0692	0.0268 ^A	0.0588	0.1818 ^A	0.3413	-0.3862 ^A
M2PD IV left	2.3142	-1.0307 ^B	3.7332	-2.1162 ^C	1.7062	1.7400 ^C	2.4042	-0.8731 ^A	0.7673	0.9345 ^A	4.9029	-1.2540 ^B
M2PD IV right	2.4166	-0.9962 ^A	0.5954	-0.9807 ^A	0.0171	0.1386 ^A	4.7616*	-1.3135^B	2.1840	1.2103 ^B	2.3696	-0.9798 ^A
M2PD I left	4.3672*	-1.5715^C	11.7936***	2.7239^C	5.4043*	-1.9620^C	0.1544	-0.0065 ^A	9.8571**	-0.4057^C	2.4205	-0.6586 ^A
M2PD I right	0.3786	-0.2885 ^A	1.0245	0.5113 ^A	2.5826	-0.9839 ^A	0.5719	-0.6291 ^A	3.6514	-0.8986 ^A	0.3172	0.5554 ^A
Vibration IP left†	5.1613*	1.3385^B	0.0068	0.0478 ^A	8.2484**	-2.9753^C	0.3754	-0.4099 ^A	0.0028	0.0005 ^A	1.3950	-0.7671 ^A
Vibration IP right†	5.1613*	1.3385^B	0.0068	0.0478 ^A	8.2484**	-2.9753^C	0.3754	-0.4099 ^A	0.0028	0.0005 ^A	1.3950	-0.7671 ^A
Vibration MM right†	2.6708	0.9519 ^A	0.1773	0.2982 ^A	7.9371**	-2.9383^C	0.3507	-0.4522 ^A	1.6736	-0.8111 ^A	0.4969	0.4048 ^A
Vibration MM left†	3.4723	1.0701 ^B	1.0747	0.8036 ^A	11.1110***	-3.9039^C	0.2031	-0.2761 ^A	3.2788	-1.0465 ^B	0.0008	-0.0003 ^A
S1PD I left	0.1029	-0.3149 ^A	2.4233	1.8520 ^C	2.6638	-3.3845 ^C	0.5049	0.6082 ^A	1.0958	-0.8506 ^A	0.0080	-0.0415 ^A

Supplementary table B (continued)

Differential Item Functioning due to												
Items	Gender	Type of diabetes		Age		Duration of diabetes		Neuropathy complaints		Tinel sign		
		MH stat.	Effect size	MH stat.	Effect size	MH stat.	Effect size	MH stat.	Effect size	MH stat.	Effect size	
S1PD I right	1.7059	1.0395 ^B	0.6198	0.7811 ^A	2.2919	-2.9575 ^C	1.5859	0.8986 ^A	5.8911*	-1.9105^C	0.2934	0.3038 ^A
S1PD V left	0.8836	0.7257 ^A	0.2733	-0.5180 ^A	2.0536	-2.2819 ^C	0.1561	0.2077 ^A	4.6585*	-1.9787^C	6.2694*	2.1784^C
Numbness†	1.2785	0.7266 ^A	10.1499**	3.1837^C	1.0526	-1.1811 ^B	3.0666	1.1715 ^B	44.8044***	-5.6660^C	4.9470*	1.5341^C
S1PD V right	0.3121	0.4121 ^A	0.0017	-0.1872 ^A	4.0874*	-5.7978^C	1.3976	1.3513 ^B	9.9168**	-3.1900^C	1.2180	0.8435 ^A
S1PD II right	0.7342	-0.6637 ^A	7.9669**	3.7534^C	1.8364	-2.2167 ^C	0.1132	0.2632 ^A	0.7767	-0.5945 ^A	2.1270	-1.3217 ^B
S1PD II left	0.2329	-0.4209 ^A	2.2216	1.5819 ^C	2.6848	-2.4404 ^C	0.1130	-0.3625 ^A	0.1843	-0.2646 ^A	3.6697	-1.6070 ^C
S1PD III left	0.7078	1.0113 ^B	6.8299**	-	0.4947	-1.6595 ^C	0.0859	-0.4809 ^A	4.2861*	-2.7353^C	0.1794	0.5906 ^A
S1PD III right	0.0905	-0.3152 ^A	3.5056	2.6938 ^C	1.6756	-3.1007 ^C	0.9519	1.1228 ^B	3.7902	-2.0036 ^C	0.2577	-0.5956 ^A
S1PD IV left	0.3002	0.5499 ^A	1.1045	1.7120 ^C	0.3204	-0.9681 ^A	0.1984	0.4630 ^A	2.2278	-1.9057 ^C	0.3765	-0.6981 ^A
S1PD IV right	0.0005	-0.0218 ^A	2.4545	2.2396 ^C	0.2737	-0.8717 ^A	1.9954	1.6113 ^C	4.6777*	-2.7823^C	0.0000	0.0026 ^A
Prior ulcer	0.3271	0.5524 ^A	0.3676	0.6768 ^A	0.3800	-1.0603 ^B	0.0504	0.2328 ^A	10.1146**	-4.3678^C	2.1277	1.3046 ^B
Cold stimulus left†	5.3990*	1.8497^C	1.7661	1.3838 ^B	0.4246	0.7689 ^A	2.9826	-1.5624 ^C	1.9828	-1.1186 ^B	0.0011	0.1129 ^A
Cold stimulus right†	2.1124	1.2948 ^B	2.5539	1.8153 ^C	0.4206	0.6742 ^A	4.8095*	-2.3452^C	0.7923	-0.7016 ^A	0.1826	0.4876 ^A
Romberg test†	4.2072*	-1.4774^B	5.6151*	2.7116^C	4.4038*	-3.5326^C	0.6278	-0.6456 ^A	1.5404	-0.9650 ^A	2.5280	1.1487 ^B
Amputation left†	0.0437	0.6014 ^A	0.9521	-	0.2857	-	0.3328	1.3813 ^B	1.0000	-	2.9002	-
Amputation right†	0.9536	2.4490 ^C	1.5539	-	0.7285	-	0.0694	-0.5388 ^A	0.7492	-3.3747 ^C	0.4137	1.0876 ^B

Legend: MH stat., Mantel-Haenszel Chi-square statistics; *, p < .05; **, p < .01; ***, p < .001. For clarification, significant statistics/effect sizes are displayed in bold. -, infinite; A, negligible effect (≤1.0); B, moderate effect (≤1.5); C, large effect (>1.5) (ETS Delta Scale of item difficulty).

The log odds ratio δ_{MH} is commonly used for the DIF effect size of the item. Holland and Thayer (1985) proposed computing $\delta_{MH} = -2.35 \delta_{MH}$ and classifying the effect with the before mentioned ETS Delta Scale of item difficulty. An effect size value of -1, for example, means that the item is estimated to be more difficult for the focal group than the reference group by an average of one delta point, conditional on ability. The odds-ratio can be calculated with $-2.35 \ln q_{MH} = -1$ or $q_{MH} = 1.530$, meaning the odds for endorsing the item in the reference group are 53% higher than the odds in the focal group (a δ_{MH} of +1 means $q_{MH} = 1/1.530 = .653$).

Grading loss of sensation

Chapter VI

Item reduction of the 39-item Rotterdam Diabetic Foot Study Test Battery using decision tree modelling

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Abstract

Aims

Pedal sensory loss due to diabetes-related neuropathy can be graded by testing static- and moving two-point discrimination (S2PD, M2PD), static one-point discrimination (S1PD, e.g. 10 g monofilament) and vibration sense, and are included in the Rotterdam Diabetic Foot Study Test Battery. The aim of this study is to investigate if decision tree modeling is able to reduce the number of tests needed in estimating pedal sensation.

Methods

39-item RDF Study Test Battery (RDF-39) scores were collected from the prospective RDF-study and included baseline (n=416), first follow-up (n=364) and second follow-up (n=135) measurements, supplemented with cross-sectional control data from a previous study (n=196). Decision tree analysis was used to predict total RDF-39 scores using individual test item data. The tree was developed using baseline RDF Study data and validated in follow-up and control data. Spearman correlation coefficients assessed the reliability between the decision tree and original RDF-39.

Results

The tree reduced the number of items from 39 to 3 in estimating the RDF-39 sum score. M2PD (hallux), S2PD (first dorsal web, fifth toe), vibration sense (interphalangeal joint) and S1PD (first dorsal web, fifth toe) measurements proved to be predictive. The correlation coefficients to original scores were high (0.76 to 0.91).

Conclusions

The decision tree was successful at reducing the number RDF Test Battery items to only 3, with high correlation coefficients to the scores of the full test battery. The findings of this study aids medical decision-making by time-efficiently estimating pedal sensory status with fewer tests needed.

Introduction

Diabetes-related neuropathy is the most important risk factor for diabetic foot ulceration (DFU) and is associated with amputations and falls, indicating that neuropathy is a serious medical and public health problem¹⁻⁵. Since diabetes-related neuropathy is prevalent, the annual incidence of DFU is high, ranging from 1.0 to 4.1%, with prevalence rates from 4.0 to 10.0%⁶. Although poor outcomes in DFU disease have been reported, healing of the foot pathology is achieved in most patients, with major amputation (i.e. above ankle level) necessary in less than 5% of all patients⁷⁻⁹. Yet, minor amputations (i.e. below ankle level) occur more frequently, with rates ranging from 5 to 40%, conditional on the population studied^{8,9}. Neuropathy induced falls occur in up to 31 to 35% of older diabetic adults in a 5-year follow-up window, with a reported risk ratio of 1.64 (95% CI: 1.27-2.11) compared to healthy controls¹⁰⁻¹². The associated costs are high with both American and Dutch studies reporting mean costs per fall of US\$ 9463, nearing the in-hospital costs of an DFU episode (mean US\$ 10,827)^{13,14}.

Only few treatments exist targeting the underlying nerve damage of these three complications; therefore, prevention is the cornerstone of diabetes care¹⁵. Recently published consensus documents emphasize the importance of providing foot care, identification of the at-risk foot, educating patients, family and healthcare providers about foot care and treatment of pre-ulcerative signs¹⁶. There is an important role for screening on sensory loss, as this does not necessarily correlate with experienced symptoms^{17,18}. Recently, the 39-item Rotterdam Diabetic Foot Study Test Battery (RDF-39) was developed to create a valid and reliable tool for the objective assessment of sensory status of the feet^{17,18}. The RDF-39 is a 40-point scale, ranging from 0 (no aberrant tests) to 39 (all tests aberrant) and includes tests on static and moving two-point discrimination (S2PD, M2PD), vibration sense, 10 g monofilaments and cold stimuli that are applied on various sites of the feet, supplemented with information on experienced numbness, Romberg test, prior ulceration and lower extremity amputations. A low score on the RDF-39 represents little deafferentation (i.e. sensory loss), while a high score represents severely diminished pedal perception that increasingly relates to risk of DFU development and falls^{17,19,20}.

The RDF-39 is a dichotomized version of the full RDF-study Test Battery and takes about 10 minutes to complete¹⁸. Since shorter measures can improve efficiency, especially in a busy outpatient clinic, reduction in the number of tests might be of benefit. Decision tree analysis is one of few methods to reduce item length of questionnaires or test batteries²¹. A potential advantage of this analysis is its efficiency in data reduction^{22,23}. The aim of this study is to investigate if item reduction techniques are able to reduce the number of tests needed in

estimating the RDF-39 sum score, without compromising the psychometric performance of the full test battery.

Materials and Methods

Study design and subjects

The current study is part of the Rotterdam Diabetic Foot (RDF) Study, a prospective cohort study of unselected type 1 and type 2 diabetic patients followed at the outpatient Diabetes Clinic of the Franciscus Gasthuis & Vlietland hospital, Rotterdam, the Netherlands. The aim of the RDF-study is to investigate the natural history of neuropathy, including deterioration of sensation of the feet. The RDF-study participants were recruited from patients visiting the specialized outpatient diabetes clinic. RDF-study inclusion criteria were: diabetes mellitus (treated by oral blood glucose lowering drugs and/or insulin), age over 18 years, no significant cognitive impairment, speaking Dutch and signed informed consent. Exclusion criteria were: active radicular syndrome and neurological disease interfering with sensibility of the feet, as assessed at the interview and with the screening questionnaire. RDF-study design and methods are described in more detail in previous papers^{17,24}. Patients were subjected to an interview, to a physical examination and were requested to fill in a questionnaire, which was repeated in follow-up visits 1-1.5 years later. The Medical Research Ethics Committee of Erasmus University Medical Center, Rotterdam, the Netherlands approved the study (MEC-2009-148).

Healthy controls

A total of 196 healthy volunteers were tested with the same measurement instruments and the same protocol as the RDF-study population, as part of a separate study to obtain normative data for cutaneous threshold and spatial discrimination in the feet²⁵. Volunteers were recruited from hospital and university personnel and relatives and friends of patients visiting the outpatient clinic. Inclusion criteria included patients age $\geq$ 18 years, with no significant cognitive impairment, who spoke Dutch or English and provided signed informed consent. Exclusion criteria were a positive history of active radicular syndrome, a neurological disease that interfered with sensation in the feet, diabetes mellitus, thyroid malfunction, alcohol abuse, human immunodeficiency virus, or chemotherapy - all these were established at the interview using a screening questionnaire.

Data collection and tests

Lower limb sensory status information (full RDF-study Test Battery) was collected at RDF-study baseline and follow-up visit one and two. Datasets of RDF-study baseline

measurements, follow-up visits and cross-sectional data from a previous study on normative test data were combined for current analyses.

The 39-item Rotterdam Diabetic Foot Study Test Battery

The RDF-39 includes both instruments and test sites to measure overall foot sensation and consists of 39 individual items that measure the unidimensional construct of foot sensation^{17,26}. This scoring system contains dichotomized items on static- and moving 2-point discrimination (S2PD and M2PD), static 1-point discrimination (S1PD), vibration sense, cold stimulus tests, Romberg's test, experienced numbness, prior DFU and prior amputation (see Table A for a clinical scoring sheet). Both feet were examined. S2PD and M2PD were tested with a Disk-Criminator™ (US Neurologicals LLC, Poulsbo, WA, USA), with the threshold set at 8 mm (abnormal: > 8 mm), based on previously published normative values²⁵. S1PD was tested with a 10 g Semmes-Weinstein monofilament (Baseline® Tactile™, Minneapolis, MN, USA), based on current international standards of medical care in diabetes¹⁶. S2PD, M2PD, and S1PD test sites were chosen in concordance with the nerve territories of the foot: I, plantar hallux (medial plantar nerve [tibial nerve]); II, medial heel (calcaneal nerve [tibial nerve]); III, first dorsal web (deep peroneal nerve); IV, lateral foot (sural nerve) and V, plantar fifth toe (lateral planter nerve [tibial nerve]). Vibration sense was tested with a Rydel-Seiffer tuning fork (Martin, Tuttlingen, Germany) at the medial malleolus and dorsal interphalangeal joint of the hallux and compared with normative threshold data²⁷. Cold sensation was tested by applying a cold piece of metal to the arch of the foot. Information on numbness was derived from the Michigan Neuropathy Screening Instrument (MNSI), which was administered before the physical examination. Information on prior ulceration and/or amputation, as indicators of severe sensory loss, was derived from the patient interview. Sensory test items consisted of both a sensory test and test location (e.g., S1PD at the lateral foot [S1PD IV], S2PD at the plantar fifth toe [S2PD V]). All 39 individual items were scored with 1 or 0. A score 1 indicated abnormality on a test item (i.e., could not feel the stimulus). A patient's level of foot sensation is then estimated by taking the sum of the test item scores. The maximum score is 39 points (including both ankles and feet), with higher scores indicative of more severe sensory loss (Figure 1)^{17,28}.

Table 1 The 39-item Rotterdam Diabetic Foot Study Test Battery scoring sheet.

Left lower extremity	Test result (0 = non-aberrant, 1 = aberrant)	Right lower extremity	Test result (0 = non-aberrant, 1 = aberrant)
S2PD II left		S2PD II right	
S2PD I left		S2PD I right	
S2PD III left		S2PD III right	
S2PD V left		S2PD V right	
S2PD IV left		S2PD IV right	
M2PD II left		M2PD II right	
M2PD III left		M2PD III right	
M2PD IV left		M2PD IV right	
M2PD I left		M2PD I right	
Vibration sense IP left		Vibration sense IP right	
Vibration sense MM left		Vibration sense MM right	
S1PD I left		S1PD I right	
S1PD V left		S1PD V right	
Numbness	(derived from MNSI)		
S1PD II left		S1PD II right	
S1PD III left		S1PD III right	
S1PD IV left		S1PD IV right	
Prior ulcer	(scored for any extremity)		
Cold stimulus left		Cold stimulus right	
Romberg test			
Amputation left		Amputation right	
Sub-total		Sub-total	
Total RDF-39 score			

Legend: Roman capitals are indicatives of test locations: I, plantar hallux; II, medial heel; III, first dorsal web; IV, lateral foot; V, plantar fifth toe. S2PD, static two-point discrimination; M2PD, moving two-point discrimination; S1PD, static one-point discrimination (10 g Semmes-Weinstein monofilament). IP, interphalangeal joint; MM, medial malleolus; MNSI, Michigan Neuropathy Screening Instrument.

Statistical analysis

Missing item data were replaced by imputed data using the procedure of expectation maximization, using 25 iterations. Statistical analysis was carried out using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, New York, USA) and R package 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). We considered *p* values below 0.05 (two-sided) to be statistically significant.

Figure 1 Person-Item Map and Person Parameter Distribution of RDF-study participants.

Decision tree analysis

The decision tree was created using the 39 individual test item scores from RDF-study baseline (n=416 patients). Classification and Regression Tree (CART) analysis was used to create a decision tree with the RDF-39 sum score as dependent outcome and all individual test items (n=39) as independent variables. The CART method identifies the test item that provides the most equal split in patients' RDF-39 sum score. Within the consequent subgroups, CART will again identify the test item that provides an equal split, based on the RDF-39 sum score. The algorithm will stop when a maximum of 3 splits (i.e. the maximal number of questions that is allowed, called 'depth') has been executed or when no more than 20 patients remain in a subgroup^{29,30}. Mean and standard deviations of RDF-39 scores per subgroup are given.

Validation

Using a 25-fold bootstrap the decision tree was validated. Follow-up data of RDF-study participants and data of healthy controls was used to internally validate the decision tree version of the RDF-39 (DT-RDF-39) in predicting the original RDF-39 sum score from the different cross-sectional measurements (n=4).

Reliability and agreement

Bland-Altman plots were used to plot the differences between the original RDF-39 and predicted DT-RDF-39 sum scores. The plots describe whether the agreement between the predicted score and the original score is dependent on the original score and what the difference is, together with 95% confidence intervals³¹. These comparisons were made for all cross-sectional measurements (baseline, follow-up year one and year two and in the healthy controls data set). Additionally, Spearman correlations were calculated between the original RDF-39 and DT-RDF-39 sum scores.

Results

Included subjects

Between January 2014 and July 2017, a total of 1111 individual patient measurements were completed in both diabetic subjects and healthy controls. 416 diabetic patients were included in the RDF-study; of which the data of 364 patients at first follow-up and data of 135 patients at second follow-up, supplemented with data from 196 healthy controls, were available for current analyses.

Classification and regression tree

CART analyses reduced the number of test items from 39 to three to estimate the total RDF-39 sum score in 416 diabetic subjects, for which only a Disk-Criminator (S2PD and M2PD), Rydel-Seiffer tuning fork and 10 g monofilament are needed. Patients in the lowest range of the RDF-39 sum score (mean (SD): 5.4 points (3.7)) could be identified with only two tests: M2PD at the hallux (left) and S2PD at the first dorsal web (right). The full decision tree, together with predicted mean RDF-39 sum scores (SD) per subgroup, can be found in Figure 2.

The bootstrapped decision tree identified M2PD I left (plantar hallux of the left foot) as the most discriminating test (step 1). Patients that are unable to discriminate this moving 9 mm stimulus as two separate points on that particular site (M2PD I left), should be tested with the 10 g monofilament test at the left fifth toe (S1PD V left), which is then the most discriminating test (step 2). When this stimulus is felt, vibration sense at the left interphalangeal joint (vibration sense IP left) is tested. Finally, in patients that are insensate to the 10 g monofilament at the left fifth toe (S1PD V left), continuation of 10 g monofilament testing of the left first dorsal web (S1PD III left) is the most discriminative (step 3) in estimating overall pedal sensory status (i.e. the RDF-39 sum score).

Patients that are able to discriminate the M2PD stimulus at the left hallux (step 1), then need to be tested with S2PD at the first dorsal web (S2PD III right, step 2). When the patient is unable to discriminate this static 9 mm stimulus as two separate points, the same test is applied at the left fifth toe (S2PD V left), as final step (step 3) to predict the RDF-39 sum score.

Validity, reliability and agreement

Figure 3 shows the four Bland-Altman plots for which RDF-study baseline measurements (panel A, n=416), first follow-up (panel B, n=364), second follow-up (panel C, n=135) and cross-sectional data from healthy controls (panel D, n=196) was used. All plots show that the differences between the original scores and DT-RDF-39 sum scores were marginal, in which the 95% confidence interval is at most ± 10 points, with the difference between the two scores not being dependent of the RDF-39 sum score itself. Agreement is highest for high and low scores, while for scores in the mid-range area sometimes the confidence limit threshold is exceeded. Spearman correlations between original scores and DT-RDF-39 scores were high (baseline measurement data: 0.91, first follow-up: 0.88, second follow-up: 0.88 and in data from controls: 0.76).

Figure 2 Decision tree for predicting the RDF-39 sum score.

Legend: M2PD, moving two-point discrimination; S2PD, static two-point discrimination; S1PD, static one-point discrimination (10 g monofilament); I, plantar hallux; III, first dorsal web; V, plantar fifth toe; IP, interphalangeal joint of the hallux; yes, could feel the stimulus; no, could not feel the stimulus. Predicted mean (SD) values per subgroup are: 5.4 (3.7), 8.7 (4.3), 15.3 (4.1), 16.3 (3.7), 21.4 (3.8), 24.8 (4.1) and 33.2 (4.3), which are rounded in the figure itself.

Figure 3 Bland-Altman plots between RDF-39 and DT-RDF-39 sum scores.

Legend: Panel A, RDF-study baseline measurements; Panel B, first follow-up; Panel C, second follow-up; Panel D, cross-sectional data from healthy controls.

Discussion

We showed that particular sites of sensibility testing could precisely categorize patients with diabetes according to the overall sensory status of their feet. The results of our study suggest that a high accuracy can be achieved by using only three instruments on a maximum of three test sites, reducing patient burden and aiding efficient medical decision-making, at lower costs. The decision tree was found to be valid in predicting the RDF-39 sum score, after cross validation the tree in RDF-study follow-up data and data from controls.

Current guidelines suggest the use of monofilament and/or tuning fork to assess loss of sensation in diabetic subjects³². However, thresholds and cut-off values on how many test sites to be used for predicting, for example, first onset diabetic foot ulceration are often conjectured^{2,33-35}. A recent study using prospective RDF-study data showed that particular sites of monofilament and vibratory testing outperformed composite scores of tuning fork (up to four test sites) and 10 g monofilaments (up to ten test sites) in the prediction of ulcer-free survival²⁹. It is the combination of sensory test and test site that allows for staging of sensory loss, according to recently developed grading scales, with both test and test site having predictive properties regarding the degree of sensory loss observed^{17,26}. The consecutive steps of the presented decision tree are in line with these grading scales as these steps represent the modalities that are successively lost in the natural course of diabetes related neuropathy³⁶.

Previous literature has shown that peripheral nerve problems can be graded with an elaborate somatosensory examination³⁷⁻³⁹. In its earliest forms, neuropathy could be detected when the pressure threshold to discriminate two static points increases. An abnormal innervation density, reflected by a widening two-point discrimination, is the next step in this process, which is followed by both an abnormal innervation density and pressure threshold⁴⁰. Yet, only computer-assisted devices are capable of detecting both pressure threshold and innervation density. In a portion of RDF-study participants' computer-assisted measurements were carried out, in which the same sequence of abnormality of functions was observed. However, it was concluded that these computer-assisted measurements are not ideal for larger population studies since it is a time consuming and a difficult test for both patient and operator⁴¹.

The RDF Study Test Battery consists of instruments that are able to grade patient's peripheral nerve problems in a more practical manner, by measuring a subset of before mentioned somatosensory functions. Simple to use instruments examine innervation density by testing the function of large myelinated nerve fibers (slowly adapting fiber-receptor system (S2PD)

and the quickly adapting fiber-receptor system (M2PD)), vibration sense (tuning fork), the presence of protective sensation (10 g monofilament) and c-fiber function (cold stimulus)^{17,36}. According to the developed grading scale of pedal sensory loss (RDF-39), the functional loss seen in diabetes related neuropathy are clustered; meaning that for all test sites on the feet S2PD becomes aberrant before M2PD and vibration sense in the natural course of the disease³⁶. In the natural history of loss of sensory modalities, the loss of protective sensation differs per test site, with the first dorsal web and lateral foot becoming insensitive to the 10 g monofilament as last of all test locations. This is reflected in the presented decision tree of the current study, as being insensate to the 10 g monofilament at the first dorsal web is associated with a mean RDF-39 sum score of 33, the highest predicted mean sum score of the seven subgroups patients were allocated to. Since neuropathy is the most important factor in the cascade to diabetic foot ulceration, we suggest from this study that patients should be stratified according to degree of sensory loss⁴².

Strengths of our study are the large amount of individual measurements from an unselected group of patients with diabetes, together with data from a control population, in which the decision tree was also found to be valid^{17,36}. Moreover, the multi sensory modalities included in the RDF-39 are reflected in the decision tree, that was developed using modern statistical techniques. Decision tree analysis has been demonstrated useful in item reduction of questionnaires and test batteries and has been used in different fields of medicine^{29,43}. Several caveats relating to our study are important to highlight. Firstly, the RDF-39 was developed to grade patients' overall lower limb sensory status. The RDF-39 is a dichotomized version of the full RDF-study Test Battery, by which the exact thresholds at test locations are determined^{25,36}. Consequently, some information is lost when using the RDF-39 alone. For a more thorough assessment of, for example, tibial nerve function, the full test battery is needed (S1PD, S2PD and M2PD) at the respective test sites. In the present study, overall lower limb sensory status could be estimated due to the high agreement between the RDF-39 and DT-RDF-39. The DT-RDF-39 is especially of use in the annual foot examination diabetic patients are subjected to, since this approach is more a screening than full somatosensory assessment, but presumably more accurate compared to current strategies^{29,32,44}. Secondly, no test-retest, inter-rater and intra-rater studies of the RDF-39, as measures of reliability, have been executed yet. From current practice in hospital settings we observe that diabetic patients without neuropathy symptoms and intact spatial acuity have valid test results with low measurement error, suggesting high specificity (i.e. the true negative rate). This may especially be of importance in a screening setting, for example, at the general practitioner, by whom the majority of diabetic patients are annually evaluated regarding their risk of DFU development. However, if symptoms of neuropathy (e.g. hyperalgesia, allodynia) are present, we often observe that S2PD and M2PD measurements are more difficult to

conduct, resulting in aberrancy of test results. However, other RDF-39 items such as 10 g monofilament and vibratory testing are generally more tolerated and conducted with less measurement error. Future studies should assess the before mentioned measures of reliability, together with the use of parameters of measurement error, in different (clinical) settings and populations²¹. We expect that correlation coefficients may differ dependent of the sensory modality tested, with more unreliable results in the more difficult to conduct tests (i.e. S2PD, M2PD) that become aberrant first in the natural course of the disease^{17,36}.

In summary, this study may help the clinician by presenting a decision tree that quickly estimates patients' ability at the feet without the need of scoring all 39 items of the 39-item RDF Study Test Battery. The decision tree suggests that patients can be categorized in subcategories of sensory loss in only three steps, which might be helpful in a busy outpatient clinic, reducing costs and in improving patient's compliance.

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Predicting the RDF-39 sum score

Chapter VII

Validity of the Tinel sign and prevalence of tibial nerve entrapment at the tarsal tunnel in both diabetic and nondiabetic subjects: a cross-sectional study

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Abstract

Background

Nerve entrapments like carpal tunnel syndrome are more prevalent in patients with diabetes, especially in those with diabetic polyneuropathy. Our study aims were to investigate the validity of the Tinel sign in diagnosing tibial neuropathy and determine the prevalence of tibial nerve entrapment in both a diabetic and non-diabetic population.

Methods

240 non-neuropathic subjects with diabetes and 176 diabetic subjects with neuropathy participating in the prospective Rotterdam Diabetic Foot Study and 196 reference subjects without diabetes and without neuropathy complaints were evaluated. All subjects underwent sensory testing of the feet and complaints were assessed using the Michigan Neuropathy Screening Instrument. The Tinel sign was defined as discriminative valid to diagnose tibial nerve entrapment when the nerve related MNSI sub-score of neuropathic symptoms differed at least 5% between the Tinel-positive and Tinel-negative subjects. When valid, prevalence estimates of tibial nerve entrapment at the tarsal tunnel were calculated.

Results

Significantly more neuropathic symptoms ($p < .002$) and higher sensory thresholds ($p < .0005$) were observed in (compressed) tibial nerve innervated areas, indicating that a positive Tinel sign at the tarsal tunnel is a valid measure of tibial nerve pathology. The prevalence of tibial nerve entrapment in diabetic patients was 44.9% (CI: 40.1-49.7%) vs. 26.5% (CI: 20.3-32.7%) in healthy controls ($p < .0001$).

Conclusions

Tibial nerve entrapment is more prevalent in diabetic subjects than in controls. The significantly more frequently reported neuropathic complaints and concomitant sensory disturbances provide evidence for the role of super-imposed entrapment neuropathy in diabetes related neuropathy.

Introduction

Tarsal tunnel syndrome (TTS) is an entrapment neuropathy of the tibial nerve or its branches (calcaneal, medial and lateral plantar nerves) within its fibro-osseous tunnels beneath and distal to the flexor retinaculum of the ankle^{1,2}. These nerves are more prone to compression due to the rigid boundaries of these tunnels, with any swelling compressing the nerve resulting in dysfunction and consequent symptoms^{3,4}. Symptoms are mostly sensory in nature, and include pain, burning and numbness affecting the plantar side of the foot. TTS is often not recognized, as symptoms are similar to those associated with other neuropathies of the lower extremity, for example diabetic sensorimotor polyneuropathy (DSP). Consequently, TTS is probably underdiagnosed.

Its diagnosis in diabetic patients is important, since entrapment can worsen neuropathy complaints on top of DSP associated symptoms, while treatment options for the entrapment component of neuropathy are available and effective⁵⁻⁷. The validity of tests is important so that the prevalence estimates can be determined and the natural history in affected and nonaffected subjects can be characterized. As the prevalence has not been studied extensively yet, the interpretation of disease burden is challenging⁸.

The aim of this study was twofold. The first was to test the discriminative validity of the Tinel sign as a test to identify patients with nerve compression and exclude patients without entrapment neuropathy. The second, assuming the Tinel sign is a valid diagnostic test, was to determine the prevalence of tibial nerve entrapment at the tarsal tunnel and its associated clinical impairments (i.e., complaints, sensory loss), in both a large unselected diabetic and a healthy nondiabetic population.

Patients and methods

This cross-sectional study consisted of two groups: a study group of unselected type 1 and type 2 diabetic patients from the prospective Rotterdam Diabetic Foot Study (RDF-study), an ongoing cohort of 416 subjects followed at the outpatient Diabetes Clinic of the Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands; and a reference group of healthy non-diabetic controls. The aim of the RDF-study is to investigate the natural history of neuropathy and to study the diagnostic yield of tibial nerve entrapment². Study participants were recruited randomly from patients visiting the outpatient clinic, for regular monitoring of their diabetes. Inclusion criteria were: proven diabetes mellitus, age >17 years, no significant cognitive impairment, speaking Dutch and written informed consent. Exclusion criteria were: neurological disease interfering with sensibility of the feet. Between January 2014 to June 2015, RDF-patients were subjected to an interview on medical history and medication use and a physical examination, and were invited to fill in a questionnaire.

The second group of 196 nondiabetic controls were recruited from hospital and university personnel, relatives, and friends of patients⁹. Inclusion criteria were age older than 17 years and written informed consent. Exclusion criteria were known diabetes, known thyroid malfunction, neurological disease interfering with sensation of the feet, presence of neurologic symptoms at the leg or feet as reported in the interview and screening questionnaire, history of chemotherapy, ulcerations or autoimmune disease. Eligible controls were measured using the same test protocol between July and December 2015. All subjects provided informed consent. The Medical Research Ethics Committee approved the study (MEC-2009-148).

Physical examination

Both legs were examined. Cutaneous threshold (static one-point discrimination, S1PD) was tested on five locations per foot, with a set of Semmes-Weinstein monofilaments (SWMs) ranging from 0.008 to 300 g. Test sites were chosen in line with the nerve distribution of the foot (Figure 1)⁹. A Rydel-Seiffer tuning fork was used to test the vibration threshold on the medial malleolus and dorsal interphalangeal joint of the hallux. The Tinel sign was used to assess localized nerve compression, as recommended in international standards of care, and scored positive when subjects reported tingling and electrical sparks elicited when tapping the tibial nerve at the tarsal tunnel, radiating distally along the course of its branches^{2,10,11}. A negative sign was scored when subjects did not report these symptoms when tapping the nerve. The null hypothesis was that sensory thresholds in tibial nerve innervated areas (test site I, II and V) did not differ between Tinel-positive and Tinel-negative subjects.

Definitions

Neuropathic symptoms in diabetic subjects were assessed using the reliable and validated Michigan Neuropathy Screening Instrument (MNSI), with four or more abnormal questionnaire items indicative of DSP^{12,13}. To minimize diagnostic inconsistencies of tibial nerve compression prevalence, a definition was used based on the presence of the Tinel sign, which in turn reflects the pathophysiology of nerve entrapment. In the early stages of nerve entrapment, demyelination occurs which remains unnoticed by the patient, but changes the cutaneous threshold. A positive Tinel sign represents signaling from these mechanically sensitive axonal sprouts at the site of chronic nerve compression (i.e. tarsal tunnel) and is therefore used as clinical indicator¹⁴⁻¹⁷. We distinguished tibial nerve compression from TTS. Subjects with a positive Tinel who endorsed no symptoms on the MNSI questionnaire were considered asymptomatic, but with clinical signs of tibial nerve compression. The definition of TTS was based on a systematic review by the American Association of Neuromuscular and Electrodiagnostic Medicine, with TTS diagnosed when

both a positive Tinel sign and neuropathic complaints were present (in this study MNSI items 1, 2, 3, 5 or 6 describe neuropathic complaints, see Results¹⁰). There is no standardized way for eliciting the Tinel sign. For this reason, all five examiners were instructed according to a standardized test protocol by a single researcher to minimize intra- and inter-examiner variability. The Tinel sign was defined as discriminative valid when the nerve related MNSI sub-score of neuropathic symptoms differed at least 5% (0.3 points on the 0 to 6 subscale) between the Tinel-positive and Tinel-negative subjects, and when the non-nerve-related MNSI subscore of nonneuropathic symptoms differed less than 5% (0.5 points on the 0 to 10 subscale) between the Tinel-positive and Tinel-negative subjects¹⁸.

Statistical analysis

Differences between two independent proportions were assessed with Pearson chi-square tests. Differences in continuous variables with skewed distributions (S1PD, vibration sense) between two independent groups were assessed with Mann-Whitney *U* tests. Kolmogorov-Smirnov tests were used to assess normality. SWM values in grams were converted to a linear scale using a logarithmic transformation of S1PD measurements. A threshold of greater than 300 g was noted as 300 g. To improve readability, untransformed data are presented. Crude estimates of tibial nerve compression prevalence rates in the study and control groups were calculated as the total number of cases with a positive Tinel sign, divided by the total number of subjects in the respective groups. Confidence intervals were obtained as 95% Wald confidence intervals (CI) using binary logistic regression analysis. The prevalence rates of TTS (i.e. a positive Tinel sign and neuropathic symptoms at the plantar side of the foot) were estimated as numerator divided by the total number of subjects, with 95% Wald CIs obtained by binary logistic regression analysis. Age-adjusted and age- and gender-adjusted prevalence rates (with 95% Poisson CIs) for tibial nerve compression were estimated using direct standardization, with the age distribution and age and gender distribution of the study group as reference. Statistical analysis was carried out using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, New York, USA) and Microsoft Excel 15.14 (Microsoft Corp., Redmond, Washington, USA). P-values <.05 (two-sided) were considered statistically significant.

Results

Included subjects

For this study, 416 diabetic patients with a median age of 64.0 years (inter-quartile range (IQR), 55.0-70.3 years) and 196 healthy nondiabetic controls (50.5 years (36.5-65.7)) were included. The diabetic patients were a diverse group regarding age, diabetes duration, presence and degree of neuropathy complaints (Table 1 and 2).

Table 1 Demographic table.

	Diabetic patients		TTS		Healthy controls	
	Total population (n = 416)	Tinel positive* (n = 185)	Tinel positive* + sensory complaints (n = 112)	Total population (n = 196)	Tinel positive* (n = 52)	
Age (mean (y), SD)	61.8 (12.4)	61.6 (12.2)	61.9 (12.4)	51.1 (17.9)	53.0 (17.4)	
Diabetes, n (%)						
Type 1	93 (22.4)	51 (27.6)	26 (23.3)	-	-	
Type 2	323 (77.6)	134 (72.4)	86 (76.8)	-	-	
BMI (mean (kg/m²), SD)	30.4 (6.2)	30.5 (6.6)	31.3 (6.8)	24.5 (3.8)	24.1 (4.0)	
Duration of diabetes (mean (y), SD)	18.0 (12.0)	19.1 (13.0)	19.5 (13.6)	-	-	
Stratified by gender, 95% (CI)						
Male	241	48.5% (42.2-54.9)	31.3% (25.2-37.5)	66	24.2% (13.9-34.6)	
Female	175	39.9% (32.6-47.2)	27.8% (20.9-34.8)	130	27.7% (20.0-35.4)	
Age-standardized, 95% (CI)		1.6% (1.4-1.8)	-		0.6% (0.5-0.8)	
Stratified by age (y), n (%)						
< 40	25 (6.0)	11 (44.0)	7 (28.0)	62 (31.6)	15 (24.2)	
40 to 50	38 (9.1)	18 (47.4)	8 (21.1)	32 (16.3)	8 (25.0)	
50 to 60	92 (22.1)	43 (46.7)	30 (32.6)	33 (7.9)	8 (24.2)	
60 to 70	157 (37.7)	69 (43.9)	37 (23.6)	31 (15.8)	9 (29.0)	
70 to 80	87 (20.9)	38 (43.7)	27 (31.0)	31 (15.8)	12 (38.7)	
> 80	17 (4.1)	6 (35.3)	3 (17.6)	7 (3.6)	0 (0)	

Legend: *, at either the left or right tarsal tunnel; y, year; SD, standard deviation; CI, confidence interval; TTS, tarsal tunnel syndrome (Tinel positive + MNSI items 1, 2, 3, 5 or 6, see Table 2).

Table 2 Complaints of neuropathy in diabetic Tinel-negative and Tinel-positive subjects assessed with the Michigan Neuropathy Screening Instrument (MNSI).

Neuropathic symptoms	Diabetic subjects		P-value
	Tinel negative (n = 227)*	Tinel positive (n = 185)*	
1) Are your legs and/or feet numb?	47 (26.7)	62 (42.8)	
2) Do you ever have any burning pain in your legs and/or feet?	42 (23.9)	58 (39.7)	
3) Are your feet too sensitive to touch?	46 (26.1)	50 (34.2)	
5) Do you ever have any prickling feelings in your legs or feet?	57 (32.4)	61 (41.8)	
6) Does it hurt when the bedcovers touch your skin?	10 (5.7)	16 (11.0)	
Mean subscore (SD)	1.0 (1.1)	1.4 (1.5)	.005^a
Non-neuropathic symptoms			
4) Do you get muscle cramps in your legs and/or feet?	120 (68.2)	90 (61.2)	
7) When you get into the bath or shower, are you able to tell the hot water from the cold water? [†]	15 (8.6)	14 (9.5)	
8) Have you ever had an open sore on your foot?	31 (17.7)	32 (21.8)	
9) Has your doctor ever told you that you have diabetic neuropathy?	37 (21.1)	36 (24.7)	
10) Do you feel weak all over most of the time?	43 (24.6)	34 (23.3)	
11) Are your symptoms worse at night?	43 (24.6)	37 (25.5)	
12) Do your legs hurt when you walk?	49 (28.0)	46 (31.5)	
13) Are you able to sense your feet when you walk? [†]	31 (17.7)	21 (14.4)	
14) Is the skin on your feet so dry that it cracks open?	45 (25.7)	49 (33.6)	
15) Have you ever had an amputation?	8 (4.6)	6 (4.1)	
Mean subscore (SD)	2.4 (1.8)	2.7 (1.8)	.153^a

Legend: MNSI, Michigan Neuropathy Screening Instrument; *, at either the left or right tarsal tunnel; †, score reversed so that negative responses indicated an abnormality and counted as one point in the sum score; ^a, Independent samples T-Test; SD, standard deviation.

Validity of the Tinel sign

Neuropathic symptoms such as numbness, burning pain, allodynia and prickling were significantly more frequently observed in diabetic Tinel-positive subjects compared with Tinel-negative subjects ($p=.005$), with an observed clinically meaningful difference ($\geq 5\%$) of 0.53 point on the neuropathic subscale (Table 2). Moreover, no clinically meaningful difference ($<5\%$) in nonneuropathic symptoms was found between the groups (0.10 point), $p=.153$. Neuropathy complaints (MNSI ≥ 4) were reported by 42.3% (CI: 37.1-47.5%) of diabetic participants. The prevalence of a bilateral Tinel sign was observed significantly more in those with a MNSI score ≥ 4 compared to those with a MNSI score < 4 (34.5% (CI: 26.7-42.2%) vs. 23.4% (CI: 17.5-29.2%), $p=.024$). A similar trend was observed regarding a unilateral sign

(left or right) (50.3% (42.2-58.5) vs. 43.3% (36.4-50.1), $p=.194$). In patients with complaints of neuropathy (MNSI score ≥ 4) and a positive Tinel, significantly more neuropathic complaints were reported compared to Tinel-negative subjects and complaints of neuropathy (MNSI score ≥ 4 , $p=.018$).

In diabetic subjects, cutaneous thresholds in Tinel-positive subjects were significantly higher on test locations related to the tibial nerve (I, hallux; II, medial heel; V, fifth toe), compared to Tinel-negative subjects (left: $p<.0001$, right: $p=.046$, Figure 1, Table 3). A same trend was observed in controls; however, differences were small and did not reach statistical significance (left: $p=.349$, right: $p=.069$, Table 3). No significant differences between Tinel-positive and Tinel-negative subjects were found on test locations related to the deep peroneal nerve (III, first dorsal web) and sural nerve (IV, lateral foot), in either in diabetic subjects (left: $p=.075$, right: $p=.381$) or controls (left: $p=.201$, right: $p=.062$), which suggests that the presence of the Tinel sign at the tarsal tunnel only affects tibial nerve innervated locations. In diabetic patients, vibration sense did not differ between both groups. However, in controls vibration sense differed significantly between Tinel-positive and Tinel-negative subjects at the interphalangeal joints. No significant differences were observed between both groups at the medial malleoli. All sensory thresholds were significantly higher and more divergent in subjects with diabetes compared to controls ($p<.0005$). Therefore, it can be concluded that a positive Tinel sign at the tarsal tunnel is a valid measure of tibial nerve abnormality.

Figure 1 Test locations and associated nerve territories of the feet.

Legend: Test sites on the foot: I, plantar hallux (medial plantar nerve [tibial nerve]); II, medial heel (calcaneal nerve [tibial nerve]); III, first dorsal web (deep peroneal nerve); IV, lateral foot (sural nerve) and V, plantar fifth toe (lateral planter nerve [tibial nerve]).

Table 3 Sensory thresholds in clinical tibial nerve compression.

		Diabetic patients		P-value	Controls		P-value
Test site		Tinel negative	Tinel positive		Tinel negative	Tinel positive	
Left foot		Left tarsal tunnel (n=261)	Left tarsal tunnel (n=154)		Left tarsal tunnel (n=152)	Left tarsal tunnel (n=44)	
S1PD, median amount of force (g) (IQR)	Hallux	2.00 (5.40)	2.00 (25)	.002 ^a	1.18 (1.00)	1.40 (3.32)	.751 ^a
	Medial heel	2.00 (7.40)	4.00 (13.6)	.005 ^a	1.00 (1.40)	1.18 (2.76)	.189 ^a
	First dorsal web	0.60 (1.84)	1.00 (3.60)	.068 ^a	0.40 (0.44)	0.60 (0.84)	.410 ^a
	Lateral foot	1.00 (1.60)	1.40 (3.60)	.083 ^a	0.60 (0.60)	1.00 (0.80)	.119 ^a
	Fifth toe	1.40 (4.30)	2.00 (14.00)	.001 ^a	1.00 (0.31)	1.00 (1.56)	.381 ^a
Right foot		Right tarsal tunnel (n=267)	Right tarsal tunnel (n=145)		Right tarsal tunnel (n=153)	Right tarsal tunnel (n=42)	
Vibration sense, median (IQR)	Hallux	2.00 (7.40)	2.00 (12.56)	.059 ^a	1.00 (1.40)	1.40 (3.43)	.099 ^a
	Medial heel	2.00 (9.40)	2.00 (8.60)	.049 ^a	1.00 (1.40)	1.40 (1.98)	.286 ^a
	First dorsal web	0.60 (1.84)	1.00 (1.59)	.319 ^a	0.60 (0.80)	0.60 (0.68)	.278 ^a
	Lateral foot	1.00 (2.43)	1.00 (1.59)	.756 ^a	0.60 (1.00)	1.00 (0.80)	.055 ^a
	Fifth toe	1.40 (5.40)	2.00 (9.32)	.077 ^a	0.60 (1.00)	1.00 (1.00)	.019 ^a
Left foot		Left foot			Left foot		
Vibration sense, median (IQR)	Medial malleolus	5.0 (3.0)	4.0 (4.0)	.132 ^a	7.0 (2.0)	6.0 (2.0)	.058 ^a
	Interphalangeal joint hallux	4.0 (4.0)	4.0 (4.0)	.254 ^a	6.0 (2.0)	5.0 (4.0)	.029 ^a
	Right foot	Right foot			Right foot		
Vibration sense, median (IQR)	Medial malleolus	4.0 (4.0)	4.0 (4.0)	.251 ^a	7.0 (1.5)	6.0 (2.3)	.121 ^a
	Interphalangeal joint hallux	4.0 (5.0)	4.0 (3.8)	.897 ^a	7.0 (2.0)	5.5 (3.3)	.013 ^a

Legend: S1PD, static one-point discrimination (measured with Semmes-Weinstein monofilaments); IQR, interquartile range; ^a, Mann-Whitney U test; For nerve distributions at the foot, see also Figure 1: light blue, tibial nerve innervated test locations (hallux, medial heel, fifth toe); Yellow, deep peroneal nerve innervated test location (first dorsal web); Rose, sural nerve innervated test location (lateral foot).

Prevalence of tibial nerve compression

The crude prevalence rate of the Tinel sign in diabetic subjects was 37.1% (95%CI 32.5-41.8%) at the left ankle and 35.2% (CI: 30.6-39.8%) at the right, including bilaterally affected patients. In the control group, the crude prevalence rates were 22.4% (CI:16.6-28.3%) and 21.5% (CI:15.8-27.3%), respectively. A positive Tinel sign at either the left or right tarsal tunnel was found in 44.9% (CI:40.1-49.7%) of diabetic subjects, and in 26.5% (CI:20.3-32.7%) of controls ($p<.0001$). In 27.7% (CI:23.4-32.1%) of diabetic subjects, a bilateral Tinel sign was observed; in controls, this was 17.4% (CI:12.1-22.8%, $p=.006$). A unilateral Tinel sign was present at the left tarsal tunnel in only 13.1% (CI:9.3-17.0%) of diabetic subjects versus 10.4% (CI:7.0-13.9%) at the right. Compared with controls, these numbers were 5.6% (CI:2.0-9.1%, $p<.0001$) and 5.0% (CI:1.6-8.3%, $p=.001$), respectively. In diabetic subjects, crude prevalence rates (left or right) were slightly higher in men than in women, but this did not differ in the control group. Regarding the differences in age and sex between diabetic subjects and healthy controls, we also estimated the adjusted prevalence rates (Figure 2).

Figure 2 Adjusted prevalence estimates of the Tinel sign.

Legend: The Y-axis represents the ratio of the prevalence of the Tinel sign among diabetic subjects and the prevalence of the Tinel sign among healthy controls. For example, a bilateral Tinel sign is 1.68 times more prevalent in diabetic subjects compared to controls, when adjusted for sex.

Prevalence of tarsal tunnel syndrome

TTS (left or right) was present in 29.9% (CI:25.2-34.5%) of diabetic subjects (Table 1). A bilateral TTS was observed in 17.7% (CI:13.9-21.5%) of subjects. Unilateral TTS was present at the left foot in 8.5% (CI:5.1-11.9%) of subjects versus 8.3% (CI:4.9-11.7%) at the right foot.

Sex- and age-specific prevalence values of tibial nerve entrapment in affected and unaffected individuals are listed in Table 1.

Discussion

The findings of this study suggest that tibial nerve entrapment can be validly assessed using the Tinel sign. It is highly prevalent in both diabetic and nondiabetic subjects and is also accompanied by significant higher cutaneous thresholds and significant more neuropathic symptoms in diabetic patients. These observations are in line with the higher prevalence of entrapment neuropathies in patients with diabetes^{2,19-22}. This information may help in clinical practice to discriminate diabetic subjects with tibial nerve entrapment superimposed on top of their existing DSP. Its diagnosis is essential, as therapeutic interventions directed toward relief of entrapment may be effective regardless of the presence of diffuse DSP^{5,6,23}.

Two observations were evident in our populations. First, a positive Tinel sign at the tarsal tunnel was indicative of tibial nerve compression; and second, because not every patient with a positive Tinel sign reports symptoms, only patients with both a positive Tinel sign and complaints at the feet were labeled as having TTS. A previous study in 81 diabetic subjects on the presence of a positive Tinel sign at the tarsal tunnel showed slightly lower estimates regarding the prevalence of tibial nerve compression (unilateral, 19.8%; bilateral, 18.5%). However, in patients with neuropathy symptoms (MNSI >4), estimates were comparable with our findings⁸. A strong point of our study is the assessment of concomitant sensory loss, which was seen in both entities. This suggests that this process may occur without being noted by the patient. Tibial nerve entrapment in diabetes was highly prevalent across all age categories; in controls without known neuropathy, an increase in prevalence was noticed when age was older than 60 years. The latter may be explained by the high prevalence of chronic polyneuropathy in the general, elderly population, in which the cause remains unknown in 25 to 30% of cases^{24,25}. The prevalence of TTS did not have a clear relation with age, although the small number of subject numbers in the higher age categories might be the cause. The same ratio of type of diabetes was observed in both the tibial nerve compression and TTS groups compared with the total population, suggesting that type of diabetes is not a strong predictor for tibial neuropathy. However, risk factors for tibial nerve entrapment should be subject of future studies to further unravel which patients are prone to develop signs and symptoms^{24,26}.

To investigate if DSP could explain any differences between patients with and without a positive Tinel sign at the tarsal tunnel, or whether a positive Tinel sign is diagnostic of DSP, sensory thresholds in areas next to tibial nerve-innervated areas were compared.

As expected, the first dorsal web and lateral foot did not exhibit differences in sensory thresholds, which suggests that tibial nerve entrapment causes segmental nerve demyelination and axonal damage on top of DSP-associated axonopathy, with its own demyelination^{27,28}. For this reason, entrapment neuropathy is difficult to diagnose with electrophysiological studies in diabetic patients with complaints of DSP^{1,10,19}. Therefore, it has been concluded that the diagnosis is a clinical one made by history and physical examination, independent of electrophysiological findings^{1,2,10}. This study has validated the Tinel sign and has confirmed the observation of higher sensory thresholds^{10,29,30}.

Not every patient with diabetes will have signs of superimposed nerve compression³¹. However, the prevalence of nerve compression increases when patients report complaints associated with DSP²⁸. The fact that tibial nerve entrapment does occur usually unilaterally, suggests that superimposed nerve compressions do not follow the DSP definition of a distal, symmetrical neuropathy in the extremities. Therefore, it should be distinguished from DSP, with consequences regarding therapeutic interventions.

We screened participants with a protocol that included questionnaires, sensory testing and percussion for the Tinel sign, with the latter tested last, thereby minimizing possible bias effects. Tibial nerve-innervated areas (i.e., hallux, fifth toe and medial heel) had significant higher cutaneous thresholds in Tinel-positive diabetic subjects. However, in controls, these differences were less profound compared with differences in vibration threshold. Although measured at the dorsal interphalangeal joint of the hallux, vibration thresholds in controls differed significantly between Tinel-positive and Tinel-negative subjects. The waveform nature of vibratory testing suggests that the tibial nerve (i.e., medial plantar nerve, plantar side of the hallux) is also tested concomitantly. We propose from our data that diabetic subjects had more nerve damage compared to controls because of a combination of both DSP and tibial nerve entrapment. As vibration sense becomes aberrant before the cutaneous threshold elevates, only differences in vibration threshold were found significant in tibial nerve tested locations of controls^{16,31,32}.

Limitations of this study include the following: 1) multiple, self-reported symptoms to define TTS were used and 2) the control population was not evaluated for, for example, prediabetes, as possible cause of peripheral neuropathy³³. The most informative symptoms for neuropathy are numb and tingling feet, which were exclusion criteria for study participation (control population), but we cannot rule out that some misclassification occurred because controls were not subjected to further risk factor analysis and/or full neurological examination⁹. However, we tried to minimize this possible bias by using an extensive questionnaire on relevant medical history, a validated questionnaire on neuropathy (MNSI) and a somatosensory examination of both extremities.

Our decision to report the prevalence rates of both tibial nerve compression and TTS acknowledges the diagnostic limitations of self-reported symptoms and may help the external validation of these findings. External validity of our findings is likely, regarding the use of a large unselected study population with patients of varying age, disease duration, and complaints, representative of patients seen in the out-patient clinic of a large teaching-hospital. Additional epidemiologic investigations of other (concomitant) nerve entrapments (e.g. common peroneal nerve and proximal tibial nerve) in the diabetes population are needed to better understand the significance of concurrent syndromes on neuropathy complaints^{2,34}. The high prevalence rate observed in this study lends additional evidence for the clinical importance of tibial nerve entrapment and for the need for a better identification of patient groups at risk. There is still a significant difference in neuropathy between diabetic patients with and without a Tinel sign, indicating that the double-crush neuropathy in diabetic patients is more severe, resulting in more complaints and sensory deficits²⁰. The latter is important, regarding possible differences in the natural history of lower extremity complications like diabetic foot ulcers and consequent amputations. However, this should be subject of further study.

The treatment of choice in tarsal tunnel syndrome remains surgical, with potentially substantial health benefits and reported low risks of complications^{1,6,35}. To unravel the (relative) contribution of super-imposed entrapment on neuropathy complaints, the release of the compression component would be the ultimate experiment^{36,37}. It is important to note that not every diabetic patient with signs of tarsal tunnel syndrome is an appropriate candidate for surgery. Important effect modifiers include the preoperative degree of sensory loss, indicative of the extent of nerve damage and its consequent regenerative capabilities⁷.

This study establishes a baseline for tibial nerve entrapment prevalence in a large and broad diabetic population, including controls. Although further study is needed to elicit the epidemiology of entrapment neuropathy at the ankle, this study provides insight in the magnitude of the problem and may form a basis for the development of clinical screening criteria.

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Prediction of adverse events

PART III

Chapter VIII

Predicting ulcer-free survival using the discriminative value of screening test locations

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Abstract

Aims

Current guidelines recommend screening the feet of diabetic subjects with a 10 g monofilament or tuning fork. We investigated which tests and locations on the feet have the best predictive value regarding one-year ulcer-free survival, in diabetic subjects participating in the prospective Rotterdam Diabetic Foot Study.

Methods

Decision tree analysis was used to predict ulcer free survival, based on responses from individual test locations (monofilaments on 10 sites, vibration sense was tested on both halluces and medial malleoli). Separate trees for patients with and without a history of diabetic foot ulcer (DFU) were developed.

Results

416 subjects (mean (SD) age, 61.8 years (12.4); range, 21.6-90.2) were measured, of which 24 developed new DFUs. Three tests exhibited discriminative and predictive properties: testing vibration sense on the medial malleolus and monofilament testing on heel and hallux. The decision tree to predict ulcer-free survival in patients with a history of DFU yielded a sensitivity of 87.0%, which was 99.6% for the tree of patients without a history of DFU.

Conclusion

The findings of this study aids medical decision making by discriminating between high and low-risk patients of developing DFU using selective testing on sites with predictive properties.

Introduction

Diabetes-related foot disease is an increasing health problem leading to considerable morbidity and cost^{1,2}. Altered glucose metabolism and cardiovascular risk factors such as raised triglyceride levels, body-mass index, smoking and hypertension lie at root of diabetes-related neuropathy, which comes in different forms, but all have a role in the development of diabetic foot ulcers (DFUs)³. Autonomic neuropathy, for example, results in decreased sweating and thereby dry skin, whereas motor neuropathy results in altered muscle innervation leading to foot deformities and consequent biomechanical abnormalities. Sensory neuropathy, however, is regarded as the most important factor leading to DFUs, especially in first-onset ulcers, since it results in loss of sensation⁴.

Current guidelines recommend screening the feet of diabetic patients with a 10 g monofilament or tuning fork^{5,6}. For patients without a history of ulceration or amputation, the odds of diabetes-related foot ulceration are 3.2 (95% CI 2.7-3.8) when insensate to this monofilament, the odds for new ulcers in patients with a prior DFU are 13.7 (95% CI 6.6-29.6)⁷. Loss of vibration sense is associated with a lower risk of DFU compared to losing protective sensation (tested with a 10 g monofilament), as it indicates an earlier phase of sensory loss seen in diabetic sensorimotor polyneuropathy (DSP)^{7,8}. However, the sequence in which the screening with these instruments should be performed, or the test location where they should be tested on the feet to achieve greatest discriminative power, has not been established⁹.

We investigated which tests and locations on the feet have the best predictive value regarding one-year ulcer-free survival, in diabetic subjects participating in the Rotterdam Diabetic Foot Study (RDF-study)^{8,10}. Especially in a screening setting sensitivity of tests are of value, because the beforementioned factors (e.g. foot deformities) also contribute to the development of DFU. We distinguished between people with and without a history of DFU, regarding the differences in relative risks and screening programs. The aim of this study is to aid the clinician in patients' risk stratification and guide individualized medical decision making.

Materials and Methods

Between January 2014 and June 2015, a total of 416 subjects with type 1 and type 2 diabetes were assessed prospectively for the sensory status of their feet at the outpatient Diabetes Clinic of Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands. The RDF-study

investigates the natural history of neuropathy, including deterioration of sensation of the feet. Study participants were recruited randomly from patients visiting the outpatient clinic, for regular monitoring of their diabetes. Patients with and without neuropathy symptoms were evaluated. Inclusion criteria were: proven diabetes mellitus, age >17 years, no significant cognitive impairment, speaking Dutch and written informed consent. Exclusion criteria were: active neurological disease interfering with sensibility of the feet (e.g. radicular syndrome). Demographic information was obtained from the patient records. No reimbursement was given. Symptoms of neuropathy were assessed using the Michigan Neuropathy Screening Instrument¹¹. Data on incident diabetic foot ulceration was assessed at one-year follow-up and included ulcer characteristics. RDF-study design and methods are more elaborately communicated in previous papers^{10,12}. All subjects provided informed consent. The Medical Ethics Research Committee of Erasmus MC Medical University Center, Rotterdam, the Netherlands approved the study (MEC-2009-148).

Physical examination

Protective sensation was measured with monofilaments (Baseline® Tactile™, USA) on five sites per foot: hallux, medial heel, first dorsal web, lateral foot and fifth toe, according to international standards of care⁶. The test sites were chosen in line with the nerve distribution of the foot: I, hallux (medial plantar nerve [tibial nerve]); II, medial heel (calcaneal nerve [tibial nerve]); III, first dorsal web (deep peroneal nerve); IV, lateral foot (sural nerve) and V, fifth toe (lateral planter nerve [tibial nerve])¹². Vibration sense (Rydel-Seiffer tuning fork (Martin, Tuttlingen, Germany)) was tested on both halluces and medial malleoli and compared to normative values¹²⁻¹⁴. Scores were dichotomized per test location (i.e. 1, not feeling the stimulus (aberrant) or 0, feeling the stimulus (nonaberrant)). Composite scores per screening instrument (i.e. monofilament and tuning fork) were calculated as the sum of the test results from the respective test sites. Lower extremity artery pulsations were palpated on both feet.

Foot appearance

Foot appearance was scored using a standardized scoring form on foot morphology, subdivided in domains, encompassing the broad range of factors associated with developing foot ulcers. The domains used were skin morphology, nail morphology, foot morphology and vascular status. The appropriate definitions of the symptoms were given. Amputation or signs of an active or previous ulcer were scored as well. Assessors were asked to make a verdict on the risk of developing an ulcer in the near future, based on the domain scores. High risk was defined as a bad foot condition with the necessity of intervention or referral to a specialist to prevent further progressing into an ulcer. Low risk was defined as no urgent interventions needed. For the current analysis, only the proportion of high-risk limbs is reported.

Statistical analysis

Differences between two independent proportions were assessed with Pearson Chi-square tests. Differences in continuous variables with skewed distributions (age, height, weight, body mass index, duration of diabetes, blood pressure) between two independent groups were assessed with Mann-Whitney U tests. Kolmogorov-Smirnov tests were used to assess normality. The incidence rate of new DFUs were estimated as the numerator divided by the total number of subjects, with 95% Wald confidence intervals obtained by binary logistic regression analysis.

Classification And Regression Tree technique

Decision tree analysis, using the Classification And Regression Tree (CART) technique, was used to predict one-year ulcer-free survival, based on responses from individual test locations. The CART method we used is based on statistically optimal splitting (i.e. partitioning) of the patients in pairs of subgroups^{15,16}. Splits are based on cut-off levels of the test items, which produce maximal separation among the two subgroups. By doing so, a minimal variety within the respective subgroups is achieved regarding the outcome. The item with the largest discriminative ability is situated at the top of the tree, followed by the item causing the next largest separation. The splitting process continues until all subgroups reach a minimum size or when no improvement in discriminative ability can be achieved. Since the best predictor of future ulceration is a history of DFU, patients with a history of DFU and patients without a history of DFU were considered being different at relative risk of new DFU development^{2,7}. Therefore, CART subgroup analyses were done for these two subgroups. K-fold cross-validation was used, using 10 folds, to validate both decision tree models.

Sensitivity, specificity, negative and positive predictive values and likelihood ratios are reported for both trees¹⁷. To assess accuracy of the decision trees compared to currently used instruments, composite scores of monofilaments tests (up to ten locations) and tuning fork tests (up to four locations) were compared with the decision trees, using Receiver Operator (ROC) curves^{18,19}. All statistical analysis was carried out using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, New York, USA) and R package 'rpart'¹⁶. P-values < .05 (two-sided) were considered statistically significant.

Results

General characteristics

416 diabetic participants (mean (SD) age, 61.8 years (12.4); range, 21.6-90.2) were studied. Two hundred forty-one men and 175 women were included (Type 1: 22.4%, type 2: 77.6%).

Patients with a history of DFU were more frequently male, were taller, had a higher systolic blood pressure, reported more complaints of DSP, had a lower proportion of palpable lower extremity arteries and had more often high-risk limbs, including previous amputations, as assessed with the physical examination, compared to patients without a history of DFU (Table 1).

Table 1 Baseline characteristics.

	No history of DFU (n=364)	History of DFU (n=52)	P-value
Gender (M/F)	204/160	37/15	.039 [#]
Age (median (y), IQR)	63.5 (54.1-69.6)	65.9 (60.6-72.9)	.058 [*]
Ethnicity (n (%))			
- Caucasian	298 (81.9)	43 (82.7)	
- Indo-Surinamese	34 (3.0)	1 (1.9)	
- African	11 (3.0)	3 (5.8)	
- Asian	7 (1.9)	-	
- Other	14 (3.8)	5 (9.6)	
Height (median (m), IQR)	172.9 (165.0-180.0)	180.0 (170.3-185.0)	.001 [*]
Weight (median (kg), IQR)	87.0 (77.0-102.6)	90.1 (80.0-115.8)	.098 [*]
BMI (median (kg/m²), IQR)	29.3 (26.3-33.6)	30.4 (25.2-34.6)	.789 [*]
Duration of diabetes (median (y), IQR)	16.0 (9.0-25.0)	17.0 (10.3-27.3)	.463 [*]
Type of diabetes (n (%))			.100 [#]
- Type 1	86 (23.6)	7 (13.5)	
- Type 2	278 (76.4)	45 (86.5)	
Mean Arterial Pressure (brachial)(median (mmHg), IQR)	96.7 (88.7-103.6)	98.0 (89.4-106.7)	.234 [*]
Systolic blood pressure	135.0 (125.0-147.0)	140.0 (130.3-156.8)	.022 [*]
Diabetic Sensory Polyneuropathy (n (%))			
- MNSI score >3	107 (35.2)	41 (89.1)	< .0005 [#]
Number of previous DFUs			
- One	-	39	
- Two	-	11	
- Three	-	1	
- Four	-	1	
Previous amputations (n (%))			
- Left extremity	-	6 (11.5)	
- Right extremity	-	8 (15.4)	
Palpable lower extremity arteries (%)			
- Left posterior tibial artery	73.5	34.8	.001 [#]
- Right posterior tibial artery	72.7	54.2	.096 [#]
- Left dorsalis pedis artery	82.4	47.8	.001 [#]
- Right dorsalis pedis artery	82.1	54.2	.007 [#]
Verdict by physical examination of limb (e.g. foot deformities, calluses) (%)			
- High risk left limb	15.2	96.0	< .0005 [#]
- High risk right limb	18.8	100.0	< .0005 [#]

Legend: M, male; F, female; IQR, inter-quartile range; *, Mann-Whitney U test, #, Pearson Chi-Square test; BMI, Body Mass Index; MNSI, Michigan Neuropathy Screening Instrument.

At one-year follow-up, 24 new DFUs had developed, in 5.8% (95%CI: 3.5 to 8.0) of participants. Six new DFUs developed in 1.6% (95%CI: 0.3 to 3.0) of participants without a history and eighteen ulcers (34.6% (95%CI: 21.7 to 47.5)) in patients with a history of DFU. Since a large proportion of patients with previous DFUs developed new ulcers, factors associated with new DFU development were comparable to the factors of patients with a history of DFU, which includes previous amputations, see Table 2.

Table 2 Characteristics of patients with and without diabetic foot disease during follow-up.

	No DFU during follow-up (n=392)	DFU during follow-up (n=24)	P-value
Gender (M/F)	221/171	20/4	.039 [#]
Age (median (y), IQR)	63.3 (54.9-69.9)	67.1 (58.8-75.4)	.058 [*]
Ethnicity (n (%))			
- Caucasian	320 (81.6)	21 (87.5)	
- Indo-Surinamese	35 (8.9)	-	
- African	13 (3.3)	1 (4.2)	
- Asian	7 (1.8)	-	
- Other	17 (4.3)	2 (8.3)	
Height (median (m), IQR)	172.0 (165.0-181.0)	177.5 (173.0-182.5)	.001 [*]
Weight (median (kg), IQR)	88.0 (77.0-103.5)	86.0 (80.0-103.5)	.098 [*]
BMI (median (kg/m²), IQR)	29.5 (26.2-33.8)	27.9 (24.8-30.8)	.789 [*]
Duration of diabetes (median (y), IQR)	16.0 (9.0-25.0)	18.5 (11.5-29.0)	.463 [*]
Type of diabetes (n (%))			.100 [#]
- Type 1	88 (22.4)	5 (20.8)	
- Type 2	304 (77.6)	19 (79.2)	
Mean Arterial Pressure (brachial) (median (mmHg), IQR)	96.7 (89.4-104.3)	93.0 (82.7-98.8)	.031 [*]
Systolic blood pressure	136 (126.0-148.0)	132.0 (121.8-147.0)	.448 [*]
Diabetic Sensory Polyneuropathy (n (%))			
- MNSI score >3	128 (39.0)	20 (90.9)	< .0005 [#]
Previous DFUs (n (%))	34 (8.7)	18 (75.0)	< .0005 [#]
Previous amputations (n (%))			
- Left extremity	4 (1.0)	2 (8.3)	< .0005 [#]
- Right extremity	5 (1.0)	3 (12.5)	< .0005 [#]
Palpable lower extremity arteries (%)			
- Left posterior tibial artery	68.4	33.3	.019 [#]
- Right posterior tibial artery	73.1	33.3	.006 [#]
- Left dorsalis pedis artery	77.2	50.0	.046 [#]
- Right dorsalis pedis artery	78.5	50.0	.034 [#]
Verdict by physical examination of limb (e.g. foot deformities, calluses) (%)			
- High risk left limb	29.1	91.7	< .0005 [#]
- High risk right limb	33.8	91.7	< .0005 [#]

Legend: M, male; F, female; IQR, inter-quartile range; *, Mann-Whitney U test, #, Pearson Chi-Square test; BMI, Body Mass Index; MNSI, Michigan Neuropathy Screening Instrument.

Classification and regression trees

Of the 14 sensory test locations, four exhibited discriminative and predictive properties (Figure 1).

Figure 1 Decision trees for predicting one-year ulcer-free survival in patients with and without a prior ulcer.

Legend: MM, medial malleolus; MF, monofilament; NPV, negative predictive value (in red); PPV, positive predictive value (in green); n, number of patients per subgroup; number of patients with ulcers between brackets.

Decision tree for patients with a history of DFU

After cross-validating the decision tree model, three tests were discriminative and predictive in one-year ulcer-free survival in patients with a history of DFU (right tree, Figure 1). The first discriminative test is testing vibration sense at the medial malleolus. When this vibration sense is present, the likelihood of ulcer-free survival is 94.4% (positive predictive value (PPV)). When vibration sense is lost, the decision tree suggests testing protective sensation with a 10 g monofilament at the heel. When protective sensation is lost there, the negative predictive value for developing a DFU is 38.1%. When the patient feels the 10 g monofilament at the heel, it is suggested to continue testing with the monofilament at the hallux. When protective sensation is intact at this location, the PPV for ulcer-free survival is 60.0%. When aberrant, the negative predictive value to develop a DFU at one-year follow-up is 87.5%. When the decision tree for patients with a history of DFU was considered one diagnostic

tool to predict one-year ulcer-free survival, a sensitivity of 87.0%, specificity of 51.7%, a PPV of 58.8% and NPV of 83.3% was observed. The effect on posttest probability of disease was moderate (negative likelihood ratio: 0.25). The ROC curve comparing the composite scores of tuning fork and monofilaments to the prediction made by the decision tree showed that in patients with a history of DFU, a greater accuracy (area under the curve) of 71.1% was achieved by the decision tree, compared to tuning fork (69.7%) and monofilaments (52.8%), see Figure 2.

Figure 2 Receiver Operating Characteristic (ROC) curves of the decision tree, composite 10 g monofilament score (up to 10 test sites) and composite vibration sense score (up to 4 test sites) to predict ulcer-free survival at one-year follow-up in patients with a history of DFU.

Decision tree for patients without a history of DFU

After cross-validating the decision tree model, one test predicted one-year ulcer-free survival in the group of patients without a history of DFU best (left tree, Figure 1). When patients have an intact vibration sense at the medial malleolus, the likelihood of ulcer-free survival is 99.6% (PPV). When vibration sense is absent, the decision tree identifies a subgroup with a higher risk of developing DFU. The NPV in this group is 4.4%. In the RDF study population, patients

without a history of DFU have a one-year risk of 1.4% of developing a DFU. The risk-ratio in the group who lost vibration sense is 10, compared to patients with intact vibration sense at the medial malleolus. When the decision tree for patients without a history of DFU was considered one diagnostic tool to predict one-year ulcer-free survival, a sensitivity of 99.6%, specificity of 4.4%, a PPV of 69.8% and NPV of 83.3% was observed. The effect on posttest probability of disease was large (negative likelihood ratio: 0.09). The ROC curve comparing the composite scores of tuning fork and monofilaments to the prediction made by the decision tree showed that in patients with a history of DFU, a greater accuracy (area under the curve) of 76.6% was achieved by the decision tree, compared to tuning fork (75.0%) and monofilaments (68.7%), see Figure 3.

Figure 3 Receiver Operating Characteristic (ROC) curves of the decision tree, composite 10 g monofilament score (up to 10 test sites) and composite vibration sense score (up to 4 test sites) to predict ulcer-free survival at one-year follow-up in patients without a history of DFU.

Discussion

We showed that particular sites of monofilament and vibratory testing have predictive value in the estimation of ulcer-free survival. The results of our study suggest that a high sensitivity can be achieved by using only two instruments on four test sites, which might complement the foot exam where diabetic patients are subjected to⁶. Our study results are applicable in patients with and without a history of DFU, which were distinguished regarding the differences in relative risks of future DFU these groups are confronted with. Performance of both trees was evaluated by K-fold cross validation, suggesting the internal validity of our results. However, the generalizability of our findings should be studied in other settings.

Current literature suggests the use of multiple test locations to achieve greater specificity of monofilament testing, however, this was not studied in a prospective setting in light of DFU development¹⁸. Other studies are less clear in the discriminative properties of a composite measure, in relation to risk of ulceration^{19,20}. Moreover, testing is often suggested on areas with excessive callus (e.g. metatarsal heads), which lowers validity and results in greater inter- and intratest reliability⁹. From a previous study we recommend the use of test sites with less callus formation, like hallux, fifth toe, medial heel, first dorsal web and lateral foot to get a true estimate of foot sensation¹³. The current prospective study adds that screening on a multitude of locations does not result in a more accurate risk estimation. Yet, specific sites on the foot have certain predictive properties, minimizing the number of tests needed and thereby saving time.

Risk factors for ulcer development include peripheral neuropathy, foot deformities and repetitive stress over an area exposed to vertical or shear stress, causing tissue breakdown². Peripheral artery disease is predominantly associated with ulcer healing rates, rather than ulcer development^{21,22}. Study subjects who developed new ulcers during follow-up more frequently had a history of previous lower extremity complications like DFUs and amputations. Incidence rates for ulcer recurrence are estimated to be 65% in 5 years, which suggests that the patient where wound closure is achieved should be regarded as in remission rather than being healed². In line with these figures, high recurrence rates were also observed in our data. High attention should be given to these high-risk limbs. The presented decision tree aids in this objective, since it suggests that in patients with a prior ulcer, being insensate to the monofilament at the hallux results in a one-year recurrence rate of 87.5%, but a predicted ulcer-free survival of 60.0% was observed when protective sensation was present. Frequency of screening strategies could be more tailored based on this information.

Our data have the virtues of a prospective study design, a complete one-year RDF-study follow-up regarding ulcer incidence, the assessment of multiple sensory modalities, with a careful selection of valid test locations to assess sensory thresholds. Limitations of our study include the single center design of the RDF-study and the limited duration of follow-up, with the conclusions drawn from one-year follow-up only. Future measurements of the cohort will reveal if the estimates (i.e. decision trees) change when a longer follow-up is achieved. External validity of the decision trees should be investigated in other settings, such as academic hospitals, other teaching hospitals, general practices or podiatry practices.

A significant reduction in disease burden might be expected if high and low risk populations could be identified and treated accordingly^{23,24}. In patients with a history of DFU, degree of sensory loss, and thereby risk of ulceration, was still gradable. The findings of this study suggest that patients can be stratified into high and low risk categories by using information on prior ulceration, testing the vibration sense on the medial malleolus and monofilament testing on medial heel and hallux, instead of all 14 locations. Yet, the high PPV of the suggested test locations may especially be of value in the annual screening of diabetic subjects without a history of ulceration²⁵. The accuracy of traditional methods of sensory testing on fewer test locations does not result in less precision and is likely to be quicker and easier to perform on a busy outpatient clinic. The likelihood ratio of both trees may be of value in individualized medical decision-making and the findings of this study might complement the current prediction models for diabetic foot ulceration^{23,26,27}.

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Chapter IX

Balance, risk of falls, risk factors and fall-related costs in individuals with diabetes

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Abstract

Aims

Sensory loss and impaired balance are considered risk factors of incident falls. The aim of this study was to assess the relationship between degree of foot sensation and balance, risk of falls, incidence of fall-related injuries and costs in a cohort of patients with diabetes.

Methods

(Non)-neuropathic subjects participating in the Rotterdam Diabetic Foot Study were followed prospectively. Subjects underwent sensory testing of the feet (39 item Rotterdam Diabetic Foot Study Test Battery (RDF-39)); balance was assessed at the second follow-up (Brief-BESTest) as were data on incident falls. Medical records and financial data were abstracted to estimate fall-related morbidity and in-hospital costs.

Results

A higher RDF-39 score, cerebral artery disease, type 2 diabetes, height and age were predictors of the Brief-BESTest total score. 41/296 patients (13.9%) reported two or more falls during follow-up. Predictors for recurrent falls were a higher RDF-39 score (aOR: 1.124, $p < .0005$), male gender (aOR: 0.319, $p = 0.016$), age (aOR: 0.938, $p = 0.003$) and type 2 diabetes (aOR: 3.157, $p = 0.100$). Thirty-one patients used medical resources (median € 370 (IQR: 150-977)).

Conclusions

Degree of sensory loss correlates significantly with an increased imbalance and risk of falls. The RDF-39 may be used as stratification tool in medical decision-making and patient information.

Introduction

Balance is the ability to maintain the body's line of gravity over its base of support. A correctly functioning balance system allows a person to maintain a proper vision while moving, to determine the direction and speed of movement, to identify the body's position in its space and to make automatic postural adjustments to maintain posture and stability in varying circumstances¹.

Balance is achieved and maintained by a complex set of sensorimotor control systems that necessitates sensory input from vision (sight), proprioception (touch) and the vestibular system (motion, equilibrium, spatial orientation)². This input information is integrated in the brain, together with motor output to the eye and body muscles as effector organs. Ageing, disease, injury and certain drugs can affect one or more of these components, resulting in an elevated risk of balance impairment and gait disorders^{3,4}. Diabetes mellitus, for example, may affect sensory input from the feet, resulting in an increased risk of falls, fractures and death^{5,6}.

One of the sequelae of diabetes is diabetic sensorimotor polyneuropathy (DSP), which is prevalent in the diabetes population and associated with both neuropathic symptoms like burning, tingling and pain, and an insidious simultaneous process of loss of sensation at the feet⁷⁻⁹. Prevalence rates of DSP in type 2 diabetes increase to 50% after 10 years of disease duration and in type 1 diabetes this is 20% after 20 years¹⁰. Severe loss of sensation may also result in balance problems and falls^{8,11}. Patients with reduced cutaneous sensation have different plantar pressure distributions compared to healthy individuals¹². However, little is known about the influence of reduced sensation to balance impairment¹²⁻¹⁵. To further quantify the relationship between diabetes related sensory loss and balance impairment, we evaluated whether the Rotterdam Diabetic Foot Study Test Battery (RDF-39), a validated instrument to grade the loss of sensation, is capable of stratifying patients in high or low risk categories of accidental falls^{8,11}. The RDF-39 contains dichotomized test items on incremental severity of sensibility loss at the feet, ranging from loss of static- and moving two-point discrimination to prior ulceration and amputation^{8,9,16}.

The aim of this study was to assess the relationship between degree of foot sensation and balance, risk of falls and its consequences in terms of incident fall-related injuries and fall-related costs in a cohort of individuals with diabetes.

Methods

Study design and subjects

The current study is part of the Rotterdam Diabetic Foot Study (RDF-study), a prospective cohort study of unselected diabetes type 1 and type 2 patients followed at the outpatient Diabetes Clinic of the Franciscus Gasthuis & Vlietland hospital, Rotterdam, the Netherlands. RDF-study design and methods have been reported in detail elsewhere^{11,17}. In short, the aim of the RDF-study is to investigate the natural history of neuropathy, including deterioration of sensation of the feet. The RDF-study participants were recruited from patients visiting the outpatient diabetes clinic. RDF-study inclusion criteria were: diabetes mellitus (treated by oral blood glucose lowering drugs and/or insulin), age over 18 years, no significant cognitive impairment, speaking Dutch and signed informed consent. Exclusion criteria were: active radicular syndrome and neurological disease interfering with sensibility of the feet, as assessed at the baseline interview and with the screening questionnaire. The Medical Research Ethics Committee of Erasmus University Medical Center, Rotterdam, the Netherlands approved the study (MEC-2009-148).

Data collection and tests

Baseline measurements were conducted between January 2014 and June 2015, with patients first subjected to an interview (history taking (e.g. prior ulceration, amputation, comorbidities), Michigan Neuropathy Screening Instrument (MNSI)), then to a physical examination (full Rotterdam Diabetic Foot Study Test Battery) together with gathering of demographic (age, sex), anthropometric (height, weight) and laboratory (routine measurements) data, which was repeated in follow-up visits 1-1.5 years later. At the second follow-up visit, balance tests (The Brief-Balance Evaluation Systems Test (Brief-BESTest)) were performed in an unselected group of participants. Data on falls were collected at each follow-up visit and included the circumstances of each fall, usage of medical resources and whether hospitalization was required. Non-fallers and recurrent fallers were distinguished. Medical resource use and associated costs were retrieved from the hospital's financial systems or general practitioner. Costs were originally estimated in Euros and later converted in the US dollars 2016 exchange rate: one Euro equaled approximately 1.11 US dollars.

Brief-BESTest

The primary outcome of this study was patients balance status. The Brief-BESTest is a valid balance test that constitutes of 6 balance control system items from the original BESTest¹⁸⁻²⁰, referring to biomechanical constraints, stability limits, sensory orientation and stability in gait. The assessor scores each item from 0 (severe balance impairment) to 3 (no balance impairment). Two of the 6 items (transition-anticipatory postural adjustment, reactive

postural response) are scored bilaterally, resulting in an 8-item balance test. The score range is 0-24 points, with higher scores indicative of a better balance performance^{18,21}. The Brief-BESTest has a high interrater (ICC = .86 - .96) and test-retest (ICC = .90 - .98) reliability in subjects with and without neurological diagnosis. The Brief-BESTest is able to validly discriminate between patients with and without a history of falls (mean total score 12.5 and 15.5, respectively)^{18,19}. The Brief-BESTest was only administered in RDF-study patients who entered the second follow-up visit.

Falls

The secondary outcome of this study was the risk of falls. A fall was defined as a person inadvertently ending up on the ground or at a lower level²². Because multiple falls are associated with an increased risk of falling and isolated falls are not, a fall in this study was defined as multiple or recurrent falls^{23,24}. Individual patients reported their history of falls using standardized questions and were provided with a clear definition of falls. Other secondary measures were the incidence of fall-related injuries and cumulative fall-related costs.

The Rotterdam Diabetic Foot Study Test Battery

The 39-item RDF-39 includes both instruments and test sites to measure overall foot sensation^{11,25}. This scoring system contains 39 dichotomized items on static- and moving two-point discrimination (S2PD and M2PD), static one-point discrimination (S1PD), vibration sense, cold stimulus tests, Romberg's test, experienced numbness, prior diabetic foot ulcer and prior amputation (Supplementary Table A). The RDF-39 is unidimensional and valid in the assessment of sensation at the feet^{8,11}. S2PD and M2PD were tested with a Disk-Criminator™ (US Neurologicals, LLC, Poulsbo, Washington, USA), with the threshold set at 8 mm, based on previously published normative values¹⁶. S1PD was tested with a 10 g Semmes-Weinstein monofilament (Baseline® Tactile™, USA), based on current international standards of medical care in diabetes^{26,27}. S2PD, M2PD and S1PD test sites were chosen in concordance with the nerve territories of the foot: I, hallux (medial plantar nerve [tibial nerve]); II, medial heel (calcaneal nerve [tibial nerve]); III, first dorsal web (deep peroneal nerve); IV, lateral foot (sural nerve) and V, fifth toe (lateral planter nerve [tibial nerve]). M2PD was not tested at the fifth toe due to its small surface area. Vibration sense was tested with a Rydel-Seiffer tuning fork (Martin, Tuttlingen, Germany) at the medial malleolus and dorsal interphalangeal joint of the hallux and compared to normative threshold data²⁸. Cold sensation was tested by applying a cold piece of metal to the arch of the foot. Information on numbness was derived from the MNSI, which was administered by the physician before the physical examination. Information on prior ulceration and/or amputation, as indicators of severe sensory loss, was derived from the patient interviews. Sensory test items constituted of both a sensory

test and test location (e.g. S1PD at the lateral foot (S1PD IV), S2PD at the fifth toe (S2PD V)). For each RDF-39 item, a score 1 was noted when a patient scored above the threshold. The maximum score is 39 points (including both ankles and feet), with higher scores indicative of more severe sensory loss^{8,11}.

Statistical analysis

Analyses were based on the 296 included patients who were assessed at the second follow-up. Baseline characteristics were presented as mean (SD) for variables with normal distributions, median (IQR) for variables with skewed distributions, and n (%) for categorical variables. The Shapiro-Wilk test was used to assess normality. Differences between categories were assessed using a Kruskal-Wallis test.

Brief-BESTest predictors

Relationships between the Brief-BESTest and baseline continuous predictor variables (RDF-39, MNSI total score, body mass index (BMI), age and diabetes duration) were explored using Spearman's correlation coefficients. Univariate linear regression analysis was used to explore the relationship between each potential predictor variable with the Brief-BESTest. Only baseline variables with a realistic potential contribution to the outcome variable and availability in the RDF-study dataset were included in the models (i.e. sex, age, weight, height, duration and type of diabetes, medical history and pedal sensory status (RDF-39)). Significant factors, as determined by a $p < .10$, were included in the multivariable linear regression model with backward selection and considered significant with $p < .05$ (two-sided).

Relationships between Brief-BESTest and falls and RDF-39 and falls

Receiver operating characteristic analysis and area under the curves (AUCs) were used to determine the optimal cut-off points (Youden's J statistic) of both the RDF-39 and Brief-BESTest to differentiate individuals with and without a history of (recurrent) falls (Brief-BESTest) or future falls (RDF-39)²⁹. Prognostic accuracy at the optimal cut-off was expressed as sensitivity and specificity.

Predictors of falls

A binary logistic regression analysis was used to explore the relationship between each potential predictor variable with incident future falls. Again, only variables with a realistic potential contribution to the outcome variable were included in the models. Significant factors with $p < .10$ were included in the multivariable logistic regression model with backward conditional selection and considered significant with $p < .05$. When two or more covariables were highly correlated, only one was selected for the analysis to avoid multicollinearity. As a result, weight and height were selected instead of BMI.

Fall- and fracture incidence per person-time

Fall- and fracture incidence was calculated using standard person-time methods.

All statistical analysis was carried out using IBM SPSS Statistics 24.0 (IBM Corp., Armonk, New York, USA). P-values < 0.05 (two-sided) were considered statistically significant.

Results

Included subjects

Included were 416 subjects. During RDF-study follow-up, 32 patients withdrew from study participation, 66 patients were lost to follow-up and 22 patients died. The remaining 296 patients (71.2%) were assessed at the second follow-up (median follow-up: 885 days (IQR): 833-1000). Of these, 134 patients (65.5%) underwent the balance tests. 255 of 296 patients (86.1%) were non-fallers and the remaining 41 patients (13.9%) were recurrent fallers. Table 1 shows the baseline characteristics of the different groups. Demographic and anthropometric data were comparable between groups. Recurrent fallers had more often type 2 diabetes, neuropathy complaints (MNSI score), increased sensory loss (RDF-39 score) and impaired balance tests (Brief-BESTest).

Impact of sensory loss on balance parameters

Figure 1 shows that RDF-39 and Brief-BESTest total scores were significantly negatively associated ($r_s = -.446$, $p < 0.0005$) with the RDF-39 sum score, accounting for 21.0% of the variation in total Brief-BESTest scores with adj. $R^2 = 20.5\%$, despite considerable heterogeneity among patients. A Brief-BESTest score of 13 points correlates with a RDF-39 score of 22 points. Table 2 displays the relationship between increasing categories of RDF-scores, the separate Brief-BESTest subscores and the total MNSI score. The negative association seen in Figure 1 is also present for each of the Brief-BESTest sub scores.

Impact of balance and sensory loss on recurrent falls

The Brief-BESTest had an acceptable ability to differentiate participants with and without a history of recurrent falls (AUC (CI) = 0.746 (0.624 to 0.868)). At the optimal probability cutoff point of 13 points, the Brief-BESTest yielded a sensitivity of 71.9% (correctly classifying the group with a history of recurrent falls during follow-up) and specificity of 70% (correctly classifying the group without a history of falls during follow-up).

Table 1 Baseline and outcome data.

	Patients with Brief-BESTest at second follow-up (n=134)	Patients without Brief-BESTest at second follow-up (n=162)	Non-fallers (second follow-up) (n=255)	Recurrent fallers (second follow-up) (n=41)
Gender (M/F)	84/59	89/73	152/103	21/20
Age (median (y), IQR)	63.2 (55.2 – 68.6)	64.4 (55.8 – 72.3)	64.0 (55.2 – 69.9)	62.7 (56.6 – 72.2)
Ethnicity (n (%))				
- Caucasian	116 (86.6%)	130 (80.2%)	211 (82.7%)	35 (85.4%)
- Indo-Surinamese	8 (3.0%)	16 (9.9%)	21 (8.2%)	3 (7.3%)
- African	4 (3.0%)	5 (3.1%)	9 (3.5%)	-
- Asian	3 (2.2%)	3 (1.9%)	6 (2.4%)	-
- Other	3 (2.2%)	8 (4.9%)	8 (3.1%)	3 (7.3%)
Height (median (m), IQR)	176.0 (167.8 – 183.0)	172.0 (164.0 – 179.0)	175.0 (166.0 – 180.0)	172.0 (164.5 – 181.5)
Weight (median (kg), IQR)	90.0 (79.0 – 106.2)	85.5 (75.0 – 98.2)	87.0 (76.0 – 102.0)	94.3 (77.0 – 113.0)
BMI (median (kg/m²), IQR)	29.7 (26.8 – 34.4)	29.1 (25.6 – 32.5)	29.1 (25.7 – 32.8)	30.9 (27.0 – 36.5)
Duration of diabetes (median (y), IQR)	16.0 (9.0 – 26.0)	16.0 (9.8 – 24.3)	16.0 (9.0 – 26.0)	16.0 (11.0 – 24.5)
Type of diabetes (n (%))				
- Type 1	32 (23.9%)	37 (22.8%)	64 (25.1%)	5 (12.2%)
- Type 2	102 (76.1%)	125 (77.2%)	191 (74.9%)	36 (87.8%)
Mean Arterial Pressure (median (mmHg), IQR)	97.2 (91.0 – 103.3)	96.7 (88.7 – 104.3)	96.7 (89.0 – 103.3)	97.3 (90.7 – 106.2)
Systolic blood pressure (median (mmHg), IQR)	136.0 (126.8 – 149.3)	136.0 (125.0 – 146.0)	136.0 (125.0 – 146.0)	140.0 (127.0 – 155.0)
Diastolic blood pressure (median (mmHg), IQR)	77.0 (70.0 – 82.0)	77.5 (69.0 – 82.0)	77.0 (125.0 – 146.0)	77.0 (70.0 – 84.0)
Drugs (n (%))				
- Lipid lowering drugs	80 (59.7%)	107 (66.0%)	166 (65.1%)	21 (51.2%)
- Oral blood glucose lowering drugs	76 (56.7%)	88 (54.3%)	143 (56.1%)	21 (51.2%)
- Insulin	109 (56.7%)	141 (87.0%)	216 (84.7%)	34 (82.9%)
Medical history (n (%))				
- Hypertension	83 (61.9%)	91 (56.2%)	144 (43.5%)	30 (73.2%)
- Myocardial infarction	14 (10.4%)	26 (16.0%)	29 (11.4%)	11 (26.8%)
- Angina pectoris	12 (9.0%)	21 (13.0%)	25 (9.8%)	8 (19.5%)
- Coronary artery disease	18 (13.5%)	39 (24.1%)	44 (17.3%)	13 (31.7%)
- CABG/PCI	13 (9.8%)	37 (22.8%)	37 (14.6%)	13 (31.7%)
- CVA/TIA	14 (10.4%)	14 (8.6%)	26 (10.2%)	2 (4.9%)
- Cancer	14 (10.4%)	22 (13.6%)	30 (11.8%)	6 (14.6%)
- COPD	15 (11.2%)	12 (7.4%)	23 (9.0%)	4 (9.8%)
- Peripheral arterial disease	7 (5.2%)	11 (6.8%)	15 (5.9%)	3 (7.3%)

Table 1 Baseline and outcome data. (continued)

	Patients with Brief-BESTest at second follow-up (n=134)	Patients without Brief-BESTest at second follow-up (n=162)	Non-fallers (second follow-up) (n=255)	Recurrent fallers (second follow-up) (n=41)
Diabetic Sensory Polyneuropathy (n (%))				
- MNSI score >3	53 (41.7%)	54 (41.5%)	82 (36.6%)	25 (75.8%)
Rotterdam Diabetic Foot Study Test Battery (median score, IQR)				
- RDF-39	17.0 (8.0 – 22.0)	14.0 (8.0 – 22.0)	15.0 (7.0 – 21.0)	21.0 (14.5 – 29.5)
Brief-BESTest (median score, IQR)	16.0 (10.0 – 21.3)	-	16.5 (11.8 – 22.0)	8.0 (0.50 – 15.0)
Retinopathy (n (%))	21 (25.0%)	28 (26.7%)	42 (25.8%)	7 (26.9%)
Single fallers (n (%))	25 (18.7%)	20 (12.3%)	45 (17.6%)	-
Recurrent fallers (n (%))	20 (14.9%)	21 (13.0%)	-	41 (100%)
Laboratory measurements				
HbA1c (median (mmol/L), IQR)	61.0 (52.5 – 69.0)	60.0 (53.0 – 70.5)	61.0 (53.0 – 70.0)	56.5 (52.3 – 65.8)
MDRD (median ml/min/1.73 m ² , IQR)	78.3 (60.2 – 96.7)	77.1 (53.0 – 70.5)	79.3 (60.9 – 96.2)	72.7 (57.3 – 96.3)
Total cholesterol (median (mmol/L), IQR)	4.1 (3.5 – 4.7)	4.0 (3.5 – 4.8)	4.0 (3.5 – 4.8)	4.0 (3.7 – 4.7)
LDL-C (median (mmol/L), IQR)	1.8 (1.3 – 2.5)	1.8 (1.4 – 2.5)	1.8 (1.4 – 2.5)	1.8 (1.5 – 2.4)
HDL-C (median (mmol/L), IQR)	1.4 (1.1 – 1.6)	1.3 (1.1 – 1.6)	1.3 (1.1 – 1.6)	1.2 (1.0 – 1.5)
Non-HDL-C (median mmol/L, IQR)	2.6 (2.1 – 3.3)	2.6 (2.2 – 3.2)	2.6 (2.1 – 3.2)	2.7 (2.3 – 3.6)
TG (median (mmol/L), IQR)	1.5 (1.0 – 2.4)	1.6 (1.0 – 2.4)	1.5 (1.0 – 2.3)	1.9 (1.3 – 3.1)
ApoB (median (g/L), IQR)	0.9 (0.8 – 1.1)	0.9 (0.8 – 1.1)	0.9 (0.8 – 1.1)	0.9 (0.7 – 1.0)
Microalbumin urine (median (mg/L), IQR)	14.0 (8.0 – 47.0)	18.0 (7.0 – 46.5)	16.0 (7.0 – 48.3)	21.0 (10.0 – 44.0)

Legend: M, male; F, female; BMI, Body Mass Index; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; ApoB, apolipoprotein B; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MNSI, Michigan Neuropathy Screening Instrument.

Table 2 Brief-BESTest and several categories of incremental sensory loss (n=134 subjects).

Total RDF-39 score*	Intact sensation (RDF-39: 0), n=1	Loss of S2PD and/or M2PD (RDF-39: 1≤18), n=80	Loss of vibration sense (RDF-39: 19≤22), n=24	Loss of protective sensation (plantar) (RDF-39: 23≤29), n=16	Aberrant Romberg test. Insensate to cold stimulus. Prior ulcer or amputation (RDF-39: 30≤39), n=13	P-value
Median total Brief-BESTest score (IQR)	24 (0)	18 (10.5)	15.5 (10)	14 (11.25)	3 (11)	< .0005 [#]
Median sub-scores (IQR)						
Section I: Biomechanical constraints	3 (0)	3 (1)	2 (2)	2 (3)	1 (2)	< .0005 [#]
Section II: Stability limits	3 (0)	3 (1)	2 (1)	2.5 (1)	2 (2)	.003 [#]
Section III: Transitions-Anticipatory Postural adjustment						
- Left	3 (0)	2 (2)	1.5 (1)	1 (1.75)	0 (1)	< .0005 [#]
- Right	3 (0)	2 (2)	1 (1)	1 (1.75)	0 (0)	< .0005 [#]
Section IV: Reactive Postural Response						
- Left	3 (0)	3 (3)	2.5 (3)	2.5 (3)	0 (0.5)	.075 [#]
- Right	3 (0)	2 (3)	1 (3)	0.5 (3)	0 (0.5)	.058 [#]
Section V: Sensory orientation	3 (0)	3 (1)	1 (3)	1 (2.75)	0 (2)	.001 [#]
Section VI: Stability in gait	3 (0)	3 (0)	3 (0)	3 (0.75)	0 (3)	< .0005 [#]
Total MNSI score (IQR)	3 (0)	2 (3)	3 (5)	5 (3.75)	8 (4)	< .0005 [#]

Legend: A higher RDF-39 score indicates a higher degree of sensibility loss. A higher Brief-BESTest score indicates less impairment.

RDF-39, Rotterdam Diabetic Foot Study Test Battery 39; *, see *Supplementary Table A*; IQR, inter-quartile range; [#], Kruskal-Wallis test; MNSI, Michigan Neuropathy Screening Instrument.

The baseline RDF-39 score had an acceptable ability to predict participants with and without future recurrent falls during follow-up (AUC (CI) = 0.687 (0.596 to 0.779)). At the optimal probability cutoff point of 18 points, the RDF-39 yielded a sensitivity of 70.7% (correctly classifying the group with recurrent falls during follow-up) and specificity of 60.4% (correctly classifying the group without falls during follow-up). A total RDF-39 score of 18 points indicates aberrant S2PD and M2PD measurements, but intact vibration sense and protective sensation, as assessed with a 10 g monofilament (Figure 1, Table 2).

Figure 1 The correlation between balance, foot sensation and falls.

Legend: ROC-analysis showed that a Brief-BESTest of 13 points was associated with a history of recurrent falls. A baseline RDF-39 score of 18 points was associated with future recurrent falls. The mean Brief-BESTest with 95% confidence intervals is displayed.

Brief-BESTest predictors

Table 3 shows the results of univariate and multivariable linear regression analysis for total Brief-BESTest scores. A higher RDF-39 score (i.e. more severe degree of sensory loss; beta coefficient: -0.37), a higher age at study entry (beta: -0.35 per year), a higher weight (beta: -0.09 per kilogram), type 2 diabetes (beta: -6.59), a medical history of hypertension (beta:

-4.80), myocardial infarction (beta: -4.75), COPD (beta: -4.24) or peripheral artery disease (beta: -8.56) significantly reduced the Brief-BESTest total score at the second follow-up, implying increased balance impairment. In the multivariable analysis, only a higher RDF-39 score (beta: -0.31), a higher age at study entry (beta: -0.21) and height (beta: 0.13) added independently and significantly to the prediction of the Brief-BESTest total score ($p < 0.0005$, adj. $R^2 = 0.46$).

Table 3 Univariate and multivariable linear regression analysis of balance status at second follow-up.

	Univariate model B (95% CI)	P-value	Multivariable model B (95% CI)	P-value
Male sex	1.002 (-1.594 to 3.598)	.446		
Age (years)	-0.346 (-0.445 to -0.246)	<.0005	-0.210 (-0.349 to -0.072)	.003
Weight (kg)	-0.091 (-0.146 to -0.036)	.001	0.134 (0.018 to 0.250)	0.024
Height (cm)	0.075 (-0.045 to 0.195)	.218		
Duration of diabetes (years)	0.034 (-0.066 to 0.133)	.503		
Diabetes type 2	-6.589 (-9.313 to -3.864)	<.0005	-2.924 (-6.164 to 0.316)	0.076
Medical history				
- Hypertension	-4.804 (-7.260 to -2.348)	<.0005		
- Myocardial infarction	-4.754 (-8.785 to -0.722)	.021		
- Angina pectoris	-2.816 (-7.213 to 1.581)	.207		
- CVA/TIA	-3.956 (-8.013 to 0.101)	.056	-3.271 (-7.044 to 0.501)	.088
- Cancer	-3.398 (-7.469 to 0.674)	.101		
- COPD	-4.236 (-8.159 to -0.312)	.035		
- Emphysema	-1.856 (-12.228 to 8.516)	.724		
- Peripheral artery disease	-8.561 (-14.021 to -3.102)	.002		
- Retinopathy	-1.429 (-5.112 to 2.255)	.443		
Rotterdam Diabetic Foot Study Test Battery (score)				
- RDF-39	-0.366 (-0.487 to -0.244)	<.0005	-0.307 (-0.462 to -0.152)	<.0005

Legend: Dependent variable: Brief-BESTest total score (a higher score indicates less balance impairment); B, beta coefficient; CI, confidence interval; CVA, cerebrovascular accident; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; RDF-39, 39 item Rotterdam Diabetic Foot Study Test Battery.

Predictors of falls

Table 4 shows the results of univariate and multivariable binary logistic regression analysis for recurrent falls. A higher RDF-39 score (crude OR: 1.08) and a history of myocardial infarction (crude OR: 2.86) significantly increased the odds for recurrent falls during follow-up. The multivariable logistic regression model showed that a higher RDF-39 score (adj. OR: 1.12), male gender (adj. OR: 0.32) and age (adj. OR: 0.94) remained independently significant predictors for future falls (model $X^2(4) = 25.386$, $p < 0.0005$; proportion of cases correctly classified: 86.2%). The RDF-39 score proved to be an independent predictor of recurrent falls (BriefBESTest < 16 : OR: 1.08, $p = 0.11$ versus BriefBESTest > 15 : OR 1.07, $p = 0.30$).

Table 4 Univariate and multivariable binary logistic regression analysis on risk of future falls at second follow-up.

	Univariate model OR (95% CI)	P-value	Multivariable model OR (95% CI)	P-value
Male sex	0.712 (0.364 to 1.379)	.313	0.319 (0.126 to 0.811)	.016
Age (years)	1.003 (0.975 to 1.031)	.844	0.938 (0.899 to 0.979)	.003
Weight (kg)	1.009 (0.994 to 1.024)	.261		
Height (cm)	0.992 (0.961 to 1.025)	.642		
Duration of diabetes (years)	0.996 (0.969 to 1.024)	.783		
Diabetes type 2	2.413 (0.908 to 6.411)	.077	3.157 (0.804 to 12.398)	.100
Medical history				
- Hypertension	2.102 (1.009 to 4.379)	.047		
- Myocardial infarction	2.857 (1.295 to 6.307)	.009		
- Angina pectoris	2.221 (0.925 to 5.331)	.074		
- CVA/TIA	0.452 (0.103 to 1.980)	.292		
- Cancer	1.286 (0.499 to 3.312)	.603		
- COPD	1.090 (0.357 to 3.332)	.879		
- Peripheral artery disease	1.263 (0.349 to 4.570)	.722		
- Retinopathy	1.061 (0.417 to 2.704)	.901		
Rotterdam Diabetic Foot Study Test Battery (score)				
- RDF-39	1.080 (1.040 to 1.121)	<.0005	1.124 (1.056 to 1.196)	<.0005

Legend: Dependent variable: incidence of recurrent falls; OR, odds ratio; CI, confidence interval; CVA, cerebrovascular accident; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; RDF-39, Rotterdam Diabetic Foot Study Test Battery.

Incidence of falls, resource use and costs

The incidence of recurrent falls in our cohort was 2.3 falls (95% CI: 1.6-3.3) per 100 person-years. Thirty-one patients made use of healthcare resources due to falls by visiting a general practitioner (n=6), physiotherapist (n=3) or were in need of secondary care (n=24). Twelve patients (five women, seven men) suffered from fall-related fractures or ruptures (0.9 fractures (95% CI: 0.5-1.5) per 100 person-years). Two hip fractures were observed, one patella fracture, two broken ankles, one metatarsal bone fracture and two broken halluces. Upper extremity injuries included a fractured humerus, a broken wrist, a fractured digitus five and a rupture of the supraspinatus tendon. Total healthcare expenditures were US\$ 59,947.07, median costs of US\$ 440.45 (IQR: 179 – 1162) per fall (2016 price level).

Discussion

Any person older than 65 years who has not fallen in the previous year has a pre-test probability of 19% to 36% to fall the next year^{30,31}. As a previous fall is a sensitive prognosticator of future falls, exploration of its predictors appears sensible. Previous studies

suggest that the highest potential yield comes from screening on balance and gait, as these factors are independent predictors of future falls and have more impact than orthostatic hypotension, visual impairment, medication use, limitation in activities of daily living and cognitive impairment³². This is important, because strategies to improve gait and balance of patients with diabetes have been proven effective to avoid falls³²⁻³⁴. So far, little attention has been given to the influence of degree of sensory loss at the feet in relation to both balance impairment and falls^{12,14}. Our study showed that degree of sensory loss significantly relates to the risk for imbalance and risk of falls.

A previous study showed a positive association between peripheral neuropathy and pedal sensibility on the one hand and balance on the other, but sensibility was not assessed using an unambiguously outcome measure¹⁴. The advantage of the RDF-39 in assessing foot sensation lies in the fact that both early stages of sensory loss (i.e., S2PD, M2PD) as well as more advanced stages of sensory loss (e.g. loss of cold sensation, prior ulceration etc.) are measured with validated and easy to apply screening instruments. The RDF-39, a dichotomized version of the full RDF Study Test Battery, takes around 10 minutes to complete. This information enables quantification of the sensibility scores as it worsens over time^{11,33,35}. Moreover, this study showed that at a cut-off of 18 points, patients become at increased risk for recurrent falls.

We used the Brief-BESTest to measure balance, of which reliability and its ability to discriminate between patients with and without a history of falls have been demonstrated^{18,19}. Current study adds that the total Brief-BESTest score is also able to differentiate a history of recurrent fall status with favorable test characteristics when using a cut-off value of 13 points. Moreover, we found that the Brief-BESTest score is predominantly influenced by pedal sensation.

Neuropathy has long been considered the most dominant predictor of falls in diabetes, because diminishing somatosensory function of the lower extremity reduces the ability to detect changes in balance and make the necessary adjustments to avoid falls³⁶. Yet, the basis of proprioception is related to cutaneous afferents, rather than joint afferents. Therefore, we restricted our attention in this study to cutaneous sensation³⁷. Previous studies reported the influence of retinopathy and cataracts on contrast sensitivity and its contribution to balance impairments, which is important especially in low light conditions (e.g. bathroom visits at night)^{38,39}. Only three out of 11 studies from the literature found visual impairment a statistically significant factor of the occurrence of falls (ORs ranging 1.6 to 2.0). We found that retinopathy was not significantly associated with the Brief-BESTest score or with falls. This suggests that it is not retinopathy alone and decreased foot sensation, rather than ocular

changes, that is more likely to be responsible for balance impairment and associated with falls. Previous research has shown that vestibular dysfunction is 2.6 times more likely to be related to falls in the previous year⁴⁰. However, the influence of diabetes on the quality and availability of vestibular information to the vestibulo-spinal tract to relay motor commands has not been examined in our study and may be accounted for in future studies^{2,41}.

In our study, the estimated incidence of falls was 2.3 per 100 person-years, which is less than other reports (125 per 100 person-years). This is mainly due to the unselected population of patients included in the RDF-study (both neuropathic and non-neuropathic subjects), compared to a study of patients with prior foot ulcers only (indicative of end-stage sensory loss)²². Our study also showed that falls lead to considerable burden for society. Falls account for approximately 10% of emergency department visits among elderly persons, with a strong age gradient. One in ten falls results in serious injury, such as fractures and brain or head injuries^{31,42}. In the Dutch healthcare setting, average costs per fall were estimated to be € 9370 (2009 price level), which increased with being female, a higher age and comorbidity⁴². A US study found average costs per fall of US\$ 9463 (2015 price level)⁴³. In our study, we found lower costs, most likely related to the less serious or non-fatal injuries observed, differences in healthcare systems and the overall higher costs of healthcare in the United States. Moreover, we only included in-hospital costs, while out-of-hospital care (e.g. nursing homes) are known to account for considerable additional costs of approximately one-third of total costs⁴².

Strengths of our study are the relatively large sample size, the prospective study design in an unselected group of patients with diabetes with substantial follow-up and the appreciation of pedal sensation as a new and valid measure of neuropathy instead of the conventional assessment of symptoms of neuropathy¹⁵. Several caveats relating to our study are important to highlight. Firstly, results of retrospective assessment of patients' fall status annually may have been sensitive to recall bias with a reported specificity of 91-95% and sensitivity of 80-89% when recalling falls in the previous year⁴⁴. Secondly, selection bias may have played a role since 120 patients dropped-out from study start (n=416) and 134 patients measured with the Brief-BESTest. However, the impact of selection bias appears limited. Selection bias due to mortality is likely to be absent as patients who died during follow-up had a slightly higher RDF-39 score at baseline, but this effect is explained by the correlation of a higher age and RDF-39 score. Withdrawals (n=32) and patients lost-to-follow-up (n=66) did not significantly differ with patients available for follow-up regarding age and duration of diabetes. Overall, sample size was sufficient to answer our hypothesis without the risk of under power with estimations unlikely to change with higher patient numbers tested. Thirdly, prognostic characteristics of RDF-39 and Brief-BESTest could not be compared head-to-

head because the latter was not measured at study entry. Yet, the observed association between pedal sensory loss and balance deserves further investigation.

In summary, assessment of patient's sensory loss using the total RDF-39 score may help clinicians to better stratify patients at risk for balance impairment and falls. Patients already become at risk when having lost two-point discrimination. This information is important regarding patient information and may be used in recommendations on specific intervention strategies to prevent falls. One such intervention is decompressing lower extremity peripheral nerves in selected patients, which has been shown to restore sensation and improves balance^{45,46}. We conclude that patients with loss of vibration sense should be subjected to a multifactorial falls risk assessment for prevention that includes gait and balance testing. The model suggests that patients can be categorized in medium and high-risk categories, which might be helpful in tailored preventive interventions.

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Supplementary material

Supplementary Table A The Rotterdam Diabetic Foot Study Test Battery (RDF-39).

Left lower extremity	Test result (0 = non-aberrant, 1 = aberrant)	Right lower extremity	Test result (0 = non-aberrant, 1 = aberrant)
S2PD II left		S2PD II right	
S2PD I left		S2PD I right	
S2PD III left		S2PD III right	
S2PD V left		S2PD V right	
S2PD IV left		S2PD IV right	
M2PD II left		M2PD II right	
M2PD III left		M2PD III right	
M2PD IV left		M2PD IV right	
M2PD I left		M2PD I right	
Vibration sense IP left		Vibration sense IP right	
Vibration sense MM left		Vibration sense MM right	
S1PD I left		S1PD I right	
S1PD V left		S1PD V right	
Numbness	(derived from MNSI)		
S1PD II left		S1PD II right	
S1PD III left		S1PD III right	
S1PD IV left		S1PD IV right	
Prior ulcer	(scored for any extremity)		
Cold stimulus left		Cold stimulus right	
Romberg test			
Amputation left		Amputation right	
Sub-total		Sub-total	
Total RDF-39 score			

Legend: Roman capitals are indicatives of test locations: I, plantar hallux; II, medial heel; III, first dorsal web; IV, lateral foot; V, plantar fifth toe. S2PD, static two-point discrimination; M2PD, moving two-point discrimination; S1PD, static one-point discrimination (10 g Semmes-Weinstein monofilament). IP, interphalangeal joint; MM, medial malleolus; MNSI, Michigan Neuropathy Screening Instrument.

Chapter X

The natural history of tarsal tunnel syndrome in diabetic subjects

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Abstract

Introduction

Tibial nerve entrapment is highly prevalent in diabetic subjects, resulting in significantly more neuropathic complaints and concomitant sensory disturbances. The study aim was to assess the impact of tarsal tunnel syndrome (TTS) and sensory loss at baseline on incident diabetic foot ulceration (DFU) in diabetic patients, since decompressing the tibial nerve might change the natural history of the disease.

Methods

113 subjects with TTS (69 bilateral, 23 left-sided and 21 right-sided) participating in the prospective Rotterdam Diabetic Foot Study were compared to 303 diabetic controls without TTS, regarding incident DFU. Kaplan-Meier analysis and Cox's regression analysis was used to determine the independent hazard of baseline variables for new DFU.

Results

The median observation period was 836.5 days (IQR, 459-1077.8). In bilateral TTS, 17.4% (95%CI: 8.4% to 26.3%) of subjects experienced DFU versus 8.3% (95%CI: 5.1% to 11.6%) in controls (left or right) during follow-up ($p=0.0036$). In left-sided TTS, no subjects versus 6.2% (95%CI: 3.4% to 9.0%) in controls had DFUs ($p=0.243$). Incident ulceration was seen in 14.3% (95%CI: -0.7% to 29.3%) of right-sided TTS subjects versus 4.1% (95%CI: 1.5% to 6.3%) in controls ($p=0.034$). Besides HbA1c, diminished sensation at the hallux independently increased the risk of ulceration, in patients with (HR: 4.692, $p=0.003$) and without (HR: 2.307, $p=0.002$) prior DFU.

Discussion

Elevated sensory thresholds in TTS render diabetic patients at a higher risk for DFU. With effective surgery, TTS is likely to be an amenable factor to potentially prevent diabetic foot disease and thereby reduce amputation risk.

Introduction

Tibial nerve entrapment at the tarsal tunnel was first reported in 1962, when Keck described a patient with anesthesia over the sensory distribution of the tibial nerve with localized tenderness and paresthesias of the foot sole when tapping the nerve posterior to the medial malleolus¹. Since then multiple reports have been published on diagnostic criteria, including the physical examination, electrodiagnostic studies and imaging, together with studies on treatment modalities, which are mainly surgical²⁻⁴. In the 1980s, diabetic patients were identified for having higher rates of tarsal tunnel syndrome (TTS), as diabetes predisposes the peripheral nerve to chronic compression (i.e. the double crush syndrome)^{5, 6}. Only a few studies have been published related to the beneficial effects of a tibial nerve release, these effects include relief of complaints, gain of sensory function and prevention of lower extremity ulcers and amputations⁷⁻¹⁴.

TTS is a more common condition of the foot and ankle than has been historically appreciated in the literature, but no studies exist on its natural history. Therefore, the prospective and observational Rotterdam Diabetic Foot (RDF) Study was initiated to investigate the natural course of tibial nerve entrapment in diabetic subjects. A previous cross-sectional analysis of baseline RDF-study measurements has shown that TTS in diabetic subjects is prevalent and accompanied by significantly higher plantar cutaneous thresholds and significantly more neuropathic symptoms⁴. The aim of the current study was to investigate the degree to which sensory deficits observed in uni- and bilateral TTS in diabetic subjects result in an increased risk of diabetic foot ulceration (DFU) compared to those without signs of tibial nerve entrapment.

Methods

Study design and subjects

The RDF-study is a prospective cohort study of unselected diabetic patients followed at the outpatient Diabetes Clinic of Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands. The aim of the RDF-study was to investigate the natural history of neuropathy, including deterioration of sensation of the feet. The RDF-study participants were recruited from patients visiting the specialized outpatient diabetes clinic. RDF-study inclusion criteria were: type 1 or type 2 diabetes mellitus (treated by oral blood glucose lowering drugs and/or insulin), age over 18 years, no significant cognitive impairment, speaking Dutch and signed informed consent. Exclusion criteria were: active radicular syndrome and neurological disease interfering with sensibility of the feet, as reported in the interview and screening

questionnaire. RDF-study design and methods have been described in detail^{4, 15}. Baseline measurements were carried out between January 2014 to June 2015, for which patients were subjected to an interview, to a physical examination and were requested to fill in a questionnaire (on smoking history, neuropathic symptoms and history of foot or leg ulcer and amputation), which was repeated during the follow-up visits with 1-1.5 years' intervals. Demographic, anthropometric and care data (e.g., weight, length, blood pressure, diabetes type, duration, and treatment) and laboratory results were retrieved from the patient file. The Medical Research Ethics Research Committee of Erasmus MC Medical University Center, Rotterdam, the Netherlands approved the study (MEC-2009-148).

Physical examination: The Rotterdam Diabetic Foot Study Test Battery

Both feet were examined. Static- and moving two-point discrimination (S2PD and M2PD) were tested with a Disk-Criminator™ (from 2 to 15 mm) (US Neurologicals, LLC, Poulsbo, WA, USA). Static one-point discrimination (S1PD) was tested with a set of Semmes-Weinstein monofilaments (from 0.008 to 300 g) (Baseline® Tactile™, Minneapolis, MN, USA). S2PD, M2PD and S1PD test sites were chosen in agreement with the nerve territories of the foot: I, plantar hallux (medial plantar nerve [tibial nerve]); II, medial heel (calcaneal nerve [tibial nerve]); III, first dorsal web (deep peroneal nerve); IV, lateral foot (sural nerve) and V, plantar fifth toe (lateral planter nerve [tibial nerve]). M2PD was not tested at the fifth toe due to its small surface area. Vibration sense was tested with a Rydel-Seiffer tuning fork (scored from 0 to 8) (Martin, Tuttlingen, Germany) at the medial malleolus and dorsal interphalangeal joint of the hallux. Neuropathy symptoms were assessed using the Michigan Neuropathy Screening Instrument (MNSI), which was administered before the physical examination. Sensory test items consisted of both a sensory test and test location (e.g., S1PD at the lateral foot [S1PD IV], S2PD at the plantar fifth toe [S2PD V]). Lower extremity artery pulsations were palpated for each foot separately. TTS was diagnosed at study baseline when both a positive Tinel sign at the tarsal tunnel and neuropathic complaints were present, according to a previous study⁴. Patients were categorized in 1) bilateral TTS, 2) unilateral TTS (right), 3) unilateral TTS (left) and 4) diabetic patients without TTS.

Data collection

Demographic (age, sex, medical history), anthropometric (height, weight, body mass index) and lower limb sensory status information (full RDF Study Test Battery) was collected at RDF-study baseline and follow-up visit one (January 2015 to October 2016) and two (March 2017 to July 2017). Data on incident diabetic foot ulceration was collected half-yearly using telephone call follow-up and included the circumstances of each ulcer (e.g. side, date), usage of medical resources and the need for hospitalization. The reporting standards of studies on the prevention and management of foot ulcers in diabetes are followed¹⁶.

Statistical analysis

Shapiro-Wilk tests were used to assess the normality of continuous data. Differences between groups were assessed using Kruskal-Wallis tests. A subscore on nerve-related neuropathic MNSI items is reported for the three groups⁴. Crude estimates of ulcer incidence rates in the different groups were calculated as the total number of cases with DFUs, divided by the total number of subjects in the respective groups. Confidence intervals (CIs) were obtained as 95% binomial confidence intervals. Kaplan-Meier analysis was conducted to compare the time to DFU of bilateral, unilateral (left and right) TTS in diabetic patients to those without TTS, in terms of DFU development. Incidence of ulceration was considered an event. A log rank test was conducted to determine if there were differences in the distributions for the different groups. The Kaplan-Meier curves were not adjusted for covariates. Cox proportional hazards models were fit to identify independent predictors of DFU development, in which RDF-study subjects with TTS were compared with subjects without TTS. Potential predictor variables were chosen on the basis of 1) current literature; 2) expert opinion and 3) availability in the RDF-study dataset. Since S1PD measurements correlated highly, only monofilament measurements of both halluces were included in the models. A univariate model was fitted that included the baseline measurement variables only. A multivariable adjusted model included all exposure variables, the final adjusted model was determined using backward stepwise (likelihood ratio) reduction, maintaining all univariate exposure variables with $p < 0.10$, in 20 iterations. Differences were expressed in unadjusted and adjusted hazard ratios (HR) with 95% CIs. Since previous DFU was an interaction variable, Kaplan-Meier curves are depicted that show the differences in occurrence according to degree of sensory loss (S1PD). Two curves were plotted separately for patients with and without a previous DFU. Statistical analysis was carried out using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, New York, USA). We considered p values below 0.05 (two-sided) to be statistically significant.

Results

Patient characteristics

At baseline, 69 diabetic patients with a median age of 62.7 years (interquartile range (IQR), 52.6-69.6) had bilateral TTS and 44 patients (65.2 years (IQR, 55.1-71.3)) had unilateral TTS (prevalence: 17.7% (95%CI: 13.9-21.5) vs. 29.9% (25.2-34.5%))⁴. The remaining RDF-study participants without TTS served as controls ($n=303$). Groups were comparable regarding the majority of demographic data, but patients with bilateral TTS had a higher body weight ($p=0.005$), had more often retinopathy ($p=0.032$) and on average higher HbA1c levels ($p=0.016$) at study entry compared to the other groups (Table 1, Baseline data). During RDF-study follow-up, 32 patients withdrew from study participation, 66 patients were lost to follow-up and 22 patients died.

Table 1 Baseline data.

	Bilateral TTS	Unilateral TTS	Other RDF-study participants	P-value
Subjects (n)	69	44	303	
Gender (M/F)	25/44	20/24	130/173	0.097*
Age (median (y), IQR)	62.7 (52.6-69.6)	65.2 (55.1-71.3)	64.0 (55.2-69.9)	0.645#
Ethnicity (n (%))				0.669*
- Caucasian	58 (84.1)	40 (90.9)	243 (80.2)	
- Indo-Surinamese	5 (7.2)	1 (2.3)	29 (9.6)	
- African	1 (1.4)	2 (4.5)	11 (3.6)	
- Asian	1 (1.4)	-	6 (2.0)	
- Other	4 (5.8)	1 (2.3)	14 (4.6)	
Height (median (m), IQR)	178.0 (167.5-183.0)	175.0 (164.3-180.8)	172.0 (165.0-180.0)	0.272#
Weight (median (kg), IQR)	94.6 (82.5-112.2)	86.1 (75.3-99.9)	86.8 (76.0-102.0)	0.005#
BMI (median (kg/m²), IQR)	31.4 (26.9-35.3)	29.1 (25.7-32.6)	29.0 (25.8-33.4)	0.053#
Duration of diabetes (median (y), IQR)	18.0 (8.5-27.5)	17.0 (9.3-26.0)	16.0 (9.0-24.0)	0.688#
Type of diabetes (n (%))				0.980*
- Type 1	16 (23.2)	10 (22.7)	67 (22.1)	
- Type 2	53 (76.8)	34 (77.3)	236 (77.9)	
Insulin use (n (%))	59 (85.5)	37 (84.1)	255 (63.1)	0.961*
Systolic blood pressure (median mmHg, IQR)	140.0 (126.5-150.0)	135.5 (124.8-144.5)	136.0 (125.0-147.0)	0.518#
Diastolic blood pressure (median mmHg, IQR)	80.0 (69.5-85.0)	75.5 (69.0-80.0)	77.0 (70.0-82.0)	0.587#
Retinopathy (n (%))	19 (40.4)	5 (22.7)	42 (22.0)	0.032*
Lifetime smoking history (n (%))	42 (73.7)	23 (67.6)	121 (60.5)	0.167*
Laboratory measurements				
HbA1c (median (mmol/L), IQR)	63.0 (55.0-74.5)	61.0 (54.0-75.0)	59.0 (51.0-68.0)	0.016#
MDRD (median ml/min/1.73 m ² , IQR)	77.1 (57.7-100.8)	77.0 (51.6-100.6)	79.1 (61.1-95.7)	0.948#
Total cholesterol (median (mmol/L), IQR)	4.2 (3.6-5.0)	4.3 (3.5-4.6)	4.0 (3.5-4.8)	0.931#
LDL-C (median (mmol/L), IQR)	1.9 (1.4-2.7)	1.7 (1.3-2.4)	1.8 (1.4-2.5)	0.631#
HDL-C (median (mmol/L), IQR)	1.3 (1.1-1.6)	1.3 (1.1-1.6)	1.3 (1.1-1.7)	0.363#
TG (median (mmol/L), IQR)	1.5 (1.0-2.5)	1.8 (1.1-2.7)	1.5 (1.0-2.3)	0.272#
ApoB (median (g/L), IQR)	0.9 (0.8-1.1)	0.9 (0.8-1.2)	0.9 (0.8-1.1)	0.659#
Microalbumin (median (mg/L), IQR)	21.0 (8.0-72.0)	15.5 (8.0-41.0)	16.5 (8.0-54.3)	0.672#

Legend: *, Pearson-Chi Square statistic; #, Kruskal-Wallis test; M, male; F, female; IQR, interquartile range; BMI, body mass index; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; ApoB, apolipoprotein B; RDF, Rotterdam Diabetic Foot.

Limb-level characteristics

Table 2 shows that more severe sensory deficit was observed in TTS patients compared to controls, in the form of higher cutaneous thresholds (S1PD, all parameters: $p < 0.001$), impaired spatial discrimination (S2PD, all parameters: $p \leq 0.004$ and M2PD, all parameters: $p \leq 0.009$) and a more frequent history of ulceration ($p = 0.021$). The cutaneous threshold (S1PD) frequently surpassed the critical limit of 10 g in the majority of tibial nerve innervated test locations in both bilateral and left-sided TTS patients, but generally not in right-sided patients, compared to controls. Left-sided TTS patients had fewer palpable lower extremity arteries compared to the other groups, but this did not reach statistical significance. Bilateral and unilateral TTS patients had significantly more neuropathic symptoms compared to controls ($p < 0.0005$). Fifty-two participants had a history of ulceration and 14 participants a prior amputation due to previous DFU disease (before study entry).

Incidence of ulceration

During follow-up, 48 episodes of ulceration were registered, in 40 participants. The rate of new-onset ulceration from study start was 9.6% (95%CI: 7.0 to 12.9%) in a median observation period of 836.5 days (IQR, 459-1077.8). A total of 65 ulcers occurred, with nine patients developing multiple DFU episodes in the period of observation. An average number of 1.3 DFUs were observed per episode. The majority of patients presented with ulcer(s) at toes two to five (43.1%), followed by DFUs at the hallux (38.5%). A minority suffered from ulcers at the heel (9.2%), plantar-side of the metatarsophalangeal joints (3.1%), plantar-side of the midfoot (1.5%) and in 3 patients (4.6%) these data were not available.

Ulcer-related outcomes in tarsal tunnel syndrome

In bilateral affected TTS patients ($n = 69$), 12 ulcers (17.4%, 95%CI: 9.3% to 28.4%) occurred (left or right), compared to 23 ulcers (8.7%, 95%CI: 5.6% to 12.7%) in control subjects ($n = 265$) during a median follow-up of 824 days (IQR, 487-1098.5). Figure 1 shows the distributions for the bilateral, unilateral (left) and unilateral (right) TTS groups compared to controls. A log rank test showed statistically significant different distributions, $X^2(1) = 4.418$, $p = 0.036$. Unilateral affected patients had a median follow-up of 839 days (IQR, 454-1077). In left-sided affected patients ($n = 23$), no ulcers occurred in the left foot, compared to 18 ulcers (6.2%, 95%CI: 3.7% to 9.6%) in controls ($n = 290$). The distributions were not statistically significant different ($X^2(1) = 1.366$, $p = 0.243$). In right-sided affected patients ($n = 21$), 3 ulcers (14.3%, 95%CI: 3.0% to 36.3%) occurred in the right foot, compared to 12 ulcers (4.1%, 95%CI: 2.1% to 7.0%) in controls ($n = 294$). A log rank test showed statistically significant different distributions ($X^2(1) = 4.479$, $p = 0.034$).

Table 2 Limb-level measurements.

	Bilateral tarsal tunnel syndrome (n=69)	Left-sided tarsal tunnel syndrome (n=23)	Right-sided tarsal tunnel syndrome (n=21)	Other RDF-study participants (n=303)	P-value
Limb sensory status					
Static one-point discrimination [†] (median g (IQR))					
- Left hallux	4.0 (1.4-100.0)	6.0 (2.0-180.0)	2.0 (0.6-10.0)	2.0 (0.6-6.0)	< 0.0005 [#]
- Left medial heel	4.0 (1.4-15.0)	15.0 (1.4-60.0)	2.0 (0.6-8.0)	2.0 (0.6-8.0)	< 0.0005 [#]
- Left fifth toe	4.0 (1.4-26.0)	2.0 (1.0-60.0)	2.0 (1.2-4.9)	1.4 (0.6-4.0)	< 0.0005 [#]
- Right hallux	4.9 (1.4-88.0)	6.0 (2.0-180.0)	2.0 (1.0-10.0)	1.4 (0.6-8.0)	< 0.0005 [#]
- Right medial heel	6.0 (1.4-26.0)	8.0 (1.4-60.0)	2.0 (0.8-11.0)	2.0 (0.6-8.0)	0.001 [#]
- Right fifth toe	4.0 (1.0-26.0)	2.0 (1.0-60.0)	2.0 (0.8-4.0)	1.4 (0.6-4.0)	< 0.0005 [#]
Static two-point discrimination [†] (median mm (IQR))					
- Left hallux	16.0 (11.3-16.0)	16.0 (11.0-16.0)	13.0 (8.0-16.0)	11.0 (8.0-16.0)	< 0.0005 [#]
- Left medial heel	16.0 (12.0-16.0)	16.0 (10.0-16.0)	16.0 (12.0-16.0)	14.0 (8.0-16.0)	0.004 [#]
- Left fifth toe	16.0 (15.0-16.0)	15.0 (10.0-16.0)	16.0 (9.5-16.0)	12.0 (7.0-16.0)	< 0.0005 [#]
- Right hallux	16.0 (12.0-16.0)	15.0 (9.0-16.0)	11.0 (6.5-16.0)	11.0 (7.0-16.0)	0.001 [#]
- Right medial heel	16.0 (12.3-16.0)	16.0 (7.0-16.0)	16.0 (11.5-16.0)	13.0 (8.0-16.0)	0.001 [#]
- Right fifth toe	16.0 (11.5-16.0)	16.0 (9.0-16.0)	16.0 (11.5-16.0)	12.0 (7.0-16.0)	< 0.0005 [#]
Moving two-point discrimination [†] (median mm (IQR))					
- Left hallux	12.5 (8.0-16.0)	11.5 (8.0-16.0)	12.0 (8.0-16.0)	8.0 (5.0-14.0)	< 0.0005 [#]
- Left medial heel	12.0 (7.0-16.0)	14.0 (8.0-16.0)	15.0 (10.5-16.0)	9.0 (6.0-15.0)	0.009 [#]
- Right hallux	12.0 (9.0-16.0)	10.5 (6.5-16.0)	10.0 (6.0-16.0)	8.0 (5.0-14.8)	< 0.0005 [#]
- Right medial heel	13.0 (7.8-16.0)	14.0 (8.0-16.0)	13.0 (7.5-16.0)	9.0 (5.0-15.0)	0.004 [#]
Vibration sense (median (IQR))	4.0 (1.0-5.5)	3.0 (0.0-6.0)	4.0 (3.0-6.5)	4.0 (2.0-6.0)	0.157 [#]
- Left interphalangeal joint	4.0 (0.0-5.0)	4.0 (0.0-4.0)	4.0 (2.5-6.0)	4.0 (2.0-6.0)	0.049 [#]
- Right interphalangeal joint					
Michigan Neuropathy Screening Instrument					
Neuropathic symptoms (median score (IQR))	2.0 (1.0-3.0)	1.0 (1.0-3.0)	2.0 (1.0-2.0)	0.0 (0.0-2.0)	< 0.0005 [#]
Vascular limb status					
Previous diabetic foot ulceration (n %)	16 (23.2)	4 (17.4)	2 (9.5)	30 (9.9)	0.021 [*]
Previous amputations (n (%))	0	1 (4.3)	0	5 (1.7)	0.428 [*]
- Left extremity	2 (2.9)	0	0	6 (2.0)	0.749 [*]
- Right extremity					
Palpable lower extremity arteries (%)					
- Left posterior tibial artery	74.2	60.0	73.7	71.7	0.661 [*]
- Left dorsalis pedis artery	73.8	70.0	84.2	75.8	0.749 [*]
- Right posterior tibial artery	66.7	60.0	65.0	71.5	0.888 [*]
- Right dorsalis pedis artery	69.7	65.0	80.0	71.7	0.948 [*]

Legend: [†] S1PD, S2PD and M2PD are censored data. Only on tibial nerve innervated areas is reported. ^{*}, Pearson-Chi Square statistic; [#], Kruskal-Wallis test.

Figure 1 Kaplan-Meier curves of tarsal tunnel syndrome in diabetic subjects.

Legend: TTS, tarsal tunnel syndrome.

Cox-regression analysis

Table 3 shows the results of the univariate and multivariable Cox proportional hazards models, comparing the risk of ulceration in combined bilateral and unilateral TTS patients to controls. In unadjusted analyses, baseline measurements of the following characteristics were significantly associated with ulcer risk: male sex, retinopathy, diminished one-point discrimination (i.e. monofilaments), non-palpable lower extremity arteries, prior foot ulcer, prior amputation and HbA1c. In adjusted analyses, diminished one-point discrimination at the right hallux, prior ulcer and HbA1c were associated with an increased risk of ulceration, while a lower risk of ulceration was seen with a lower systolic blood pressure.

Table 3 Unadjusted and adjusted hazard ratios for incident diabetic foot ulceration among diabetic patients.

	HR (95%CI), unadjusted	P-value	HR (95%CI), adjusted	P-value
Male sex	2.614 (1.191 to 5.737)	0.017		
Age (years)	1.015 (0.986 to 1.044)	0.326		
Duration of diabetes (years)	1.012 (0.987 to 1.038)	0.333		
Diabetes type 2	1.287 (0.564 to 2.939)	0.549		
Insulin use	0.850 (0.354 to 2.042)	0.716		
BMI (kg/m²)	0.992 (0.938 to 1.048)	0.768		
Systolic blood pressure (mmHg)	1.001 (0.984 to 1.018)	0.909	0.967 (0.928 to 1.007)	0.108
Lifetime smoking history	0.817 (0.383 to 1.746)	0.603		
Retinopathy	3.400 (1.381 to 8.368)	0.008		
Tarsal tunnel syndrome	1.711 (0.876 to 3.344)	0.116		
Static one-point discrimination				
- Left hallux	3.390 (2.378 to 4.832)	< 0.0005		
- Right hallux	4.137 (2.810 to 6.092)	< 0.0005	2.401 (1.111 to 5.189)	0.026
Palpable lower extremity arteries				
- Left posterior tibial artery	0.235 (0.119 to 0.463)	< 0.0005		
- Left dorsalis pedis artery	0.392 (0.202 to 0.761)	0.006		
- Right posterior tibial artery	0.274 (0.141 to 0.531)	< 0.0005		
- Right dorsalis pedis artery	0.455 (0.236 to 0.879)	0.019		
Previous diabetic foot ulceration	17.005 (8.679 to 33.316)	< 0.0005	9.786 (2.387 to 40.127)	0.002
Previous diabetes-related amputation	9.852 (3.766 to 25.774)	< 0.0005		
HbA1c (mmol/L)	1.024 (1.002 to 1.046)	0.032	1.038 (1.002 to 1.076)	0.037
MDRD (ml/min/1.73 m²)	0.994 (0.982 to 1.007)	0.381		

Legend: HR, hazard ratio; statistically significant results appear in boldface type ($p < 0.05$); BMI, body mass index; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease.

The hazard ratio of prior ulceration in the whole group was 2.40 (CI: 1.11 to 5.19), $p=0.026$. In the group of patients with prior ulceration this was 4.69 (CI: 1.69-13.01), $p=0.003$, in the group without prior ulceration this was 2.31 (CI: 1.36-3.90), $p=0.002$. Figure 2 shows the resultant Kaplan-Meier curves.

Figure 2 Kaplan-Meier curves of diabetic subjects with (upper panel) and without (lower panel) prior ulceration, according to degree of sensory loss.

Legend: S1PD measurements are categorized according to hallux measurements (Group 0: $0 \leq 10$ g, Group 1: $>10 \leq 100$ g and Group 2: >100 g).

Discussion

This study showed that the natural history of TTS in a diabetic patient has a positive predictive value for the development of DFU. In a large prospective cohort of adults with diabetes a higher risk for DFU development was found in patients with TTS, in both bilateral and right-sided affected patients. Diagnosis-specific multivariable analysis showed a more important role for prior DFU, the level of HbA1C at inclusion and increased sensory thresholds. With regard to abnormal sensory thresholds, multivariable analysis showed, the degree of sensory loss was significantly associated with the risk of ulceration, independent of signs of tibial nerve entrapment at baseline. In our opinion, these findings may have important consequences for patient selection for tarsal tunnel decompression.

The results from our data support a complex etiology of DFU that includes both person- and limb-level factors¹⁷. As proposed earlier from baseline RDF-study measurements, the increased sensory thresholds observed in tibial nerve compression relates to the risk of ulceration⁴. In fact, neuropathy, in the form of sensory deafferentation, is arguably the most important risk factor in the cascade to ulcer development in persons with and without prior DFU. The associated hazard ratio was of the highest magnitude in the adjusted Cox proportional hazards analysis, with symptoms of TTS being surpassed by this hazard. Prior ulceration was associated with re-ulceration and therefore the foot in which wound closure is achieved should be regarded as in remission, rather than being healed^{17, 18}. Since the diagnostic limitation of self-reported symptoms is acknowledged, we conclude that the more objective somatosensory examination is key in accessing the risk of ulceration and may also serve in the decision when to decompress the tarsal tunnel in the natural history of tibial nerve entrapment. Current literature suggests a dramatic improvement in spatial acuity and cutaneous pressure thresholds after tarsal tunnel release in diabetic subjects, with studies reporting post-operative sensory thresholds of 0.5 to 0.8 g, coming from 32.9 to 65.6 g pre-operatively^{7, 8, 10, 12}. This type of surgery may therefore change the natural history of neuropathy in diabetes, since re-innervation of the foot sole may reverse the associated hazards of the insensate foot^{11, 19}. If surgical decompression is to be performed, timing of the surgery is an important factor for optimizing the operative result²⁰.

Patients are generally operated when having positive (hyperalgesia, allodynia) or negative (hypoesthesia, hypoalgesia) symptoms of neuropathy, together with a positive Tinel sign or positive provocative testing at the site of compression². The decision to decompress the tarsal tunnel depends on the physical examination, since electrodiagnostic testing does not aid to the diagnosis of TTS due to the high percentage of asymptomatic people who have abnormal sensory and motor results^{21, 22}. In all stages of neuropathy the Tinel

sign may be present, of which processes of de- and remyelination lie at root^{23, 24}. Relief of pressure sufficiently soon restores nerve function, with blood flowing in the altered neurovascular structures, after decompression²⁵. An optimal timing of surgery has not yet been established, but should include consideration of complaints, quality of life and the increased sensory thresholds at the plantar side of the foot^{10, 26}. Somatosensory function presumably correlates with the likelihood of nerve regeneration²⁰. Since a cutaneous threshold of ≥ 10 g is a significant predictor of future ulceration and surpasses the normative cutaneous threshold of the feet exceedingly, lower values should probably be avoided, supplemented with other sensory measurements, when surgery is specifically planned to prevent lower extremity complications²⁷. A recent grading scale of somatosensory function of the feet may aid this debate^{15, 20, 23}. Interestingly, recent reports on lower extremity nerve decompression (LEND) showed that nerve outgrowth could also be expected from patients with end-stage neuropathy, reversing the chance of ulcer recurrence^{12, 28, 29}.

To date, the RDF-study is the only observational cohort study to determine the prognostic value of tibial nerve compression in diabetic subjects in light of risk of ulcer development. An additional important finding is that the associated degree of sensory loss is the most important hazard in both patients with and without prior ulceration. However, our study had a number of limitations. First, the RDF-cohort is a hospital-based cohort, with patients at higher risk of lower extremity complications compared to the general diabetes population. The incidence rate of DFUs for the whole cohort was comparable with the literature and slightly higher compared to numbers seen in primary care, as expected³⁰. However, only relatively low absolute numbers of new DFUs were seen in the TTS groups, due to sample size limitations, but still with significant differences. In fact, no new ulcers were observed in the twenty-three unilateral left-sided affected limbs, resulting in a non-significant trend in this time frame, compared to controls. Our hypothesis was nonetheless confirmed in the sixty-nine bilateral and twenty-one right-sided affected patients and may also be confirmed in left-sided patients when a longer follow-up is available. The generalizability of our findings remains to be determined. Second, no complete data was available on type or severity of foot deformations, which is considered a risk factor for foot ulceration^{17, 31}. Third, in the adjusted analysis, palpable pulses in the lower limbs were not selected, although previous studies found associations between these measurements and new DFU and/or amputation^{32, 33}. A combination of tests is recommended to more reliably exclude peripheral artery disease³⁴. Finally, potential confounders of this multivariable analysis cannot be ignored, with new ulcers being influenced by risk factors not measured at baseline. Examples include compliance with foot care, healthcare provision and patient-factors such as kidney disease. Also we do not know if the condition spontaneously resolves or inexorably progress to foot ulceration. Our cohort of 416 diabetic subjects represents the most detailed

assessment of plantar sensory function in the light of tibial nerve pathology, together with a unique 3.5-year follow-up assessment of DFU development in non-operated patients with TTS. Our data seem representative; since the baseline demographic characteristics of our population and reports on TTS characteristics are comparable with other teaching hospitals and with data from the literature^{12, 35}.

In conclusion, we have demonstrated that patients with TTS are at higher risk of foot ulceration due to the observed increased cutaneous thresholds at study baseline. Bilateral affected patients do worse compared to unilateral patients and controls, and are at higher risk of DFU development than unilateral patients. Furthermore, we have now elucidated the natural history of TTS in diabetic subjects, for which surgical interventions may help change its course into DFU development^{12, 36, 37}. High expediency is anticipated from re-innervating the insensate foot, making this type of surgery a promising therapy to battle the increasingly burdensome and expensive DFU pandemic^{38, 39}. Although controversy towards LEND surgery continues to exist, our study provides the necessary evidence to progress to high quality data⁴⁰.

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Chapter XI

Degree of sensory loss predicts the risk of foot ulceration in patients with diabetes mellitus

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Abstract

Background

The aim of this study was to assess the relationship between the degree of loss of foot sensation at baseline and incident foot ulceration (DFU) in a cohort of patients with diabetes, using a valid instrument for the assessment of sensory loss.

Methods

(Non)-neuropathic subjects (n=416) participating in the observational Rotterdam Diabetic Foot (RDF) Study were followed prospectively (median 955.5 days (IQR, 841.5-1121)). Subjects underwent sensory testing of the feet (39-item RDF Study Test Battery) at baseline and were assessed regarding incident DFU. Seven groups of incremental degree of sensory loss were distinguished, according to the RDF-39 sum score. Kaplan-Meier and Cox's regression analyses were used to determine the independent hazard of baseline variables for new DFU.

Results

40 participants developed DFUs. The mean incident rate of new-onset ulceration from study start was 4.5 (95%CI: 3.3 to 6.1) per 100 person-years, which increased significantly from 0 to 67.70 in the seven groups ($X^2(6)=129.704$, $p<0.0005$). Predictors for DFUs were higher RDF-39 score (aHR: 1.173, $p<0.0005$) and kidney function (aHR: 1.022, $p=0.016$). Disease-free survival in patients without prior DFU was predicted by the RDF-39 with a positive likelihood ratio of 3.77. Prior DFU suggests increased mortality risk.

Conclusions

The degree of sensory loss at baseline was associated with progression to DFU during follow-up. Grading the loss of sensation using the RDF Study Test Battery may result in a more precise risk stratification compared to the use of the 10 g monofilament according to current guidelines.

Introduction

The prospect of a required amputation is feared more than death, foot infection or end-stage renal disease by patients with diabetic foot ulcers (DFUs)¹. Since diabetes mellitus accounts for eight out of ten non-traumatic lower extremity amputations, of which 85% are preceded by DFUs, it is reasonable to focus on risk factors for ulceration in order to prevent amputations^{2,3}.

Sensory deafferentation due to neuropathy is considered to be one of the most important risk factors in the cascade of diabetic foot ulceration⁴. The International Working Group on the Diabetic Foot (IWGDF) risk stratification system designates patients with neuropathy and without other risk factors in the low ulcer risk category, defining loss of protective sensation when insensate to the 10 g monofilament at ≥ 2 test sites⁵. However, an extensive meta-analysis of prognostic factors for foot ulceration concluded that the predictive power of this particular test does not seem to be influenced by the number of test sites on the foot³. Yet, it has been concluded from more recent studies that the place of sensory testing on the foot has prognostic properties regarding diabetic foot ulceration, necessitating fewer tests and allowing a more accurate risk stratification⁶.

The loss of protective sensation (i.e., a cutaneous threshold of >10 g) is indicative of advanced nerve damage⁷. Recently developed grading scales of sensory loss at the feet show that other measures of somatosensory testing, for example vibratory testing, becomes abnormal before the loss of protective sensation⁸. Moreover, the location of sensory testing at the feet predicts the overall degree of sensory loss. In this way, combining both test and test site will make it possible to grade lower extremity sensory deafferentation more precisely compared to random monofilament or vibratory testing⁹.

The aim of this study was to investigate how degree of sensory loss relates to the risk of future diabetic foot ulceration. We explored new dimensions of somatosensory testing by comparing several categories of sensory loss to the risk categories of the IWGDF risk classification.

Methods

Study design and subjects

The RDF-study is a prospective cohort study of unselected patients with diabetes followed at the outpatient Diabetes Clinic of Franciscus Gasthuis & Vlietland hospital, Rotterdam, the

Netherlands. The aim of the RDF-study was to investigate the natural history of neuropathy, including deterioration of sensation of the feet. The RDF-study participants were recruited from patients visiting the specialized outpatient diabetes clinic. RDF-study inclusion criteria were: type 1 or type 2 diabetes mellitus (treated by insulin and/or oral blood glucose lowering drugs and/or insulin), age over 18 years, no significant cognitive impairment, speaking Dutch and signed informed consent. Exclusion criteria were: active radicular syndrome and neurological disease interfering with sensibility of the feet, as reported in the interview and screening questionnaire. The RDF-study design and methods have been described in detail^{8,10}. Baseline measurements were carried out between January 2014 to June 2015, for which patients were subjected to an interview and a physical examination and were requested to fill in a questionnaire (on smoking history, neuropathic symptoms and history of foot or leg ulcer and amputation), which was repeated during the follow-up visits with 1-1.5 years' intervals. Demographic, anthropometric and disease-related (e.g., weight, length, blood pressure, diabetes type, duration, lower extremity complications (i.e., DFU/amputation) and treatment) and laboratory results were retrieved from the patients' files. No patients with prior major amputations were included. The Medical Research Ethics Research Committee of the Erasmus Medical Center, Rotterdam, the Netherlands approved the study (MEC-2009-148).

Physical examination: The Rotterdam Diabetic Foot Study Test Battery

Both feet were examined. The 39-item RDF-39 includes both instruments and test sites to measure overall foot sensation⁸. This scoring system contains 39 dichotomized items on static- and moving two-point discrimination (S2PD and M2PD), static one-point discrimination (S1PD), vibration sense, cold stimulus tests, Romberg's test, experienced numbness, prior diabetic foot ulcer and prior amputation (Supplemental Table S1). The RDF-39 is unidimensional and valid in the assessment of sensation at the feet⁸. S2PD and M2PD were tested with a Disk-Criminator™ (US Neurologicals LLC, Poulsbo, Washington, USA), with the threshold set at 8 mm, based on previously published normative values⁷. S1PD was tested with a 10 g Semmes-Weinstein monofilament (Baseline® Tactile™, Minneapolis, Minnesota, USA), based on current international standards of medical care in diabetes¹¹. S2PD, M2PD and S1PD test sites were chosen in concordance with the nerve territories of the foot: I, hallux (medial plantar nerve [tibial nerve]); II, medial heel (calcaneal nerve [tibial nerve]); III, first dorsal web (deep peroneal nerve); IV, lateral foot (sural nerve) and V, fifth toe (lateral planter nerve [tibial nerve]). M2PD was not tested at the fifth toe due to its small surface area. Vibration sense was tested with a Rydel-Seiffer tuning fork (Martin, Tuttlingen, Germany) at the medial malleolus and dorsal interphalangeal joint of the hallux and compared to normative threshold data¹². Cold sensation was tested by applying a cold piece of metal to the arch of the foot. Information on numbness was derived from the MNSI,

which was administered before the physical examination. Information on prior ulceration and/or amputation, as indicators of severe sensory loss, was derived from the patient interviews. Sensory test items constituted of both a sensory test and test location (e.g. S1PD at the lateral foot (S1PD IV), S2PD at the fifth toe (S2PD V)). For each RDF-39 item, a score 1 was noted when a patient scored above the threshold. The maximum score is 39 points (including both ankles and feet), with higher scores indicative of more severe sensory loss. Shorter versions of the RDF-39 are the 31-item RDF-31 and 13-item RDF-13 (Supplemental Table S1)⁸. Lower extremity artery pulsations were palpated for each foot separately.

Data collection

Demographic (age, sex, medical history), anthropometric (height, weight, body mass index) and lower limb sensory status information (full RDF Study Test Battery) was collected at RDF-study baseline and follow-up visit one (January 2015 to October 2016) and two (March 2017 to July 2017). Data on incident DFU was collected at these visits and half-yearly telephone call follow-up and included the circumstances of each ulcer (e.g. date), usage of medical resources and the need for hospitalization. The reporting standards of studies on the prevention and management of foot ulcers in diabetes were followed¹³.

Data and statistical analysis

Baseline characteristics were presented as mean (SD) for variables with normal distributions, median (interquartile (IQR)) for variables with skewed distributions, and n (%) for categorical variables. The Shapiro-Wilk test was used to assess normality. Differences between patients without ulceration and with incident ulceration were assessed using a Mann-Whitney U test and Pearson chi-square test, as were people with and without a history of DFU. Differences between patients available for follow-up and lost to follow-up were compared with the same tests. Differences between patients that were available for follow-up, withdrew from study participation, were lost to follow-up or dead were compared with Kruskal-Wallis and Pearson chi-square tests (Supplemental Table S2). A subscore on nerve-related neuropathic Michigan Neuropathy Symptom Instrument (MNSI) items is reported¹⁰. For a sub-analysis, patients were categorized according to the IWGDF 2019 Risk Stratification System (Category 0 to 3)⁵.

Kaplan-Meier survival analysis was conducted to compare the time to first DFU development for seven categories of sensory loss. Incident ulceration was considered an event. The categories were determined using the RDF-39 sum scores: Group 0, no sensory loss (RDF-39=0); Group 1, loss of S2PD (RDF-39: 0 and $\leq$ 10); Group 2, loss of M2PD (RDF-39: 11 and $\leq$ 18); Group 3, loss of vibration sense (RDF-39: 19 and $\leq$ 22); Group 4, loss of protective sensation [plantar] (RDF-39: 23 $\leq$ 29); Group 5, aberrant Romberg test or insensate to cold stimulus (RDF-39: 30 $\leq$ 34); Group 6, prior ulcer or amputation (RDF-39: 35 $\leq$ 39)⁸. A log rank

test was conducted to determine if there were differences in the survival distributions for the different groups. Moreover, survival curves were plotted separately for patients with and without prior DFU at RDF-study baseline. The Kaplan-Meier curves were not adjusted for covariates. Crude estimates of ulcer incidence rates were calculated as the total number of cases with DFUs, divided by the total number of subjects in the respective groups, using standard person-time methods. Confidence intervals (CIs) were obtained as 95% binomial confidence intervals.

Receiver operating characteristic (ROC) analysis and area under the curves (AUCs) were used to determine the optimal cut-off points (Youden's J statistic) of the RDF-39, (and short-form RDF-31 and -13) to differentiate individuals with and without DFU development. Prognostic accuracy at the optimal cut-off was expressed as sensitivity (i.e. the true positive rate (probability of detection) and specificity (i.e. the true negative rate), together with likelihood ratios¹⁴. ROCs were plotted in which the IWGDF 2019 Risk Stratification System was compared to the RDF-39 in predicting new onset ulceration.

Prediction modelling

Cox proportional hazard models were fit to identify independent predictors of DFU development, in which RDF-study subjects with incident DFU during RDF-study follow-up were compared with subjects without incident DFU. Potential predictor variables were chosen on the basis of 1) current literature; 2) expert opinion and 3) availability in the RDF-study dataset. When two or more covariables were highly correlated, only one was selected for the analysis to avoid multicollinearity. A univariate model was fitted that included the baseline measurement variables only. A multivariable adjusted model included all exposure variables, the final adjusted model was determined using backward stepwise (likelihood ratio) reduction, maintaining all univariate exposure variables with $p < 0.10$, in 20 iterations. Differences were expressed in unadjusted and adjusted hazard ratios (HR) with 95% CIs. To assess the fit of the multivariable model, a logistic regression model was fitted with adjusted predictors, together with ROC analysis. A model was also fitted for patients without prior DFU, using ulcer-free survival as outcome of interest⁶. Statistical analysis was carried out using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, New York, USA). We considered p values below 0.05 (two-sided) to be statistically significant.

Results

Patient characteristics

Baseline characteristics of the 416 RDF-study consecutive participants are shown in Table 1. Patients with a history of DFU at baseline (n=52) were more frequently male (p=0.039), were taller (p=0.001), had a higher systolic blood pressure (p=0.022), reported more symptoms of neuropathy (p<0.0005), had worse kidney function (P=0.06) and more often micro albuminuria (p=0.13), had a lower proportion of palpable lower extremity arteries (p<0.007) and more often had a history of lower extremity amputations compared with patients without a history of DFU (n=364, see Supplemental Table S3). During RDF-study follow-up, 32 patients withdrew from study participation, 66 patients were lost to follow-up and 22 patients died (5.3% (95%CI: 3.1 to 7.4)). Patients who were lost to follow-up were significantly older compared to the remaining patients (p<0.001), had worse renal function (p<0.001) and a lower percentage of palpable dorsal pedis arteries (left: p=0.013, right: p=0.080). Patients who died were older; more often had peripheral artery disease, worse renal function, more frequently a history of DFU and a higher RDF-39 score (see Supplemental Table S2). Five out of 22 (22.7%) patients who died had a prior DFU. At study baseline 39.2% (145/370) of patients were classified in IWGDF Risk Category 0 (Very low), 16.8% (62/370) in Category 1 (Low), 10.0% (37/370) in Category 2 (Moderate) and 34.1% (126/370) in Category 3 (High).

Incident ulceration

Forty patients with diabetes developed DFUs during RDF-study follow-up (median 955.5 days (IQR, 841.5-1121)). Compared to patients in whom no DFUs were observed during follow-up, patients who developed DFU during follow-up were more frequently male (p=0.008), had a lower body weight (p=0.019), had more often retinopathy (p=0.001), had more neuropathic symptoms (p=0.002), a more severe degree of sensory loss (p<0.0005), more frequently a history of DFUs (p<0.0005) and amputations (p<0.001) and fewer palpable lower extremity arteries (p<0.05) at study baseline. In the 40 participants who developed DFUs, 48 episodes of ulceration were registered. The incident rate of new-onset ulceration from study start was 4.5 (95%CI: 3.3 to 6.1) per 100 person-years. Seven patients developed multiple DFU episodes in the period of observation. In total, 65 ulcers were observed with an average number of 1.3 DFUs per episode.

The majority of patients presented with ulcer(s) at toes two to five (43.1%), followed by DFUs at the hallux (38.5%). A minority suffered from ulcers at the heel (9.2%), plantar-side of the metatarsophalangeal joints (3.1%), plantar-side of the midfoot (1.5%) and in 3 patients (4.6%) these data were not available.

Table 1 Baseline and outcome data.

	No DFUs during follow-up (n=376)	DFUs during follow-up (n=40)	P-value
Gender (M/F)	210/166	31/9	0.008*
Age (median (y), IQR)	63.6 (55.0-69.8)	65.7 (54.5-75.4)	0.473 [#]
Ethnicity (n (%))			0.180*
- Caucasian	305 (81.8%)	36 (90.0%)	
- Indo-Surinamese	34 (9.0%)	1 (2.5%)	
- African	13 (3.5%)	1 (2.5%)	
- Asian	7 (1.9%)	-	
- Other	17 (4.5%)	2 (5.0%)	
Height (median (m), IQR)	172.0 (165.0-180.0)	179.5 (173.0-184.8)	0.094 [#]
Weight (median (kg), IQR)	88.0 (77.0-102.9)	87.3 (76.3-111.5)	0.019*
BMI (median (kg/m²), IQR)	29.5 (26.4-33.8)	28.5 (24.7-32.8)	0.400 [#]
Duration of diabetes (median (y), IQR)	16.0 (9.0-24.8)	17.5 (11.0-29.0)	0.544 [#]
Type of diabetes (n (%))			0.707*
- Type 1	85 (22.6%)	8 (20.0%)	
- Type 2	291 (77.4%)	32 (80.0%)	
Insulin use (n (%))	319 (84.8%)	32 (80.0%)	0.423*
Systolic blood pressure (median mmHg, IQR)	136.0 (125.3-148.0)	139.5 (125.0-147.8)	0.402 [#]
Retinopathy (n (%))	54 (22.7%)	12 (54.5%)	0.001*
Lifetime smoking history (n (%))	95 (36.8%)	10 (30.3%)	0.464*
Lower limb sensory status			
Neuropathic symptoms [°] (median score (IQR))	1.0 (0-2.0)	2.0 (1.0-3.0)	0.002[#]
RDF-39 (median score (IQR))	16.0 (8.0-21.0)	28.5 (19.3-34.0)	< 0.0005[#]
Vascular limb status			
History of DFUs (n (%))	28 (7.4%)	24 (60.0%)	< 0.0005*
Previous amputations (n (%))			
- Left extremity	3 (0.8%)	3 (7.5%)	< 0.001*
- Right extremity	4 (1.1%)	4 (10.0%)	< 0.0005*
Palpable lower extremity arteries (%)			
- Left posterior tibial artery	75.1%	40.0%	< 0.0005*
- Left dorsalis pedis artery	77.5%	58.3%	0.011*
- Right posterior tibial artery	73.2%	39.5%	< 0.0005*
- Right dorsalis pedis artery	79.7%	52.9%	0.023*
Laboratory measurements			
HbA1c (median (mmol/L), IQR)	60.0 (53.0-70.0)	59.0 (52.8-71.5)	0.488 [#]
MDRD (median ml/min/1.73 m ² , IQR)	79.4 (61.1-96.5)	62.4 (45.4-102.3)	0.477 [#]
Total cholesterol (median (mmol/L), IQR)	4.0 (3.5-4.8)	4.3 (3.8-5.0)	0.468 [#]
LDL-C (median (mmol/L), IQR)	1.8 (1.4-2.5)	2.2 (1.2-2.7)	0.181 [#]
HDL-C (median (mmol/L), IQR)	1.3 (1.1-1.6)	1.4 (1.1-1.9)	0.261 [#]
TG (median (mmol/L), IQR)	1.6 (1.0-2.4)	1.8 (1.0-3.0)	0.170 [#]
ApoB (median (g/L), IQR)	0.9 (0.8-1.1)	0.9 (0.6-1.2)	0.127 [#]
Microalbumin (median (mg/L), IQR)	16.0 (8.0-52.0)	31.0 (10.0-85.5)	0.135 [#]

Legend: M, male; F, female; *, Pearson chi-square test; [#], Mann-Whitney U test; statistically significant results appear in boldface type (p<0.05); M, male; F, female; IQR, interquartile range; BMI, body mass index; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; ApoB, apolipoprotein B; RDF, Rotterdam Diabetic Foot; [°], a subscore on nerve-related neuropathic MNSI items is reported.

Impact of sensory loss on ulcer-related outcomes

Figure 1 shows the survival distribution (i.e., time to the event of interest: DFU) for the seven groups, according to degree of sensory loss using the RDF-39 sum score. A log rank test showed statistically significant different survival distributions, $X^2(6)=129.704$, $p<0.0005$. Patients without sensory loss (Group 1, $n=6$) did not develop DFUs. Patients with loss of S2PD (Group 2, $n=110$) had an ulcer incidence rate of 0.76 (95%CI: 0.13 to 2.50) per 100 person-years. In patients with loss of M2PD (Group 3, $n=139$) this was 2.00 (95%CI: 0.81 to 4.17) per 100 person-years, in those with lost vibration sense (Group 4, $n=65$) 2.78 (95%CI: 0.88 to 6.70). In patients who lost protective sensation at the plantar side of the foot (Group 5, $n=64$) the incidence was 10.0 (95%CI: 5.43 to 17.04) per 100 person-years, in patients with an aberrant Romberg test or being insensate to a cold stimulus (Group 6) the incidence was 36.33 (95%CI: 21.11 to 58.58). The highest incidence per 100 person-years was seen in patients with prior DFU or amputation (Group 7, $n=2$): 67.70 (95%CI: 3.40 to 334.0).

Figure 2 shows the survival distributions plotted separately for patients with and without prior DFU at study baseline ($X^2(1)=134.966$, $p<0.0005$). Since group allocation was based on RDF-39 sum scores, not every patient with DFU before study entry ($n=52$) was allotted to Group 7. In patients without prior foot ulceration, the incidence was 2.00 (95%CI: 1.20 to 3.17) per 100 person-years versus 31.20 (95%CI: 20.45 to 45.73) in patients with prior DFU.

Accuracy of the RDF-39, -31 and -13 in predicting incident ulceration

The ability of the RDF-39 to differentiate participants with and without a high risk of DFU development was (AUC (CI) = .805 (.725 to .884)) (Supplemental Figure 1). At the optimal probability cut-off point of 24 points, the RDF-39 yielded a sensitivity of 67.5% and specificity of 84.8%. The effect on posttest probability of disease was 4.44 (positive likelihood ratio (LR+)). Comparable values were seen for the RDF-31 (AUC (CI) = .799 (.720 to .878)) and RDF-13 (AUC (CI) = .825 (.751 to .898). At a cut-off of 18 points, the RDF-31 yielded a sensitivity of 70.0% and specificity of 81.6% (LR+: 3.80). The short-form RDF-13 had an optimal probability cut-off point at 7 points (sensitivity: 77.5%, specificity: 72.9%, LR+: 2.86) to differentiate the risk of ulcer development. The ulcer risk categories of the IWGDF guidelines had lower ability to differentiate patients at risk for future DFU development (AUC (CI) = .623 (.534 to .712)).

Figure 1 Kaplan-Meier curves of groups with variable degrees of sensory loss.

Legend: Median time (days (IQR)) to new DFU is given per group, alongside the number of patients with DFUs in the total period of observation (median 836.5 days (IQR, 459-1078)). Group 1, n=0 DFUs; Group 2, n=2 DFUs (median 711 days (IQR, 620-)); Group 3, n=6 DFUs (median 545 days (IQR, 197.8-857)); Group 4, n=4 DFUs (median 534.5 days (IQR, 247.8-776.3)); Group 5, n=12 DFUs (median 230.5 days (IQR, 129.8-463.5)); Group 6, n=15 DFUs (median 493 days (IQR, 342-645)); Group 7, n=1 DFU (median 124 days).

	0	183	365	548	730	913	1095	1278
No. at risk								
Group 1	6	6	5	5	4	1	1	
Group 2	110	109	103	88	84	54	35	0
Group 3	139	133	112	94	90	51	32	0
Group 4	65	63	57	49	47	20	11	0
Group 5	64	58	45	34	34	16	8	0
Group 6	30	28	20	10	6	0		
Group 7	2	1	1	0				

Cox-regression analysis

Table 2 shows the results of the univariable and multivariable Cox proportional hazards models, comparing the risk of ulceration to controls. In unadjusted analyses, the baseline RDF-39 score was significantly associated with ulcer risk (HR: 1.178 (95%CI: 1.061 to 1.308)). In adjusted analysis, the RDF-39 score (HR: 1.173 (95%CI: 1.086 to 1.267)) and MDRD (HR: 1.022 (95%CI: 1.004 to 1.040)) were associated with an increased risk of ulceration. Based on these results, the estimated logistic regression equation including those parameters showed a sensitivity and specificity for the prediction of DFU of 67.5% and 84.8%, respectively (LR+: 4.44, AUC (CI) = .801 (.722 to .880)).

Figure 2 Kaplan-Meier curves for the time until the first occurrence of new DFU of groups with and without prior DFU.

Legend: Median time (days (IQR)) to new DFU is given per group, alongside the number of patients with DFUs in the total period of observation. No prior DFU, n=16 DFUs (median 537 days (IQR, 275.5-820.8)); Prior DFU, n=24 (median 372.5 (IQR, 155.3-578.8)).

	0	183	365	548	730	913	1095	1278
No. at risk								
No prior DFU	364	356	314	263	252	140	86	0
Prior DFU	52	43	33	20	16	6	4	0

Supplemental Table S4 shows the results of Cox proportional hazards models, comparing ulcer-free survival in patients without prior DFU to controls. In unadjusted analyses, the baseline RDF-39 score was significantly associated with disease-free survival (HR: 1.039 (95%CI: 1.007 to 1.071)). In adjusted analysis, the RDF-39 score (HR: 1.023 (95%CI: 1.000 to 1.047)) and a palpable dorsalis pedis artery (HR: 0.520 (95%CI: 0.293 to 0.921)) were associated with ulcer-free survival. The resultant logistic regression showed an ability to predict ulcer-free survival with an AUC of (CI) = .794 (.671 to .917), sensitivity: 76.5%, specificity: 79.7%, LR+: 3.77.

Table 2 Unadjusted and adjusted hazard ratios for incident diabetic foot ulceration among diabetic patients.

	HR (95%CI), unadjusted	P-value	HR (95%CI), adjusted	P-value
Male sex	1.413 (0.303 to 6.596)	0.660		
Age (years)	1.043 (0.936 to 1.162)	0.445		
Duration of diabetes (years)	0.954 (0.874 to 1.041)	0.290		
Diabetes type 2	1.178 (0.105 to 13.233)	0.894		
Insulin use	0.446 (0.066 to 3.019)	0.408		
BMI (kg/m²)	0.925 (0.817 to 1.047)	0.217		
Systolic blood pressure (mmHg)	0.986 (0.955 to 1.019)	0.409		
Lifetime smoking history	1.398 (0.296 to 6.610)	0.672		
Retinopathy	3.590 (0.610 to 21.139)	0.158		
RDF-39 (points)	1.178 (1.061 to 1.308)	0.002	1.173 (1.086 to 1.267)	<0.0005
Palpable lower extremity arteries				
- Left posterior tibial artery	1.310 (0.166 to 10.320)	0.798		
- Left dorsalis pedis artery	1.377 (0.203 to 9.357)	0.743		
- Right posterior tibial artery	1.673 (0.174 to 16.100)	0.656		
- Right dorsalis pedis artery	1.386 (0.141 to 13.606)	0.780		
HbA1c (mmol/L)	1.053 (1.000 to 1.109)	0.050		
MDRD (ml/min/1.73 m²)	1.012 (0.987 to 1.038)	0.341	1.022 (1.004 to 1.040)	0.016
Total cholesterol (mmol/L)	1.225 (0.628 to 2.387)	0.552		
TG (mmol/L)	0.988 (0.639 to 1.527)	0.957		

Legend: HR, hazard ratio; statistically significant results appear in boldface type ($p < 0.05$); BMI, body mass index; RDF-39, 39-item Rotterdam Diabetic Foot Study Test Battery; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; TG, triglycerides.

Conclusions

This study showed that the degree of sensory loss at the feet of patients with diabetes predicts the development of DFU. Moreover, in both univariable and multivariable analysis, the degree of sensory loss was the most important driver in the development of DFU. The positive likelihood ratio of the prediction model implies that for every false positive there are 4.44 true positives (i.e. patients with incident DFU), suggesting that with this information it is possible to identify patients at risk. Close follow-up of these patients may ultimately help to reduce the incidence of those feared amputations. To our knowledge, this prospective cohort study in patients with diabetes is the first and only to evaluate the risk of incident DFU in relation to the degree of pedal sensory loss, as assessed with a psychometrically validated grading scale^{15,16}. The gloomy fact that DFU is associated with death¹⁷ was also confirmed in our study.

The incidence of ulcer occurrence (4.5 (95%CI: 3.3 to 6.1) per 100 person-years) in this regional teaching hospital was in line with previous reports from the literature (2.2 to 6.8 per 100 person-years)¹⁸⁻²⁰. As the current study underlines, neuropathy is the most important risk factor for DFU development and therefore it is reasonable for clinicians to focus further on this entity in order to prevent progression to tissue breakdown. Especially in the patient without a history of prior ulceration it is judicious to focus on peripheral nerve function, because patients with prior DFU fall in another risk category with consequent screening recommendations⁵. This study also adds that patients with poor renal function should be subjected to lower extremity risk analysis.

Previous studies have shown that symptoms of neuropathy do not necessarily correlate with peripheral nerve function⁸. For example, numbness at the feet is reported when S2PD, M2PD and vibration sense have already become absent in the natural history of loss of sensation, whereas hyperesthesia, hyperalgesia, allodynia and 'wind-up' may occur without overt nerve damage. Patients often report having excellent sensation because they still can feel pain, however, this is not the same as touch and intact protective sensation. Risk groups 1 to 4 in our study had a gradually increasing ulcer incidence rate of 0.76 to 2.78 per 100 person-years. We therefore recommend the use of objective measures of somatosensory function, as such presented in the RDF scales (RDF-39, -31 and -13), in order to equitably estimate the associated hazards of sensory loss.

The RDF grading scales provide an overall estimation of pedal sensory status, from ankle level to hallux, including both extremities. Early to advanced stages of (large fiber) sensory loss are assessed. The RDF-39 has been shown to correlate with postural stability and predicts recurrent falls²¹. The primary outcome of the current study was incident DFU occurring in either foot. Albeit extremity-specific item scores have not been formerly evaluated to be validly summed in a total score, the relative symmetric distribution of sensory loss in both extremities allows making judgments on the contralateral extremity when one side is tested⁹. In regard to monitoring the feet, assessing sensory status is a sensible first step in estimating the chance of DFU occurrence, with consequent recommendations on further risk factor analysis²². The screening frequency may then be more patient tailored. The presented median time to ulcer occurrence may aid this debate since there is no published evidence to support the suggested intervals⁵. Because it is very difficult to predict where the DFU will occur, in the absence of overt risk factors such as Charcot deformities, the general sensory status provided by the RDF sum score will be sufficient in estimating the overall risk of ulceration. A recent study developed the concept of 'ulcer metastasis', showing that 48% of wounds recurred to the contralateral foot and that only 17% of ulcers relapsed at the same anatomical location²³. Adding the RDF scales as measure of neuropathy to current prediction

models of first onset ulceration will likely improve accuracy of detecting the patient at risk, as well as disease-free survival²⁴.

Strengths of our study are the relatively large sample size, the longitudinal study design in an unselected group of patients with diabetes with long-term follow-up and the correlation of sensory loss to risk of ulceration with a validated instrument. Several caveats of our study are important to highlight. First, the RDF-cohort is a hospital-based cohort, with patients at an increased annual risk of foot ulceration compared to the general population (mean: 2.1% (95%CI: 1.52 to 2.29) per year)²⁵. The baseline prevalence of previous DFU was considerable (12.5% (95%CI: 9.3-15.7)) and 24 out of 40 patients (60%) suffering from reulceration during follow-up. However, we do think that the conclusions from our study may be validly extrapolated to different populations, since the majority of the RDF-cohort (n=364) was ulcer free at baseline (IWGDF Risk Categories 0 to 2), as is generally the case for the annually checked primary care population. A recently developed shorter and quicker version of the RDF-39 can estimate the RDF-39 sum score in as few as three tests, from which balance impairment, risk of falls and now risk for ulceration can be predicted. This is especially of use in primary care or the outpatient clinic, yet, external validity has to be determined in future studies.

Second, no (invasive) testing on peripheral artery disease (PAD), other than palpation of arteries, was conducted in RDF-Study participants. As concluded previously from a study that developed a foot ulcer risk model in the primary care setting, the lack of significant contribution of pedal pulses to the likelihood of foot ulceration was also found in our study. PAD is probably only relevant for healing processes, since the limb has to be end-stage ischemic to compromise soft tissue integrity leading to ulceration²⁶. Future studies should at least assess peripheral artery status with Doppler waveforms, although no definite answer is given on which test is superior⁵.

Third, information on foot deformity was only available in a subset of patients. In order not to jeopardize the power of the prediction model, it was decided to exclude those parameters, although they are considered risk factors for foot ulceration²⁷. Finally, the observation that kidney function is negatively associated with diabetic foot disease is confirmed in our population. This is especially illustrated by the fact that patients undergoing intermittent dialysis are at very high risk of developing limb complications as has been reported by others²⁸.

Previous studies advocate the use of ulcer-free survival as outcome measure to assess the effectiveness of management of DFUs^{6,29}. Ulcer-free days as outcome measure is sensible,

since from a patient perspective avoidance of amputation and remaining ulcer-free are most important¹. Prolonging ulcer-free survival presumably preserves life, since DFU is an independent risk factor for death³⁰. Grading somatosensory function in the patient with a history of ulceration may still serve as an adjunct to other risk factor analyses in this vulnerable group of patients, since selective sensory testing have proven to be predictive of ulcer-free survival (negative likelihood ratio: 0.25).

In summary, we have demonstrated that in patients with diabetes degree of sensory loss at baseline relates to the risk of ulceration at follow-up. Patients with more severe stages of sensory loss and worse kidney function are at higher risk of DFU development. This new information may serve as an extension of the currently advised instruments to predict ulceration. Moreover, grading the loss of sensation in patients allows for a closer follow-up by risk stratification and early interventions. Increased surveillance may prevent lower extremity complications from occurring, adding ulcer-free days together with prolongation of life.

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Supplementary material

Supplemental Figure 1 Receiver operating characteristic (ROC) curves.

Abbreviations: IWGDF, International Working Group on the Diabetic Foot risk stratification system; RDF, Rotterdam Diabetic Foot Study Test Battery.

Supplemental Table S1 The Rotterdam Diabetic Foot Study Test Battery scoring sheet.

Left lower extremity	Test result (0 = nonaberrant, 1 = aberrant)	Right lower extremity	Test result (0 = nonaberrant, 1 = aberrant)
S2PD II *		S2PD II *,*	
S2PD I *,*		S2PD I	
S2PD III		S2PD III *,*	
S2PD V *		S2PD V	
S2PD IV *		S2PD IV *	
M2PD II *		M2PD II *	
M2PD III *,*		M2PD III *	
M2PD IV		M2PD IV *	
M2PD I		M2PD I *	
Vibration sense IP *,*		Vibration sense IP *,*	
Vibration sense MM *,*		Vibration sense MM *,*	
S1PD I *,*		S1PD I *,*	
S1PD V *		S1PD V *	
Numbness *	(derived from the MNSI)		
S1PD II *		S1PD II *	
S1PD III *		S1PD III *	
S1PD IV *		S1PD IV *	
Prior ulcer *,*	(scored for any extremity)		
Cold stimulus		Cold stimulus	
Romberg test			
Amputation *,*		Amputation *,*	
Sub-total		Sub-total	
Total RDF-39 score			
Total RDF-31 score			
Total RDF-13 score			

Legend: Roman capitals are indicatives of test locations: I, plantar hallux; II, medial heel; III, first dorsal web; IV, lateral foot; V, plantar fifth toe. S2PD, static two-point discrimination; M2PD, moving two-point discrimination; S1PD, static one-point discrimination (10 g Semmes-Weinstein monofilament); IP, interphalangeal joint; MM, medial malleolus; MNSI, Michigan Neuropathy Screening Instrument. Black stars (*) are indicators of an item included in the 31-item scale and white stars (°) are items included in the 13-item scale.

Supplemental Table S2 Baseline characteristics of patients lost to follow-up.

	Withdrew from study participation (n=32)	Lost to follow-up (n=66)	Dead (n=22)	RDF Study participants available for follow-up (n=296)	P-value
Gender (M/F)	20/12	36/30	12/10	173/123	.868*
Age (median (y), IQR)	64.3 (51.6-71.1)	60.2 (49.1-67.5)	68.4 (64.5-80.6)	64.1 (55.3-70.1)	.001#
Ethnicity (n (%))					.164*
- Caucasian	28 (87.5)	48 (72.7)	19 (86.4)	246 (83.1)	
- Indo-Surinamese	4 (12.5)	5 (7.6)	2 (9.1)	24 (8.1)	
- African	-	4 (6.1)	1 (4.5)	9 (3.0)	
- Asian	-	1 (1.5)	-	6 (2.0)	
- Other	-	8 (12.1)	-	11 (3.7)	
Height (median (m), IQR)	174.0 (168.0-185.0)	172.0 (165.8-180.0)	173.0 (160.0-180)	173.0 (165.0-180.8)	.381#
Weight (median (kg), IQR)	96.6 (80.5-110.3)	86.8 (78.5-106.3)	83.4 (74.8-107.3)	87.0 (76.9-103.0)	.286#
BMI (median (kg/m2), IQR)	29.3 (27.8-35.8)	29.4 (26.1-34.5)	30.5 (25.4-37.4)	29.4 (26.0-33.5)	.710#
Duration of diabetes (median (y), IQR)	16.0 (9.3-25.5)	13.0 (8.0-20.3)	17.0 (10.8-26.5)	16.0 (9.0-25.8)	.228#
Type of diabetes (n (%))					.074*
- Type 1	7 (21.9)	17 (25.8)	-	69 (23.3)	
- Type 2	25 (78.1)	49 (74.2)	22 (100)	227 (76.7)	
Systolic blood pressure (median mmHg, IQR)	131.0 (124.3-144.5)	137.0 (123.0-147.0)	141.0 (126.8-168.3)	136.0 (126.0-147.8)	.443#
Retinopathy (n (%))	5 (21.7)	8 (21.6)	4 (36.4)	49 (25.9)	.761*
Lifetime smoking history (n (%))	15 (78.9)	22 (61.1)	11 (73.3)	138 (62.4)	.429*
Lower limb sensory status					
Neuropathic symptoms° (median score (IQR))	1.0 (0.0-2.0)	1.0 (0.0-2.0)	1.0 (0.3-2.8)	1.0 (0.0-2.0)	.742#
RDF-39 (median score (IQR))	17.0 (12.3-23.0)	17.0 (10.0-23.3)	18.5 (13.8-28.8)	16.0 (8.0-22.0)	.180#
Previous DFU (n (%))	3 (9.4)	11 (16.7)	5 (22.7)	33 (11.1)	.269*

Supplemental Table S2 Baseline characteristics of patients lost to follow-up. (continued)

	Withdrawn from study participation (n=32)	Lost to follow-up (n=66)	Dead (n=22)	RDF Study participants available for follow-up (n=296)	P-value
Previous amputations (n (%))					
- Left extremity	-	2 (3.0)	1 (4.5)	3 (1.0)	.319*
- Right extremity	-	3 (4.5)	-	5 (1.7)	.314*
Palpable lower extremity arteries (%)					
- Left posterior tibial artery	66.7	70.2	45.5	72.9	.255*
- Right posterior tibial artery	66.7	70.2	33.3	71.0	.228*
- Left dorsalis pedis artery	66.7	76.6	16.7	78.0	<.0005*
- Right dorsalis pedis artery	66.7	76.0	40.0	77.6	.002*
Laboratory measurements					
HbA1c (median (mmol/L), IQR)	55.0 (47.8-65.0)	61.5 (55.3-71.0)	63.0 (50.0-79.0)	60.0 (53.0-70.0)	.077#
MDRD (median ml/min/1.73 m ² , IQR)	78.7 (59.3-89.2)	87.5 (68.8-102.0)	56.5 (32.4-80.0)	78.1 (60.3-96.2)	.001#
Total cholesterol (median (mmol/L), IQR)	4.5 (3.8-5.1)	4.1 (3.5-5.1)	3.9 (3.3-4.5)	4.0 (3.5-4.7)	.158#
LDL-C (median (mmol/L), IQR)	2.2 (1.3-2.8)	2.0 (1.6-2.8)	1.8 (1.4-2.2)	1.8 (1.4-2.5)	.328#
HDL-C (median (mmol/L), IQR)	1.5 (1.3-1.8)	1.3 (1.0-1.6)	1.3 (1.1-1.7)	1.3 (1.1-1.6)	.087#
TG (median (mmol/L), IQR)	1.8 (1.1-2.7)	1.6 (1.0-2.6)	1.3 (0.9-2.5)	1.6 (1.0-2.4)	.788#
ApoB (median (g/L), IQR)	0.9 (0.8-1.0)	0.9 (0.7-1.1)	1.0 (0.8-1.1)	0.9 (0.8-1.1)	.856#
Microalbumin (median (mg/L), IQR)	30.5 (7.5-156.0)	13.0 (8.0-40.5)	101.5 (26.0-279.8)	16.0 (7.0-46.5)	.010#

Legend: M, male; F, female; *, Pearson chi-square test; #, Kruskal Wallis test; statistically significant results appear in boldface type (p<0.05); M, male; F, female; IQR, interquartile range; BMI, body mass index; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; ApoB, apolipoprotein B; RDF, Rotterdam Diabetic Foot; *, a subscore on nerve-related neuropathic MNSI items is reported.

Supplemental Table S3 Baseline characteristics of patients with and without prior ulceration.

	No history of DFU (n=364)	History of DFU (n=52)	P-value
Gender (M/F)	204/160	37/15	.039*
Age (median (y), IQR)	63.5 (54.1-69.6)	65.9 (60.6-72.9)	.058 [#]
Ethnicity (n (%))			
- Caucasian	298 (81.9)	43 (82.7)	
- Indo-Surinamese	34 (3.0)	1 (1.9)	
- African	11 (3.0)	3 (5.8)	
- Asian	7 (1.9)	-	
- Other	14 (3.8)	5 (9.6)	
Height (median (m), IQR)	172.9 (165.0-180.0)	180.0 (170.3-185.0)	.001[#]
Weight (median (kg), IQR)	87.0 (77.0-102.6)	90.1 (80.0-115.8)	.098 [#]
BMI (median (kg/m²), IQR)	29.3 (26.3-33.6)	30.4 (25.2-34.6)	.789 [#]
Duration of diabetes (median (y), IQR)	16.0 (9.0-25.0)	17.0 (10.3-27.3)	.463 [#]
Type of diabetes (n (%))			.100*
- Type 1	86 (23.6)	7 (13.5)	
- Type 2	278 (76.4)	45 (86.5)	
Systolic blood pressure (median mmHg, IQR)	135.0 (125.0-147.0)	140.0 (130.3-156.8)	.022[#]
Retinopathy (n (%))	49 (20.8)	17 (70.8)	<.0005*
Lifetime smoking history (n (%))	157 (61.8)	29 (78.4)	.050*
Lower limb sensory status			
Neuropathic symptoms ^o (median score (IQR))	1 (0-2)	2 (1-3)	<.0005[#]
RDF-39 (median score (IQR))	15 (8-20)	32 (23.3-35)	<.0005[#]
Number of previous DFUs			
- One	-	39	
- Two	-	11	
- Three	-	1	
- Four	-	1	
Previous amputations (n (%))			
- Left extremity	-	6 (11.5)	
- Right extremity	-	8 (15.4)	
Palpable lower extremity arteries (%)			
- Left posterior tibial artery	73.5	34.8	.001*
- Right posterior tibial artery	72.7	54.2	.096*
- Left dorsalis pedis artery	82.4	47.8	.001*
- Right dorsalis pedis artery	82.1	54.2	.007*
Laboratory measurements			
HbA1c (median (mmol/L), IQR)	60.0 (53.8-70.0)	59.0 (49.0-70.8)	.841 [#]
MDRD (median ml/min/1.73 m ² , IQR)	79.6 (62.4-96.6)	61.8 (43.3-95.7)	.006[#]
Total cholesterol (median (mmol/L), IQR)	4.0 (3.5-4.8)	4.3 (3.7-5.0)	.295 [#]
LDL-C (median (mmol/L), IQR)	1.8 (1.4-2.5)	2.1 (1.2-2.7)	.769 [#]
HDL-C (median (mmol/L), IQR)	1.3 (1.1-1.6)	1.3 (1.1-1.7)	.885 [#]
TG (median (mmol/L), IQR)	1.6 (1.0-2.4)	1.6 (0.9-2.8)	.873 [#]
ApoB (median (g/L), IQR)	0.9 (0.8-1.1)	0.9 (0.7-1.1)	.400 [#]
Microalbumin (median (mg/L), IQR)	15.5 (8.0-49.3)	35.0 (11.0-143.0)	.013[#]

Legend: M, male; F, female; *, Pearson chi-square test; [#], Mann-Whitney U test; statistically significant results appear in boldface type (p<0.05); M, male; F, female; IQR, interquartile range; BMI, body mass index; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; ApoB, apolipoprotein B; RDF, Rotterdam Diabetic Foot; ^o, a subscore on nerve-related neuropathic MNSI items is reported.

Supplemental Table S4 Unadjusted and adjusted hazard ratios for ulcer-free survival among diabetic patients without prior DFU.

	HR (95%CI), unadjusted	P-value	HR (95%CI), adjusted	P-value
Male sex	1.154 (0.781 to 1.705)	0.473		
Age (years)	1.003 (0.978 to 1.029)	0.809		
Duration of diabetes (years)	1.000 (0.977 to 1.024)	0.995		
Diabetes type 2	1.199 (0.668 to 2.151)	0.543		
Insulin use	0.747 (0.394 to 1.417)	0.372		
BMI (kg/m²)	0.996 (0.956 to 1.009)	0.829		
Systolic blood pressure (mmHg)	0.997 (0.985 to 1.037)	0.629		
Lifetime smoking history	1.370 (0.923 to 2.033)	0.119		
Retinopathy	0.856 (0.514 to 1.425)	0.549		
RDF-39 (points)	1.039 (1.007 to 1.071)	0.016	1.023 (1.000 to 1.047)	0.050
Palpable lower extremity arteries				
- Left posterior tibial artery	0.987 (0.502 to 1.938)	0.969	1.723 (0.946 to 3.136)	0.075
- Left dorsalis pedis artery	1.858 (0.981 to 3.519)	0.057		
- Right posterior tibial artery	1.196 (0.622 to 2.299)	0.591	0.520 (0.293 to 0.921)	0.025
- Right dorsalis pedis artery	0.504 (0.269 to 0.944)	0.032		
HbA1c (mmol/L)	0.997 (0.983 to 1.012)	0.733		
MDRD (ml/min/1.73 m²)	1.005 (0.995 to 1.015)	0.311		
Total cholesterol (mmol/L)	1.180 (0.995 to 1.458)	0.126	1.197 (0.995 to 1.441)	0.056
TG (mmol/L)	1.013 (0.892 to 1.152)	0.840		

Legend: HR, hazard ratio; statistically significant results appear in boldface type ($p < 0.05$); BMI, body mass index; RDF-39, 39-item Rotterdam Diabetic Foot Study Test Battery; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; TG, triglycerides.

Treatment

PART IV

Chapter XII

Optimization of surgical outcome in lower extremity nerve decompression surgery

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Abstract

Background

There is still debate whether the surgical release of entrapped lower extremity nerves reduces complaints of associated neuropathy and results in gain of sensory function. The aim of this study is to investigate which factors are associated with a favorable surgical outcome, by follow-up of patients previously participating in a randomized controlled trial.

Methods

We evaluated the 5-years follow-up of diabetic patients previously participating in the Lower Extremity Nerve entrapment Study (LENS). Visual Analogue Pain scores, satisfaction, complaints, quality of life (QoL, SF-36 and EQ-5D), sensory function and incident ulceration and amputations were assessed. Differences between patients who underwent unilateral versus bilateral decompressions were investigated.

Results

31 of the original 42 LENS study participants were measured, of which eight patients underwent additional decompression of the contralateral leg, after 12 months LENS follow-up. At 5-years, bilateral operated patients (n=8) had significantly lower pain scores and higher QoL compared to unilateral operated patients (n=23), were younger, had a lower age when diagnosed with diabetes and a lower body mass index (BMI) at baseline. Pain scores of the additional decompressed leg decreased similarly as the initial decompressed leg, during follow-up. Patients with severe pre-operative sensory loss did worse. 41.2% of the LENS-FU subjects underwent or considers having contralateral surgery.

Conclusions

Our results suggest that the beneficial effects of lower extremity nerve decompression surgery are reserved for a select group of patients, of which pre-operative nerve damage, age, duration of diabetes and BMI are important effect modifiers.

Introduction

With the world facing an epidemic of obesity and consequent diseases like diabetes mellitus (DM), morbidities associated with the latter are also rapidly becoming more prevalent¹⁻³. The diffuse injury to peripheral nerves is defined as diabetic sensorimotor polyneuropathy (DSP), with up to 50% of patients with DM are confronted with pain, tingling, burning and loss of sensation in both the upper and lower extremities⁴⁻⁶. Neuropathy compromises quality of life and predisposes patients to diabetic foot ulcers and consequent lower extremity amputations⁷.

It is now agreed that among patients with DM, localized nerve compressions are more prevalent⁸. These patients' peripheral nerves are more easily entrapped in areas of anatomical narrowing due to an altered glucose metabolism, resulting in swollen nerves and stiffer connective tissues^{9,10}. Carpal tunnel syndrome, for example, has a prevalence of 2% in the general population, but this percentage increases up to 14% in patients with DM and 30% in those with DSP¹¹. For the lower extremities, these numbers are not as well known. The treatment of choice in compression neuropathies remains surgical.

The Hoffman-Tinel sign can be used to diagnose nerve entrapment and is positively correlated to severeness of symptoms of neuropathy and has a predictive value regarding successful pain reduction from lower extremity nerve decompression (LEND) surgery^{12,13}. Although criticized, accumulating evidence suggests favorable effects of LEND surgery in selected patients, with fewer complaints of neuropathy, return of protective sensation and a lower incidence of ulceration and amputation reported postoperatively¹⁴⁻¹⁷. However, a recent study on this topic did not report beneficial outcomes at mid-term follow up (12 months) regarding nerve conduction parameters¹⁸, static two-point discrimination, ability to feel a 10 g monofilament¹⁵, stability¹⁹ and health-related quality of life²⁰.

As diabetes is a chronic disease, we thought it would be appropriate to assess the long-term effects of LEND surgery, with a 5-year follow-up of patients previously participating in the randomized controlled Lower Extremity Nerve entrapment Study (LENS)¹⁵. By interpreting these results, we aim to give insights into factors influencing surgical outcomes and thereby helping clinicians make an adequate estimation of who, and to what extent, are likely to benefit from this type of surgery.

Materials and methods

Study design and subjects

A blinded follow-up study of patients previously participating in the LENS study, was carried out^{10,15,18-20}. In- and exclusion criteria of that study are previously reported¹⁵. In short, 42 diabetic patients with signs of bilateral compression neuropathies of the common peroneal nerve, superficial peroneal nerve, deep peroneal nerve and tibial nerve at the tarsal tunnel and complaints of painful neuropathy were included. The patient leg was randomized to receive either LEND surgery or serve as control. Patients were followed for 12 months.

Between May 2016 and August 2016 patients were measured for 5-year follow-up at the outpatient clinic of Utrecht University Medical Center, Utrecht, the Netherlands. Inclusion criteria were: patients eligible for follow-up and provision of informed consent. Beforehand, the patient was instructed not to tell which leg or legs were operated. The outcome assessor was blinded. The tests were done in a quiet soundproof room, kept at a constant temperature. The data during follow-up of all participants of the initial LENS study were also used for analysis. All subjects provided written informed consent. The institutional review board and the Medical Ethical Committee of Utrecht Medical University Center, Utrecht, the Netherlands approved the studies (METC 16-339/D).

Baseline characteristics

To assess possible selection bias, LENS study baseline demographic characteristics and sensibility tests of patients willing to participate in this follow-up study (LENS-FU study) were compared to patients that did not. Former LENS study participants who underwent additional LEND surgery on the other extremity, after the end of the LENS study follow-up (12 months), were compared to participants that underwent unilateral surgery. Baseline demographic characteristics, sensibility tests, nerve conduction studies, ultrasound measurements and questionnaire data were compared. Factors that could have influenced people to undergo a second operation were thereby investigated.

Questionnaire data

Visual Analogue Scale (VAS) scores regarding pain were assessed for both legs separately. The 36-item Short-Form Health Survey (SF-36) and the EuroQol 5 Dimensions (EQ-5D) were used to study health-related quality of life. The domains of the EQ-5D were evaluated based on the ratio of three possible responses per domain. The EQ-5D index score was calculated from its domains, based on a time trade-off tariff, determined for a Dutch population²¹. The VAS of the EuroQol was used to let patients visually value their current health state. These outcomes were compared with baseline and follow-up measurements.

Patients were asked on the subjective effects of surgery regarding general complaints (burning, tingling, itching pain, numbness), change in sensation and pain. General complaints were scored as improved, slightly improved, unchanged and worsened. Change in sensation and pain was scored with three successive integers: none, temporarily and permanently and the dichotomous options improvement and deterioration. Satisfaction with the effects of surgery was graded (0: no satisfaction, 10: complete satisfaction).

Sensory tests

Static- and moving two-point discrimination (S2PD and M2PD, Disk-Criminator™), static one point discrimination (S1PD, set of Semmes-Weinstein monofilaments, 0.008 – 300 g), vibration sense with a Rydel-Seiffer tuning fork, cold/warmth tests, Romberg's test, Tinel's sign at the tarsal tunnel and the Michigan Neuropathy Screening Instrument (MNSI) were assessed using the protocol of a previous study²², as well as incident ulceration and lower extremity amputation since 12 months LENS study follow-up. Comparisons between baseline data and follow-up measurements of the LENS study (at 3, 6 and 12 months) were made. Percent change from before to after surgery was calculated (percent difference between the operated leg and non-operated leg as denominator). To assess overall sensory status at 5 years follow-up, a composite score was calculated per patient using the 39 items of the Rotterdam Diabetic Foot Study Test Battery (RDF-39)²³.

Data analysis

Both legs of patients were considered matched pairs and related variables were analyzed as dependent. The unilateral and bilateral subgroups were analyzed as independent. Independent t-tests and Mann-Whitney U tests for continuous variables and Chi-squared and Fisher's exact tests for binominal data were used to assess statistical differences. Differences between the legs of individuals at 5-year follow-up were assessed with a Wilcoxon signed rank test for continuous outcomes and a McNemar's test for binominal variables. A correction for correlated observations was carried out in the analysis of outcomes at multiple follow-up moments considering the longitudinal study design as well as repeated measurements for both legs of individuals. A generalized linear model with a residual covariance matrix (i.e. generalized estimation equation) was used for continuous outcomes per leg (e.g. VAS), SF-36 and EQ-5D, to correct for correlated observations. A mixed logistic model with random intercept was used for dichotomous outcomes (e.g. S1PD and S2PD). All statistical analysis was carried out using SPSS Statistics 23.0 (IBM, New York, USA) and SAS. P-values below .05 (two-sided) were considered statistically significant.

Results

General characteristics

For this follow-up study (LENS-FU study), 31 patients (mean (SD) age 66.2 y (11.0)) were measured, with a mean 4.6 y (0.5) after initial LENS surgery. Eleven of the original 42 patients were lost to follow-up (five patients died, three patients were not able to be contacted and three patients did not want to participate). One patient did fill in the questionnaires, but sensory status was not assessed. Of the patients eligible for long-term follow-up, 23 patients were operated in one leg and eight bilaterally. Patients that were operated bilaterally were satisfied with the initial unilateral surgery and were operated on the other extremity after 12 months of LENS study follow-up. Patients participating in the LENS-FU study and those who were lost to follow-up, did not differ significantly regarding baseline LENS study demographic and laboratory measurements. Group characteristics are displayed in Table 1.

Comparing bilateral operated to unilateral operated patients

Bilateral operated patients, compared to unilateral operated patients, were younger, had a significant lower age when diagnosed with DM (mean 33.9 y (SD, 17.0) vs. 50.2 y (14.0)), mean difference of 16.3 (95% CI 3.86 to 28.74, $t(29) = 2.68$, $p = .012$) and a trend was observed towards a lower body mass index (BMI). No other differences were ascertained regarding baseline LENS-FU study demographics and laboratory measurements (Table 2), except for a significant lower triglyceride level in the bilateral operated patients. No clear differences were seen in baseline electro diagnostic data (Table 3).

Table 1 Baseline demographic data of patients included in the LENS and LENS-FU study.

	LENS (n=42)		LENS-FU (n=31)	Patients not eligible for LENS-FU (n=11)	Comparison between LENS-FU and patients not eligible for LENS-FU. P-value.
Gender (M/F)	25/17		18/13	7/4	1,000 ^d
Age (mean (y), SD)	60.9 (11.4)		61.6 (11.1)	58.8 (12.5)	.475 ^b
Height (mean (m), SD)	175.7 (9.0)		176.1 (9.4)	174.7 (8.0)	.670 ^b
Weight (mean (kg), SD)	89.8 (17.2)		92.1 (16.2)	85.6 (20.1)	.351 ^b
BMI (mean (kg/m²), SD)	29.0 (4.7)		29.4 (4.3)	27.8 (5.6)	.358 ^b
Duration of diabetes (median (y), IQR)	13.1 (14.6)		12.7 (9.7)	21.9 (27.0)	.553 ^c
Type of diabetes (n (%))					1,000 ^d
- Type 1	10 (23.8)		7 (22.6)	3 (27.3)	
- Type 2	32 (76.2)		24 (77.4)	8 (72.7)	
Systolic blood pressure (mmHg, SD)	139.8 (20.1)		141.5 (19.7)	135.4 (21.4)	.396 ^b
Diastolic blood pressure (mmHg, SD)	77.4 (9.1)		77.1 (8.6)	78.3 (10.0)	.711 ^b
Smoking (n (%))					.756 ^a
- Never smoker	18 (42.9)		13 (41.9)	5 (45.5)	
- Past smoker	15 (35.7)		12 (38.7)	3 (27.3)	
- Current smoker	9 (21.4)		6 (19.4)	3 (27.3)	
Retinopathy (n (%))	8 (19.0)		6 (19.4)	2 (18.2)	1,000 ^d
Preoperative laboratory measurements					
- HbA1c (median, mmol/mol (IQR))	53.0 (23.0)		52.0 (15.0)	67.5 (21.0)	.072 ^c
- HDL (median, mmol/mol (IQR))	1.3 (51)		1.3 (65)	1.2 (4)	.651 ^c
- LDL (median, mmol/mol (IQR))	2.3 (95)		2.2 (1.0)	2.4 (1.4)	1,000 ^c
- GFR (median, mL/min/1.73 m ² IQR)	61.0 (0.0)		61.0 (0.0)	61.0 (11.75)	.623 ^c
- Micro albumin (median, mg/mmol IQR)	9.0 (52.0)		7.0 (10.0)	65.9 (290.6)	.001 ^c
- Triglyceride (median, mmol/L (IQR))	2.1 (1.52)		2.0 (1.48)	2.3 (2.0)	.618 ^c
Preoperative ultrasound findings in operated leg					
- Cross sectional area of tibial nerve					
o Tarsal tunnel, mm ² (SD)	8.45 (3.99)		8.96 (5.17)	7.28 (3.00)	.360 ^b
o Cranial to tarsal tunnel, mm ² (SD)	8.08 (3.48)		7.55 (3.58)	7.67 (4.55)	.935 ^b
- Thickness-to-width of tibial nerve					
o Tarsal tunnel, mm ² (SD)	0.64 (0.12)		0.57 (0.14)	0.64 (0.25)	.289 ^b
o Cranial to tarsal tunnel, mm ² (SD)	0.69 (0.10)		0.60 (0.14)	0.71 (0.18)	.049 ^b
- Flexor retinaculum, mm ² (SD)	1.07 (0.22)		1.21 (0.61)	0.90 (0.21)	.146 ^b

Table 1 Baseline demographic data of patients included in the LENS and LENS-FU study. (continued)

	LENS (n=42)	LENS-FU (n=31)	Patients not eligible for LENS-FU (n=11)	Comparison between LENS-FU and patients not eligible for LENS-FU. P-value.
Prior ulceration (n (%))	1 (2.4)	1 (3.2)	0 (0.0)	Operated leg vs. control leg
Preoperative S1PD with 10 g monofilament, intervention leg vs. control leg				
- Number out of 10 test sides (mean (SD))	4.4 (3.1) vs. 4.1 (3.2)	4.0 (3.0) vs. 3.8 (3.0)	5.6 (3.5) vs. 4.9 (3.6)	173 ^b
- At hallux pulp (n (%))	17 (40.5) vs. 15 (35.7)	12 (38.7) vs. 11 (35.5)	5 (45.5) vs. 4 (36.4)	.695 ^a
- At dorsum first web space (n (%))	22 (52.4) vs. 22 (52.4)	16 (51.6) vs. 16 (51.6)	6 (54.5) vs. 6 (54.5)	.867 ^a
- At fifth toe pulp (n (%))	22 (52.4) vs. 22 (52.4)	15 (48.4) vs. 16 (51.6)	7 (63.6) vs. 6 (54.5)	.867 ^a
Preoperative S2PD (≤ 15 mm), intervention leg vs. control leg				Operated leg vs. control leg
- Number out of 10 test sides (median (IQR))	1.0 (2.0) vs. .5 (2.0)	1.0 (2.0) vs. 1.0 (2.0)	1.0 (1.0) vs. 0.0 (1.0)	.592 ^c
- At hallux pulp (n (%))	8 (19.0) vs. 7 (16.7)	6 (19.4) vs. 4 (12.9)	2 (18.2) vs. 3 (27.3)	.353 ^d
- At dorsum first web space (n (%))	8 (19.0) vs. 7 (16.7)	8 (25.8) vs. 6 (19.4)	0 (0.0) vs. 1 (9.1)	.654 ^d
- At fifth toe pulp (n (%))	8 (19.0) vs. 6 (14.3)	7 (22.6) vs. 6 (19.4)	1 (9.1) vs. 0 (0.0)	.172 ^d
Side of LEND surgery (n (n))				
- Right leg (additional left leg)	20 (5)	13 (5)	7	
- Left leg (additional right leg)	22 (3)	18 (3)	4	

Abbreviations: M, male; F, female; BMI, Body Mass Index; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; GFR, glomerular filtration ratio; S1PD, static one-point discrimination; S2PD, static two-point discrimination; MNSI, Michigan Neuropathy Screening Instrument; LEND, Lower Extremity Nerve Decompression; ^a, Chi square test; ^b, independent t-test; ^c, Mann-Whitney U-test (exact significance [2*(1-tailed significance)]); ^d, Fisher's Exact test.

Table 2 Differences in unilateral and bilateral operated LENS-FU study participants.

	Unilateral operated patients (n=23)	Bilateral operated patients (n=8)	Difference between groups, P value
Gender (M/F)	12/11	6/2	.412 ^d
Age (mean (y), SD)	63.6 (11.5)	56.0 (7.6)	.094 ^b
Height (mean (m), SD)	174.4 (8.8)	181.1 (9.9)	.079 ^b
Weight (mean (kg), SD)	92.4 (15.9)	88.1 (17.6)	.533 ^b
BMI (mean (kg/m²), SD)	30.2 (3.6)	26.9 (5.4)	.057 ^b
Duration of diabetes (median (y), IQR)	11.7 (6.0)	18.1 (23.1)	.091 ^c
Type of diabetes (n (%))			.335 ^d
- Type 1	4 (17.4)	3 (37.5)	
- Type 2	19 (82.6)	5 (62.5)	
Systolic blood pressure (mmHg, SD)	143.5 (20.4)	136.0 (17.8)	.370 ^b
Diastolic blood pressure (mmHg, SD)	77.8 (9.0)	75.1 (8.7)	.478 ^b
Smoking (n (%))			.805 ^a
- Never smoker	9 (39.1)	4 (50.0)	
- Past smoker	9 (39.1)	3 (37.5)	
- Current smoker	5 (21.7)	1 (12.5)	
Retinopathy (n (%))	4 (17.4)	2 (25.0)	.645 ^d
Preoperative laboratory measurements			
- HbA1c (median mmol/mol (IQR))	51.5 (9.0)	69.5 (41.0)	.277 ^c
- HDL (median mmol/L (IQR))	1.3 (.4)	1.2 (1.1)	.611 ^c
- LDL (median mmol/L (IQR))	2.2 (1.0)	2.5 (1.2)	1.000 ^c
- GFR (median (IQR))	61.0 (12.0)	61.0 (0.0)	.349 ^c
- Micro albumin (median mg/L (IQR))	6.5 (7.5)	10.0 (108.0)	.249 ^c
- Triglyceride (median mmol/L (IQR))	2.2 (1.3)	1.2 (.8)	.007 ^c
Preoperative ultrasound findings in operated leg			
- Cross sectional area of tibial nerve			
o Tarsal tunnel, mm ² (SD)	9.36 (5.94)	7.82 (1.31)	.476 ^b
o Cranial to tarsal tunnel, mm ² (SD)	7.97 (4.03)	6.35 (1.32)	.277 ^b
- Thickness-to-width of tibial nerve			
o Tarsal tunnel, mm ² (SD)	0.58 (0.13)	0.56 (0.17)	.750 ^b
o Cranial to tarsal tunnel, mm ² (SD)	0.61 (0.14)	0.58 (0.14)	.646 ^b
- Flexor retinaculum, mm ² (SD)	1.26 (0.69)	1.05 (0.22)	.405 ^b

Table 2 Differences in unilateral and bilateral operated LENS-FU study participants. (continued)

	Unilateral operated patients (n=23)	Bilateral operated patients (n=8)	Difference between groups, P value	
Prior ulceration (n (%))	1 (4.3)	0 (0.0)	Operated leg vs. operated leg	Control leg vs. control leg
Preoperative S1PD with 10 g monofilament, intervention leg vs. control leg				
- Number out of 10 test sides (n (SD))	4.1 (3.2) vs. 3.9 (2.9)	3.8 (2.5) vs. 3.5 (3.5)	.761 ^b	.769 ^b
- At hallux pulp (n (%))	7 (30.4) vs. 9 (39.1)	5 (62.5) vs. 2 (25.0)	.206 ^d	.667 ^a
- At dorsum first web space (n (%))	12 (52.2) vs. 13 (56.5)	4 (50.0) vs. 3 (37.5)	1.000 ^d	.433 ^d
- At fifth toe pulp (n (%))	11 (47.8) vs. 11 (47.8)	4 (50.0) vs. 5 (62.5)	1.000 ^d	.685 ^d
Preoperative S2PD (≤ 15 mm), intervention leg vs. control leg				
- Number out of 10 test sides (median (IQR))	1.0 (2.0) vs. 1.0 (2.0)	.5 (6.0) vs. .5 (3.0)	.982 ^c	.912 ^c
- At hallux pulp (n (%))	4 (17.4) vs. 3 (13.0)	2 (25.0) vs. 1 (12.5)	.634 ^d	1.000 ^d
- At dorsum first web space (n (%))	6 (26.1) vs. 5 (21.7)	2 (25.0) vs. 1 (12.5)	1.000 ^d	1.000 ^d
- At fifth toe pulp (n (%))	5 (21.7) vs. 4 (17.4)	2 (25.0) vs. 2 (25.0)	1.000 ^d	.634 ^d
Side of LEND surgery (n (n))				
- Right leg (additional left leg)	8	5 (5)		
- Left leg (additional right leg)	15	3 (3)		

Abbreviations: M, male; F, female; BMI, Body Mass Index; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; GFR, glomerular filtration ratio; S1PD, Static one-point discrimination; S2PD, Static two-point discrimination; MNSI, Michigan Neuropathy Screening Instrument; LEND, Lower Extremity Nerve Decompression; ^a, Chi square test; ^b, independent t-test; ^c, Mann-Whitney U test (exact significance [2*(1-tailed significance)]); ^d, Fisher's Exact test.

Table 3 Baseline electro diagnostic data of patients participating in the LENS-FU study.

	Unilateral operated patients (n=33) Mean (SD)	Bilateral operated patients (n=8) Mean (SD)	Comparison (p-value)
Peroneal nerve			
- Extensor digitorum brevis muscle			
• Distal CMAP amplitude, mV	2.9 (2.4)	3.6 (3.9)	.563 ^a
• Distal CMAP duration, milliseconds	4.7 (1.6)	4.1 (2.6)	.413 ^a
• Distal motor latency, milliseconds	4.4 (1.0)*	4.4 (3.9)*	.696 ^b
• Motor conduction velocity: lower leg, m/s	40.5 (6.2)	27.9 (18.3)	.095 ^a
• Motor conduction velocity: fibular head, m/s	44.4 (6.1)	29.9 (19.5)	.075 ^a
• Area drop: lower leg, %			
• Area drop: fibular head, %			
- Tibialis anterior muscle			
• Distal CMAP amplitude, mV	4.9 (1.4)	5.4 (1.7)	.421 ^a
• Motor conduction velocity, m/s	53.0 (14.0)*	43.5 (11.8)*	.013 ^b
- Superficial peroneal nerve			
• SNAP amplitude, mV	2.0 (4.3)*	0.0 (4.0)*	.368 ^b
• Sensory conduction velocity, m/s	39.5 (44.3)*	0.0 (35.5)*	.056 ^b
Tibial nerve			
- Abductor hallucis muscle			
• Distal CMAP amplitude, mV	4.5 (3.9)	5.8 (3.8)	.446 ^a
• Distal CMAP duration, ms	5.0 (1.7)*	5.6 (2.1)*	.368 ^b
• Distal motor latency, ms	4.4 (1.2)*	4.7 (1.6)*	.504 ^b
• Motor conduction velocity, m/s	40.1 (6.3)*	35.5 (10.0)*	.237 ^b

Abbreviations: LENS-FU, Lower Extremity Nerve entrapment Study-Follow Up; *, Median (inter quartile range); CMAP, compound muscle action potential; mV, millivolts; ms, millisecond, ^a, independent t-test; ^b, Mann-Whitney U-test.

Visual analogue scale for pain

At 12 months, statistically significant differences in VAS pain scores (mean difference 2.39 (standard error (SE) 1.1, $t(143) = -2.17$, $p = .032$)) were observed in the bilateral compared to unilateral operated patients (mean estimate 1.8 (SE .96) vs. 4.3 (SE, .48)). The eight patients that underwent additional contralateral surgery differed significantly between legs at that time (mean difference 5.24 (SE .81, $t(143) = 6.44$, $p < 0.001$)). Pain increased significantly between 12 months and 5-years follow-up in both legs of unilateral operated patients. However, pain decreased in the additional decompressed leg of bilateral operated patients (mean difference -1.55 (.98), $t(141) = 1.58$, $p = .12$). After five years, no significant differences in VAS pain scores were seen between the two groups or compared to baseline. Further details are plotted in Figure 1.

Figure 1 VAS pain scores of uni- and bilateral operated patients.

Legend:

[†] significantly different compared to pre-operative value ($p \leq .05$)

^{*} significantly different between uni- vs. bilateral LEND ($p \leq .05$)

[°] significantly different between decompressed vs. control leg ($p \leq .05$)

Quality of life: SF-36 and EQ-5D

Preoperatively, higher scores on SF-36 domains, except for the role-physical and role-emotional domains ($p > .05$), were observed in future bilateral operated patients (Figure 2). Regarding general health at 5-year follow-up, a significant decrease of 9.5 points (SE 3.45, $t(40) = -2.67$, $p = .011$) was observed for unilateral operated patients, compared to the preoperative state (mean estimate 35.6 (SE 3.45) vs. 44.8 (SE 3.41)). Five years postoperatively, higher scores on all domains were observed in the bilateral compared to unilateral operated patients, except for physical functioning (decrease of 17.5 points (SE 7.44, $t(40) = -2.35$, $p = .024$)).

Figure 2 Short Form 36 (patient level), stratified into unilateral and bilateral LEND surgery:

Legend: * significantly different compared to pre-operative scores ($p \leq .05$).

EQ-5D index scores decreased to 56.7 (SE .06) for unilateral operated patients and to 56.9 (.11) for bilateral operated patients, respectively, and did not significantly differ from preoperative and 12-month postoperative scores ($p > .05$). EQ-5D VAS scores increased compared with preoperative and 12 months' postoperative values (to 69.1 (SE 5.86), $p > .05$) for bilateral- and decreased for unilateral operated patients (to 55.0 (SE 3.33), $p > .05$). At five years follow-up, EQ-5D VAS scores were significantly higher for bilateral- compared to unilateral operated patients (difference of 14.1 (SE 6.74, $t(40) = 2.09$, $p = .004$)), see Figure 3.

Figure 3 Quality of life (EQ-5D), stratified into unilateral and bilateral LEND surgery.

Legend: * significantly different between uni- vs. bilateral LEND ($p \leq .05$).

Questionnaire data

During follow-up, significant proportional differences in favor of the decompressed leg were observed regarding general complaints (burning, tingling, itching pain, numbness) (35.5% vs. 9.7%, $p = .021$), sensation (54.8% vs. 22.6%, $p = .006$) and pain (48.4% vs. 22.6%, $p = 0.021$). At 5-years follow-up, significant differences were observed between decompressed and

non-decompressed legs regarding subjective improvement in sensation (35.5 vs. 9.7%, $p = .021$) and decrease in pain (35.5% vs. 12.9%, $p = .039$). The treatment effect was scored with a median 5 points out of 10 (IQR, 5). 25.8% of LENS-FU participants underwent bilateral decompression, 26.1% of unilateral operated patients considered to undergo LEND surgery of the contralateral leg. The latter indicates that 41.2% of the LENS-FU subjects underwent or considers having contralateral surgery. A more permanent improvement in pain was reported in the bilateral operated group (13% vs. 50%, $p = 0.016$). The number of patients reporting permanent worsening of pain was significantly higher in contralateral legs of unilateral operated patients (43.4% vs. 0.0%, $p = 0.023$).

Sensory tests

Patients participating in this follow-up study did not differ regarding sensory status at LENS baseline, compared to those lost to follow-up ($n=11$) (Table 1). 5-year postoperative values of S1PD and S2PD at the hallux, first dorsal web, and the fifth toe did not show significant differences compared with the preoperative, 3, 6 and 12-months postoperative values in both the uni- versus bilateral operated patients ($p > .05$) (Table 4). Two patients from the unilateral operated group developed a foot ulcer in the decompressed leg, in which a hallux amputation was necessary in one patient. At 5-years follow-up, the median RDF-39 score was 33 (IQR, 24 – 34), indicative of severe sensory loss (i.e. aberrant S2PD, M2PD, vibration sense and loss of protective sensation). RDF-39 scores of LENS-FU participants were compared to those from a population of diabetics ($n=416$) with varying degrees of sensory loss and a population of healthy controls ($n=196$) (Figure 4)^{23,24}. The high median score is suggestive for severe pre-existent nerve damage in LENS-FU participants.

Table 4 Sensory tests of participants in LENS-FU study, at 5 years follow-up.

	Unilateral decompression (n=22)	Contralateral control (n=22)	Differences (%)	P-value	Bilateral decompression (n=8)	Opposite extremity	P-value
S2PD > 15 mm (n (%))							
- First toe pulp	17 (81.0)	16 (72.2)	+6.3	.625 ^b	5 (62.5)	6 (75.0)	1.000 ^b
- Medial heel	16 (72.7)	19 (86.4)	-15.8	.250 ^b	7 (87.5)	7 (87.5)	1.000 ^b
- Dorsum first web space	20 (90.0)	19 (86.4)	+5.3	1.000 ^b	8 (100)	8 (100.0)	-
- Lateral foot	17 (77.3)	17 (77.3)	0	1.000 ^b	6 (75.0)	5 (62.5)	1.000 ^b
- Fifth toe pulp	19 (86.4)	18 (81.8)	+5.6	1.000 ^b	5 (62.5)	6 (75.0)	1.000 ^b
M2PD > 15 mm (n (%))							
- First toe pulp	16 (76.2)	17 (77.3)	-5.9	1.000 ^b	5 (62.5)	6 (75.0)	1.000 ^b
- Medial heel	16 (72.2)	17 (77.3)	-5.9	1.000 ^b	6 (75.0)	6 (75.0)	1.000 ^b
- Dorsum first web space	17 (77.3)	18 (81.8)	-5.6	1.000 ^b	6 (75.0)	6 (75.0)	1.000 ^b
- Lateral foot	15 (68.2)	18 (81.8)	-16.7	.250 ^b	4 (50.0)	5 (62.5)	1.000 ^b
Median vibration sense (IQR)							
- Medial malleolus	2.5 (0 – 5.0)	3.5 (0 – 5.0)	-2.9	0.526 ^a	1.5 (0.3 – 4.8)	3.3 (0 – 5.8)	0.500 ^a
- IP joint hallux	0 (0 – 2.8)	0 (0 – 0.5)	0	0.228 ^a	0	0 (0 – 1.5)	0.593 ^a
Median S1PD (IQR) (g)*							
- First toe pulp	10 (5.0 – 14.0)	26 (10 – 180)		0.414 ^a	33 (4.5 – 60)	6.0 (1.8 – 47)	0.109 ^a
- Medial heel	8 (4.0 – 26)	8 (2.0 – 26)		0.722 ^a	60 (1.4 – 100)	37.5 (3.5 – 70.0)	0.686 ^a
- Dorsum first web space	15 (1.2 – 60)	8 (2.5 – 60)		0.445 ^a	15 (1.0 – 300)	6 (1.0 – 140.0)	0.042 ^a
- Lateral foot	8 (2.0 – 26)	8 (2.0 – 26)		0.289 ^a	15 (1.4 – 60)	63.0 (3.6 – 250.0)	0.233 ^a
- Fifth toe pulp	18 (6.0 – 80)	10 (4.5 – 90)		0.730 ^a	4.0 (1.7 – 14.0)	26.0 (4.0 – 100.0)	0.715 ^a
S1PD > 300 g (n (%))							
- First toe pulp	4 (19.0)	7 (31.8)	-42.9	0.625 ^b	4 (50.0)	4 (50.0)	1.000 ^b
- Medial heel	1 (4.5)	2 (9.1)	-50.0	1.000 ^b	1 (12.5)	2 (25.0)	1.000 ^b
- Dorsum first web space	5 (22.7)	5 (22.7)	0	1.000 ^b	1 (12.5)	3 (37.5)	0.500 ^b
- Lateral foot	3 (13.6)	3 (13.6)	0	1.000 ^b	1 (12.5)	0	1.000 ^b
- Fifth toe pulp	5 (22.7)	6 (27.3)	-16.7	1.000 ^b	3 (37.5)	3 (37.5)	1.000 ^b
Romberg's test positive (n (%))							
	12 (54.5)				5 (62.5)		1.000 ^c
Cold/warmth perception (n (%))							
	14 (63.6)	10 (45.5)	-40.0	0.125 ^b	4 (50.0)	2 (25.0)	0.500 ^b
Incident diabetic foot ulcer (n (%))							
	2 (9.1)	0	+200.0		0	0	-
Incident amputation (n (%))							
	1 (4.5)	0	+100.0		0	0	-
Tinel's sign at tarsal tunnel (n (%))							
	13 (59.1)	15 (68.2)	-13.3	0.625 ^b	5 (62.5)	2 (25.0)	0.250 ^b
Carpal tunnel syndrome in the past (n (%))							
	7 (31.8)				4 (57.1)		
- Unilateral	3 (42.9)				0		
- Bilateral	4 (57.1)				4 (100.0)		

Abbreviations: ^a, Wilcoxon signed rank test; ^b, McNemar test; ^c, Fisher's Exact Test; #, range 2 – 15 mm; *, range 0.16 – 300 g; IQR, interquartile range.

Figure 4 Sensory loss in the LENS-FU population compared to other populations.

Legend: The RDF-39 is a composite score of both screening instruments (e.g. static- and moving two-point discrimination, vibration sense, 10 g monofilaments) and test sites (e.g. hallux, medial heel, fifth toe), indicating the severeness of sensory loss at the feet. Information on prior ulceration, amputation and Romberg test is also included, resulting in 39 dichotomous items which can be summed to a total score(23). Displayed are histograms of RDF-39 scores of the Rotterdam Diabetic Foot Study population (n=416) and healthy controls without known neuropathy (n=196)(23, 24).

Discussion

In this study, we investigated the long-term effects of LEND surgery by the follow-up of patients previously participating in a randomized controlled trial. To optimize surgical outcome, patient factors influencing the results were investigated, helping clinicians make an adequate estimation of whom, and to what extent, are likely to benefit from this type of surgery. To our knowledge, no studies to this date investigated primarily the effects of patient factors on postoperative outcome.

Patients who underwent decompression of lower extremity nerves in both legs had significantly lower VAS pain scores at 12 months, were younger, had a lower age when

diagnosed with DM and had a lower BMI at baseline compared to unilateral operated patients. They also had a higher quality of life, higher percentage of intact S2PD (<15 mm) and intact S1PD (<10 g), what may have contributed to undergoing contralateral surgery. Interestingly, at five-years follow-up, VAS pain scores of additional decompressed legs decreased similarly as initial operated legs (Figure 1). More profound improvements in pain were reported in the bilateral operated group and the number of patients reporting permanent worsening of pain was significantly higher in non-operated legs compared to bilateral operated legs. In addition, VAS pain scores did not increase compared to pre-operative values. In the initial operated leg, significant pain improvement was noted during follow-up, compared to the control leg (48.4% versus 22.6%, $p = .021$). At 5-year follow-up, patients still experience pain reduction in the initial operated leg, compared to the initial control leg (35.5% versus 12.9%). Worsening of pain did not occur during the 5-year follow-up, despite the inherent progression of DSP. This suggest that LEND surgery could halt the neuropathy process due to compression, in contrast to the natural history of DSP in diabetes. Three studies observed a pain reduction of ≥ 3 points on a VAS scale (95%CI: 4.04-6.77), which we observed in 42.5% of operated legs at 12 months, compared to 15% in control legs. These differences make a placebo effect less likely. A subjective improvement in sensation was reported by 54.8% of patients. 41.2% of the LENS-FU population underwent or considers having contralateral LEND surgery. The quality of life measurements showed a significant difference after five years in favor of bilateral operated patients.

LEND surgery remains a controversial topic amongst endocrinologists and neurologists^{16,25,26}. Only those patients with signs of superimposed nerve compression at known sites of anatomical narrowing may be candidates for this type of surgery¹³. No well-controlled, double-masked randomized controlled trials on this subject are published yet, however, studies suggest the beneficial effects on pain, gain in protective sensation and reduction of incident ulceration and amputation^{14,27,28}.

Several factors might have contributed to the less profound results reported in the original LENS study¹⁵. When comparing our participants to those described in a meta-analysis on LEND surgery studies, patients were significantly younger (66.2 y (11.0) vs. 56.0 y (7.1)) and had a shorter duration of DM (20.4 y (10.9) vs. 13.9 y (2.0)), compared to our studied subjects. Preoperative S2PD was reported to be 16.2 mm (3.5), improving with 3.9 mm (95% CI: 0.1-7.7 mm) in 69% of operated legs in 2 to 26 months. A significant pain relief of >4 points (95% CI: 4.04-6.77) and a reduction in 91% of cases were reported. In 5% of patients, a worsening of symptoms was observed and 4% showed no improvement¹⁴. However, a severe preoperative nerve damage, as indicated by aberrant S2PD, vibration sense and 10 g monofilaments, was observed in LENS participants. Some patients even had a prior ulcer, suggestive of late stage

nerve damage²³. One must question the extent of preoperative nerve damage may have exerted the odds of a favorable surgical outcome in this population^{15,29}. Furthermore, the outcome measures of the initial LENS-study included sensory testing with 15 mm of S2PD and 10 g monofilaments, which were reported as proportion of patients able to discriminate those stimuli. These are, especially the 10 g monofilament, very crude cut offs to follow nerve regeneration from the point of compression and not sensitive enough to detect mid-term (i.e. one year) post-operative changes. Therefore, a test battery consisting of M2PD and S2PD (2-15 mm), a full monofilament set (0.008 – 300 g), a graded tuning fork, cold sensation and Romberg test were used to cover the full range of sensory modalities that are (partially) restored after LEND surgery, according to the literature¹⁴. However, due to the severe preoperative sensory loss, sensory modalities like monofilament and S2PD and M2PD tests were frequently still absent at five-years of follow-up²⁴.

Patients were operated when superimposed nerve entrapments were diagnosed by the presence of Tinel's sign^{8,13}. Controversy exists regarding the validity and reproducibility of Tinel's sign³⁰. However, the diagnosis of compression neuropathy is difficult with current techniques like nerve conduction studies, especially in diabetics with complaints of DSP. It has been recommended that therapeutic decisions are made independently of these findings¹¹. Axonopathy with its own demyelination will impede the demonstration, by electro diagnostic studies, of segmental nerve slowing in fibro-osseous tunnels, as is demonstrated in carpal tunnel syndrome in diabetic subjects with complaints of DSP¹¹. Moreover, nerve conduction studies have difficulties predicting outcome after carpal tunnel release surgery³¹. Therefore, surgeons should rely on their clinical examination in this vulnerable group of patients.

Processes of de- and remyelination and de- and regenerating axons are likely to lie at root of Tinel's sign, but are not fully unraveled yet¹³. Not every patient with DM and neuropathy will have signs of superimposed nerve compressions in the natural history of the disease. However, it is observed that the latter increases when patients report complaints of DSP¹². Besides distal tibial nerve compression at the tarsal tunnel, it may have been that the LENS-FU population have had concomitant proximal tibial nerve entrapment at the soleal sling, which was not investigated, or had recurrent entrapment due to inadequate decompression³². A study on sensory loss in the feet of diabetics investigated the presence of a positive Tinel at the tarsal tunnel²³. It was concluded that a positive sign at the tarsal tunnel is observed along the whole range of sensory loss, from patients with aberrant S2PD to patients with prior ulcerations and amputations. These observations are of critical importance when facing a patient seeking relief of neuropathy complaints³³. Not only the combination of complaints and Tinel's sign must be indicatives of surgery, but also sensory

tests should be carried out to estimate the extent of nerve damage. Patients with more severe sensory loss, like those who participated in this study, are likely to have had more advanced nerve damage, which lowers the likelihood of regeneration from the point of compression, for sensibility. These patients may still experience improvement in pain. The measurement instrument that is used to grade the sensory loss due to DSP and/or compression neuropathy should be reconsidered^{11,34}. It has been suggested that in nerve compression syndromes before the innervation density declines (indicated by a wider two-point discrimination), the cutaneous threshold increases regarding discrimination of two points²². Maybe that should be the point in the history of sensory loss in which the patient should be considered for surgery³⁵.

Strengths of this study include the long-term follow-up of the first randomized controlled trial in LEND surgery, allowing assessment of somatosensory reinnervation, incident ulceration and amputation five years after the initial surgery, with the investigation of patient related factors influencing long-term surgical outcome. Satisfaction and pain were predictive for bilateral surgery. Preoperative sensory loss, age and duration of diabetes determined the extent of sensory return and resolution of complaints. Limitations of the initial LENS study might be that no properly controlled, double-masked, sham-controlled clinical trial design was used.

The present study suggests the beneficial effects of LEND surgery are reserved, not only for those with a positive Tinel sign, but also for a select group of patients with DM and complaints of neuropathy. Preferably, this is a patient with relative intermediate complaints of compression neuropathy, a shorter duration of DM, lower age, adequate metabolic control and without profound sensory loss. Hence, further research is needed to determine what level of complaints and sensory loss will respond, and to what extent.

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Chapter XIII

Two-Point Discrimination Predicts Pain Relief after Lower Limb Nerve Decompression for Painful Diabetic Peripheral Neuropathy

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We read with great interest the article entitled 'Two-Point Discrimination Predicts Pain Relief after Lower Limb Nerve Decompression for Painful Diabetic Peripheral Neuropathy' by Wang et al. in *Plastic and Reconstructive Surgery*¹. The authors presented the clinical outcomes of lower extremity nerve decompression (LEND) surgery from a retrospective study and concluded that the beneficial effects of this type of surgery are more profound in patients with better baseline two-point discrimination at the hallux. We appreciate the author's contributions to this subject, as patient selection and outcome assessment is a developing field in LEND surgery. We would like to share some remarks and questions with the authors.

A numerical grading scale of peripheral nerve function has been proposed by dr. A. Lee Dellon for different peripheral nerves, including the posterior tibial nerve, to provide clinically meaningful results for a method of treatment based on the stage of the disease². Although the author's own personal experience was used to grade both sensory and motor function, the observation that an abnormal pressure threshold precedes an abnormal innervation density in diabetes related neuropathy was also observed in our own data³. Recently, we developed psychometrically validated grading scales of lower extremity peripheral nerve function that indeed show that the ability to sense static two-point discrimination is lost first, followed by moving two-point discrimination, vibration sense, protective sensation (assessed with a 10 g monofilament) and cold perception⁴. This grading allows for categorization of diabetic patients regarding the risk of developing diabetic foot ulcers, amputations and falls, but also relates to surgical outcome, as reported recently⁵. In this study, we investigated the factors of influence on surgical outcome in LEND surgery by follow-up of patients previously participating in the Lower Extremity Nerve Entrapment Study. In all participants, severe preoperative nerve damage, as indicated by aberrant static two-point discrimination, vibration sense and 10 g monofilaments was observed, which most likely have influenced the odds of a favourable surgical outcome in this population.

It is therefore of interest why Wang et al. chose a threshold of ≥ 9 mm at the hallux as inclusion criterion, which is relatively high compared to normative values. The authors stated that spatial resolution at the big toe predicted pain relief, but the side of assessment is not described nor if this was done uni- or bilaterally. Moreover, where all possible entrapment sites released, or a subset per patient? This is important information, since the number of entrapment sites is more likely to have had an effect on the Numerical Rating Scale scored post-operatively, compared to spatial discrimination at the hallux. In addition, it appears that both extremities were operated simultaneously, how did this influence post-op rehabilitation and the first follow-up assessment at 6 weeks? Lastly, we would appreciate if the authors explain how the selection of variables for the regression analysis took place, since no Diabetic Neuropathy System or Diabetic Neuropathy Examination scores were included, while the authors state that variables were assessed that might have contributed to better pain relief after surgery.

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Chapter XIV

De rol van de plastisch chirurg in het diabetische voet team

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Abstract in English

Two successful cases on the reconstruction of a diabetic foot ulcer are described. Reconstructive principles can cover chronic wounds and defects of varying size, in a tailor made approach. Still some shiver exists for using microsurgical techniques in treating the diabetic foot. Unfair, regarding the good results and similar success ratios compared to other free flap surgery. The reconstructive surgeon is not a part of the diabetic foot team in the Netherlands. The arsenal of techniques a reconstructive surgeon can add to the treatments by the diabetic foot team has shown to be of value in covering defects of varying size, resulting in preservation of the foot.

Samenvatting

Twee casus worden beschreven betreffende de reconstructie van gecompliceerde voet ulcera. De principes van de reconstructieve ladder zijn ook op diabetische ulcera toepasbaar, wat aan de hand van deze casus wordt geïllustreerd. De beslisvorming, uitdagingen en successen van deze casus laten zien dat microchirurgische technieken te gebruiken zijn voor de reconstructie van defecten veroorzaakt door diabetische ulcera.

Dames en heren,

De behandeling van de diabetische voet berust al jaren op de pijlers infectiebestrijding, streven naar een adequate bloedvoorziening, therapeutisch schoeisel (gips) en middels conventionele, dan wel chirurgische, technieken wegnemen van lokale (verhoogde) druk.

Vele Nederlandse ziekenhuizen benaderen het multifactoriële probleem van de diabetische voet met een multidisciplinair team bestaande uit een podotherapeut, internist, vaatchirurg, orthopedisch chirurg, dermatoloog en revalidatiearts. De oorzakelijke factoren die geleid hebben tot de diabetische voet worden op deze manier vanuit elk vakgebied gezien. Echter ontbreekt in dit team de wondspecialist bij uitstek, de plastisch chirurg.

De plastisch chirurg houdt zich dagelijks bezig met (chronische) wondzorg en bedekking van defecten, zoals die gezien worden bij decubitus, trauma en oncologie. De hierbij gebruikte technieken zijn goed toepasbaar op de diabetische voet, zoals onderstaande casus zullen illustreren.

Casus 1

Een 65-jarige man met diabetes meldt zich met demarcerende, ischemische necrose en ulceratie van de rechter voet (Figuur 1), welke 3 maanden daarvoor spontaan begon en snel verergerde. Conservatieve behandeling faalde in het behandelen van de wond, onder goed instellen van de bloed glucose waarden. Röntgenfoto's en bot scans gaven verdenking op osteomyelitis weer. Voet arteriën waren palpabel en een preoperatieve angiogram liet open arteriae tibialis anterior en posterior zien. Een uitgebreid débridement werd uitgevoerd (Figuur 2) met reconstructie middels een perforator (anterolaterale dijbeen (ALT)) lap. De arterie werd *end-to-side* aangesloten op de a. tibialis anterior, de vene op een aanliggende vene. De overgebleven benige structuur van de hallux werd door de lap omwikkeld (Figuur 3). Er was postoperatief sprake van minimale wond dehiscentie aan het mediale aspect van de eerste straal, hetgeen heelde zonder verdere interventies. 18 maanden postoperatief was de patiënt ADL-onafhankelijk, gebruikmakend van aangepast schoeisel. De gereconstrueerde voet had een goed gebalanceerde contour, zonder aanwijzingen voor lokaal verhoogde druk (Figuur 4).

Figuur 1

Figuur 2

Figuur 3

Figuur 4

Casus 2

Een 79-jarige man met diabetes presenteerde zich met een inert ulcus van de linker hiel bij een Charcot-voet (Figuur 5). Het 5 maanden oude defect was ontstaan na een operatie aan een subtrochantaire femurfractuur rechts. Optimaliseren van de vaatvoorziening middels Percutane Transluminale Angioplastiek (PTA) en een necrotectomie van het ulcus waren niet afdoende. Patiënt had reeds eerder een trans-metatarsale amputatie rechts ondergaan in verband met een geïnfecteerd diabetisch ulcus. Er waren adequate Doppler signalen over de a. tibialis posterior en de a. plantaris medialis. Een Magnetic Resonance Angiography liet een doorgankelijke a. tibialis anterior en posterior zien, alsook een goede perforator van de a. plantaris medialis. Gezien de mogelijkheid van een sensibele lap werd besloten tot reconstructie middels een Medial Plantar Artery lap. Helaas faalde deze lap (Figuur 6), waarna werd overgegaan tot bedekking middels een vrije lap, de zogeheten Superficial Circumflex Iliac Artery Perforator lap. Toen ook deze lap faalde werd na uitvoerig overleg de wond bedekt middels een ALT lap waarbij de arterie op een zijtak van de a. tibialis posterior werd aangesloten. De lap groeide uiteindelijk in en daarmee waren de wonden gesloten. Eén jaar postoperatief heeft patiënt aangepast schoeisel en gebruikt hij de gereconstrueerde voet als standbeen (Figuur 7). Patiënt is zeer tevreden met het behaalde resultaat.

Figuur 5

Figuur 6

Figuur 7

Beschouwing

Wij bespraken twee patiënten met een diabetische voet die zijn behandeld middels plastisch chirurgische technieken. De plastisch chirurg benadert elk defect dat gesloten moet worden volgens de principes van de zogenaamde reconstructieve ladder, variërend van eenvoudig en weinig ingrijpend voor de patiënt naar meer technisch geavanceerd voor de reconstructief chirurg en meer ingrijpend voor de patiënt. De eerste en meest eenvoudige stap is primaire sluiting, gevolgd door genezing per secundam, negatieve druk therapie, huidtransplantaat, huidmatrix, de locoregionale lap, “*distant flap*” en weefsel expansie. De laatste trede van de ladder is de behandeling middels de vrije lap, waarbij een gevasculariseerd stuk bot, spier, fascia en/of huid wordt getransplanteerd naar het defect en middels microchirurgische technieken op een lokale arterie, vene en eventueel zenuw, wordt aangesloten.

Overwegingen bij vrije lap chirurgie in de diabetes patiënt

Diabetes werd lang gezien als contra-indicatie voor vrije lap chirurgie in de onderste extremiteit. Latere studies wijzen nu microangiopathie aan als oorzakelijke factor in het ontstaan van de diabetische voet, onafhankelijk van perifeer arterieel vaatlijden in de grotere vaten van het onderbeen¹. Het ontstaan van een ulcus is vaak terug te voeren op een combinatie van gevoelloosheid door diabetische polyneuropathie, plekken van verhoogde druk en een niet adequate controle van de voeten op pre-ulceratieve laesies. Bij het bestaan van een diabetische voet en de genezing daarvan speelt de vaatvoorziening wel een grote rol.

De meeste patiënten die een amputatie moeten ondergaan hebben een slechte circulatie, waarbij de grote vaten vaak gecalcificeerd zijn. In diabetes patiënten met atherosclerose zijn de crurale vaten vaker aangedaan dan de vaten in de enkel en voet². Vaak zal gedurende de behandeling de vaatstatus al zijn nagegaan, en indien nodig behandeld met een PTA, eventueel met stent, of bypass chirurgie. In een analyse van vrije lap chirurgie voor de diabetische voet, was 66% van de patiënten behandeld met een van bovenstaande modaliteiten, voor het ondergaan van vrije lap chirurgie³. In het natuurlijke beloop van de diabetische voet wordt het weefsel langzaam meer ischemisch, waardoor het gebruik van (takken van) grote vaten lastiger wordt. Deze episode van ischemie brengt echter wel angiogenese van collateralen op gang, wat een alternatieve circulatie oplevert voor de huid van het distale been en de voet. Deze collateralen zijn vaak afkomstig uit nabij gelegen angiosomen. Op dit punt kan super-microchirurgie een belangrijke rol spelen in het behoud van de voet⁴. Het aansluiten van een vrije lap op een klein vat (< 0.8 mm) van een goed gevasculariseerd aanliggend angiosoom levert genoeg perfusie op om de lap het ischemische gebied te laten voorzien van bloed⁵.

Hoewel diabetische polyneuropathie bijna altijd ten grondslag ligt aan het ontwikkelen van een diabetische voet, is het toch nuttig om een aansluiting op een lokale zenuw te overwegen bij het reconstrueren van de diabetische voet. De kans dat bij aansluiten van een zenuw enig protectief gevoel terugkeert, is aanwezig. Echter, het niet aansluiten van de zenuw lijkt het overleven van de lap niet te beïnvloeden en blijkt niet van invloed op de termijn dat de patiënt er belast op kan lopen⁶.

Plannen van een vrije lap

Nadat de patiënt goed is ingesteld, de eventueel bestaande infectie is behandeld en een débridement is uitgevoerd, kan de chirurg de verschillende stappen van de reconstructieve ladder overwegen om het defect te bedekken. Chronische ulcera kunnen dermate resistent voor conventionele therapie zijn dat een lokale of een vrije lap nodig is om met een goed gevasculariseerd bed de wond te behandelen en amputatie te voorkomen. Transcutaan gemeten zuurstofspanning kan helpen om te bepalen of een microchirurgische interventie zinvol is (amputatie: <30 mmHg, reconstructie: >30 mmHg). 25% van de complexe diabetische voeten is een mogelijke kandidaat voor vrije lap chirurgie⁷.

De keuze van de lap hangt met name af van ervaring. Verschillende punten zijn van belang om in ogenschouw te nemen: het type lap (spier met huidtransplantaat, fasciocutane- of perforator lap), het gemak van het oogsten van de lap en de co-morbiditeit van de donor plek. Het gebruik van een spier heeft als voordelen dat deze gemakkelijker te modelleren is rondom de irregulaire vorm van de voet en zijn goede doorbloeding een functie kan hebben in het controleren van een lokaal bestaande infectie. De gedachte dat de spierbuik een voordelig 'kussen-effect' geeft lijkt niet geheel op te gaan, waarschijnlijk door het gebrek aan sensibiliteit⁷. Nadelen van het gebruik van de spier lap is soms de noodzaak van een tweede operatieve procedure waarbij de lap uitgedund wordt om de voet schoeibaar te maken, alsook het langer duurt voordat de spier kan worden belast. De fasciocutane lap heeft als voordelen dat de kans op reïnnervatie groter is en door de geringere dikte de lap makkelijker plooibaar is en bij belasting minder schuifkrachten ondervindt.

De afdeling waar de patiënt postoperatief terecht komt moet goed geïnstrueerd en geoutilleerd zijn om de lap te monitoren op tekenen van falen van de lap. In de eerste dagen na de operatie is met name de positie van het been en een bijpassend afhangschema zeer belangrijk.

Multifactorieel probleem, multidisciplinaire aanpak

De behandeling van de diabetische voet is ingewikkeld en uitdagend. Een goede metabole instelling blijft obliagaat, alsook behandeling van bestaande infecties. Voor de wondbedekking

heeft de plastisch chirurg de juiste expertise en een divers arsenaal aan mogelijkheden. Voor men aan grote (microchirurgische) reconstructies gaat denken, moeten onderliggende problemen van de vaatboom en bot- en gewrichtsdeformiteiten aangepakt worden. Bij patiënten met tekenen van zenuwcompressie in de onderste extremiteit is het zinvol deze te decomprimeren. Het succes van de behandeling wordt tevens voor een groot deel bepaald door de motivatie en voorlichting van de patiënt. Het betreft een langdurig traject, waarbij het revalidatieprogramma en de zorg thuis minstens zo belangrijk zijn als de reconstructie zelf, om herhaling te voorkomen.

Nabeschouwing

Naar schatting 15% van de diabeten wordt gedurende het leven geconfronteerd met een diabetisch ulcus. 8 van de 10 uitgevoerde non-traumatische amputaties wordt vooraf gegaan door deze conditie. De mortaliteit na het ontwikkelen van een ulcus is na één jaar 13 tot 40%, na drie jaar 35 tot 65% en na vijf jaar 29 tot 80%⁸. Door de stijging van het aantal diabeten, zullen ook de daarmee gepaarde complicaties toenemen, zoals de diabetische voet. De waarde van de vrije lap chirurgie in de behandeling van de diabetische voet wordt steeds duidelijker. In een recent review naar deze vorm van behandeling, overleefde de vrije lap in 91,9% van de casus, met daardoor een behoud van de extremiteit in 83,4% van de gevallen, bij een gemiddelde follow-up duur van 28 maanden³. Diabetes patiënten waarbij een amputatie aan de onderste extremiteit is uitgevoerd hebben een 5-jaars overleving van 41,4%, terwijl dit bij hen die een succesvolle reconstructie middels een vrije lap hebben ondergaan 86,8% is⁹. Het succesratio van deze techniek in deze patiënten groep is vergelijkbaar met een van de grootste series van beschreven vrije lappen, waarbij defecten werden gereconstrueerd na borstamputatie, kanker en trauma¹⁰. Er is dus geen basis meer om de diabetische voet als absolute contra-indicatie te zien voor vrije lap chirurgie in de onderste extremiteit. Het behoud van de voet verbetert niet alleen de kwaliteit van leven, maar verlengt ook het leven van de diabeet met een voorgaand ulcus.

Conclusie

Dames en heren, wij beschreven uitdagende, maar succesvolle reconstructies van de diabetische voet middels plastisch chirurgische technieken. Er bestaat nog steeds huivering voor het gebruik van microchirurgie in de onderste extremiteit bij diabeten. Dit is onterecht, gezien de te behalen resultaten goed zijn, met vergelijkbare succesratio's als andere vrije lap chirurgie. De plastisch chirurg is tot op heden niet een vast onderdeel van het multidisciplinaire voet team en zou een waardevolle toevoeging zijn gezien zijn specifieke expertise op het gebied van wondverzorging en het diverse arsenaal aan operatieve mogelijkheden.

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Costs and cost-effectiveness

PART V

Chapter XV

In-hospital costs of diabetic foot disease treated by a multidisciplinary foot team

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Abstract

Background

The diabetic foot imposes significant burden on healthcare systems. Obtaining knowledge on the extent of the costs of diabetic foot ulcers (DFUs) is of value to health care researchers investigating cost-effectiveness of interventions that prevent these costly complications.

Objectives

To estimate the in-hospital costs associated with the treatment of DFUs by a multidisciplinary diabetic foot team.

Methods

Persons with DFUs presenting to our team in 2013 and 2014 were followed and use of care was estimated. Exclusion criteria were a single visit only and ulcers above the ankle. Demographic data and per-person incremental clinical outcomes (e.g., healing with or without amputation and rehabilitation) were assessed. Resource use was identified, measured and multiplied by unit costs.

Results

Eighty-nine persons were identified with 56 persons meeting the inclusion criteria (with 69 DFU episodes). The median in-hospital care was 17 weeks (inter quartile range: 7-34). Average in-hospital costs were US\$ 10,827 (range: 702 – 82,880) per DFU episode. Primary healed DFUs costs on average US\$ 4,830, single minor amputations on average US\$13,580, multiple minor amputations on average US\$ 31,835 and major amputations on average US\$ 73,813 per episode. Costs differed significantly between groups ($p < .001$).

Conclusion

DFUs are associated with substantial immediate and long-term in-hospital costs. Our study provides estimates of these costs, aiding researchers and health policy analysis.

Introduction

Diabetes is often accompanied by invalidating and expensive complications like nephropathy, retinopathy and diabetic sensorimotor polyneuropathy (DSP), the latter being the most common with a prevalence ranging from 30% to 50%¹⁻³. DSP decreases the quality of life and has been associated with increased mortality as it frequently leads to a diabetic foot, a major complication in diabetes¹. It has been estimated that at least 15% of diabetics are confronted with a foot ulcer during their life, with eight out of ten non-traumatic amputations carried out, being preceded by diabetic foot ulcerations (DFUs).

Therefore, diabetes, DSP and DFUs render considerable economic costs and burden to society³⁻⁵. A study from the United Kingdom estimated an expenditure of 0.6% of National Health Service budget on diabetic foot care⁶. Another study from the United States found that DFU imposes an annual burden of US\$10.1-14.5 billion on top of costs associated with diabetes itself (US\$ 30,186 per DFU episode in Medicare patients and US\$ 33,835 for private payers)⁷. Previous studies reporting the costs of DFU disease on patient level estimated an average of US\$ 10,209 per episode when an amputation was not required, US\$ 51,646 when a minor lower extremity amputation was carried out and US\$ 78,069 when a major lower extremity amputation was needed (2015 US Dollar level)⁸. A recent systematic review on the subject demonstrated, irrespective of study design or origin, that results are comparable in suggesting substantial costs. The included studies suggest that costs are generally higher in the United States, compared to the costs in Europe. In view of the increasing economic consequences, measures have been undertaken⁹. By implementing screening programs and treatment of DFUs by a multidisciplinary foot team wound-healing time is shortened, amputations are reduced and these programs have proven to be cost-effective strategies¹⁰⁻¹⁴.

Few studies assessed in-hospital resource use in DFU disease and its consequent cost-of-illness at a person-level¹⁵⁻¹⁸. Robust estimations rely on contemporary and accurate information on the occurrence of complications and follow-up of consumed medical resources¹⁹. To study cost-effectiveness of interventions aiming at reducing complications, these measures are preferably needed at patient-level. Since no recent studies assessed DFU related resource use as such, we thought it would be appropriate to use a micro-costing method to estimate the in-hospital costs associated with DFU treatment by a multidisciplinary diabetic foot team.

Methods

A partial prospective/retrospective cost-of-illness study was conducted on data of persons with diabetes (type 1 and type 2) who presented in 2013 and 2014 with a DFU to the multidisciplinary foot team of the Franciscus Gasthuis, Rotterdam, the Netherlands, which is a large representative teaching hospital in the Netherlands. The multidisciplinary foot team includes a podiatrist, internist, vascular surgeon, orthopedic surgeon, rehabilitation specialist and dermatologists and is chaired by the internist (an endocrinologist). The 2015 International Working Group on the Diabetic Foot (IWGDF) guideline is followed in DFU care²⁰, with large roles for the internist, vascular surgeon, podiatrist and rehabilitation specialist. A cost calculation was performed to produce a current overview of different cost categories in order to identify the main cost drivers during the complete course of diabetic foot ulcer treatment¹⁹. Ulcers were defined as full thickness skin lesions distal to the ankle. Non-diabetic ulcers, (venous) ulcers above the ankle and a single visit only were exclusion criteria. Per-person incremental clinical outcomes (e.g., healing with or without amputation) were assessed. The time from presentation until discharge from in-hospital care was defined as a DFU episode (healing of all ulcers and end of rehabilitation). Persons readmitted for a recurrent or new onset ulcer were considered new DFU episodes in the two-years of observation (2013 and 2014). Demographic characteristics (e.g. age, duration of diabetes, prior ulceration and/or amputation, assessment of peripheral arterial disease) were retrieved from the patient files. No Institutional Review Board approval was obtained, regarding the non-interventional study design. Patient informed consent was unnecessary for this study.

DFUs were categorized at presentation according to the University of Texas diabetic foot classification²¹. Dimensions of the ulcer were measured. Stage and grade were assessed and combined for each DFU episode (from A0 to D3). Multiple ulcers in the same period were counted as one DFU episode. An amputation was defined as major when carried out above ankle level and minor when carried out below the ankle. An ankle-brachial index of 1.0 to 1.4 was considered normal, 0.9 or less indicative of blockage and >1.4 regarded as rigid arteries. DFU episodes were grouped according to the final outcome at follow-up. The following groups were distinguished: group 1, primary healing; group 2, primary healing with prolonged out-patient rehabilitation (defined as in-hospital resource use > 4 weeks after ulcer healing (e.g. protective casts after healing)); group 3, minor amputation; group 4, multiple minor amputations during follow-up and group 5, major amputation. Patients were followed until all ulcers or post-operative wounds healed and when discharged from in-hospital care.

2.1 Data collection

Participants' charts were reviewed for medical resources consumption from the presence of the ulcer until healing or discharge for follow-up. Time until healing and end of rehabilitation were distinguished. If the ulcer was present before January 2013, accompanying in-hospital resource use of the preceding period was also retrieved. A time frame of two years was chosen to get a broad and diverse overview of the varying natural history of DFU disease. In this study we focused on the direct, in-hospital based care and resources used during treatment of the diabetic foot. The following categories were distinguished: consultation costs by specialists, radiographic investigations, laboratory measurements (clinical chemical and microbiology), pathology laboratory, interventions (operations (e.g. débridements, amputations, plaster casts)), radiological interventions (e.g., transluminal angioplasty), in-hospital stay and drugs. Complications because of DFU disease were also considered. The financial department of our institution provided unit costs (e.g. foot X-ray US\$ 17.30). The pharmacological department provided an overview of drugs used per person, together with the accompanying costs. Both general drugs as episode specific drugs (e.g. antibiotics), were taken into account when patients were hospitalized. Extramural costs, for example productivity loss, were not considered.

2.2 Cost analysis

In-hospital resources use were identified, measured and multiplied with unit costs (charges for X-rays, casts, operations etcetera) as suggested by Gray et al. (micro-costing approach in cost-of-illness studies)²² and was based on the unit prices of the year 2015. Costs are presented in US dollars and apply to the financial year of 2015, when one Euro was equal to approximately 1.11 US dollars. The US dollar currency was used in reporting the results, to make cost estimates more comparable to the international literature and different healthcare systems. Discounting was not relevant because of the limited time horizon of follow-up. Currencies were inflated to the 2015 US dollar using the medical care component of the US Consumer Price Index and national inflation rates. To estimate costs of drugs used during inpatient hospital days, we applied the World Health Organization definitions and general considerations concerning average daily drug use. The defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication, which was then multiplied by the cost per unit²³. The DDD was predominantly used for the regular drugs taken by participants, for example primary and secondary preventive drugs for cardiovascular disease. For intravenous drugs, creams and inhaled drugs, we used total single parcel costs. A day of in-hospital stay was made up of personnel costs (48%), indirect general costs (17%), material costs (8%), facility costs (8%), direct building costs (6%), indirect nutrition costs (5%), indirect patient-related costs (5%), direct specialists costs (2%), indirect

building costs (1%) and residuals (1%), derived from data of the Financial Department of the Franciscus Gasthuis.

2.3 Statistical analysis

All analyses were carried out using IBM's SPSS Statistics 22.0 (IBM, New York, USA) and Microsoft's Excel 15.14 (Microsoft, Washington, USA). Non-parametric correlation coefficients (Spearman's rho) were used to assess relations between costs and patient characteristics. Differences between two independent binomial proportions were assessed with Pearson Chi-square tests. Differences in continuous variables with skewed distributions between two independent groups were assessed with Mann-Whitney U tests. Kolmogorov-Smirnov tests were used to assess normality. Kruskal-Wallis test was used to assess differences between multiple groups. P-values below .05 (two-sided) were considered statistically significant.

Results

Participant's characteristics

A total of 89 persons presented to the multidisciplinary foot team in the years 2013 and 2014 (Figure 1). Thirty-three persons did not meet the inclusion criteria, mainly because of single visits only or having venous ulcers of the lower limb. Forty-four men and 12 women were followed (mean (SD) age 65.1 years (13.7), range 30.0 – 90.0), in which 69 (recurrent) DFU episodes were identified (readmission for same or new lesion). Twenty-one participants had a history of ulceration and 12 participants a prior amputation due to previous DFU disease; see Table 1 for further demographic characteristics. Participants were predominantly referred to the team by general practitioners and in-hospital departments (e.g. vascular surgery and rehabilitation departments).

Presentation of DFU

Median duration of the DFU episode prior to in-hospital care was 2 weeks (interquartile range (IQR): 1-8). Most often participants presented with a stage B, grade 1 ulcer (n=23, 33.3% of DFU episodes), followed by stage A, grade 1 (n=21, 30.4%) and stage D, grade 3 (n=7, 10.1%). Other classifications (combination of grade and stage) were less common (n<5). Most participants had ulcers at the toes, which is further specified in Table 2. The seven patients that had multiple DFU episodes in 2013 and 2014 were slightly older at presentation, all had type 2 diabetes, had a significant higher average number of prior DFU episodes per patient ($p = .005$) and had lower ankle/toe brachial indices (Table 1). Consecutive DFUs did not result in a more worse outcome (higher outcome group) ($p > .05$).

Figure 1 Flowchart of patients visiting the multidisciplinary foot team in 2013 and 2014. *Follow-up during in-hospital care*

In the 69 DFU episodes identified (in 56 of participants), 100 ulcers were observed during follow-up (Table 2). In 66.7% of episodes one ulcer was present (n=46), two ulcers in 24.6% (n=17), three ulcers in 5.8% (n=4) and four ulcers in 2.9% (n=2) of patients. Median duration of a DFU episode until healing was 17 weeks (IQR: 7-34), which increased significantly with the number of ulcers during follow-up ($r_s = .475$, $p < 0.001$). Thirty-one DFU episodes healed primarily (group 1). Of the 22 DFU episodes that healed primarily, in-hospital costs rose after healing due to prolonged outpatient care, with a median rehabilitation period of 8 weeks (IQR: 4-13) (group 2). Twenty-one minor amputations were carried out and two major amputations, in a total of 16 participants. In the minor (single) amputation group (group 3)

an average number of 1.1 DFU episodes were observed, in 10 patients. In 10 DFU episodes a toe had to be amputated, a midfoot amputation was necessary in one episode. In the multiple, consecutive, minor amputations group (group 4), two patients underwent two toe amputations, the third patient three. In the major amputation group (group 5), both patients underwent a toe amputation during a DFU episode, followed by a midfoot amputation in one patient. Eventually a trans tibial amputation was necessary in both patients (Figure 1). Ten times a revascularization procedure was required, in six participants. Five participants were lost to follow-up at the end of the treatment period. No participants died before healing of the ulcers.

Table 1 Demographic data of patients presenting to the DFU team in 2013 and 2014.

	Patients with a single DFU episode in 2013/2014 (n=49)	Patients with multiple DFU episodes in 2013/2014 (n=7)	P-value
No. of episodes in 2013 and 2014, (mean (SD))		2.9 (0.9)	
Gender (M/F)	39/10	5/2	NS
Age (mean (y), SD)	64.3 (14.3)	70.3 (7.2)	NS
Duration of diabetes (median (y), IQR)	14 (8-22)	10 (8-18)	NS
Type of diabetes (n (%))			NS
Type 1	6 (12.2%)	0	
Type 2	43 (87.8%)	7 (100%)	
Average number of prior DFU episodes per patient (mean, SD)	0.9 (1.6)	2.9 (2.0)	.005
Average number of prior Charcot foot per patient (mean, SD)	0.1 (0.4)	0.1 (0.4)	NS
Average number of prior amputations per patient (mean, SD)			NS
Toe	0.2 (0.7)	1.3 (1.4)	
Forefoot	0.1 (0.3)	0	
Midfoot	0	0	
Transtibial	0.1 (0.2)	0	
Through knee	0	0	
Transfemoral	0	0	
Ankle-brachial index (mean, SD)			NS
Dorsal pedal artery (left)	1.01 (0.29)	0.79 (0.17)	
Posterior tibial artery (left)	1.19 (0.39)	0.70 (0.52)	
Dorsal pedal artery (right)	1.24 (0.39)	0.97 (0.20)	
Posterior tibial artery (right)	1.19 (0.39)	0.79 (0.22)	
Toe-brachial index (mean, SD)			NS
Left	0.67 (0.31)	0.76 (0)	
Right	0.69 (0.29)	0.45 (0.35)	

Abbreviations: M, male; F, female; y, year; DFU, diabetic foot ulcer; IQR, interquartile range; SD, standard deviation; n, number; NS, not significant.

Table 2 Ulcer characteristics per group, during follow-up.

During follow-up					
	Group 1: Primary healed (n=31)	Group 2: Primary healed with prolonged rehabilitation (n=22)	Group 3: Minor amputation (n=11)	Group 4: Multiple minor amputations (n=3)	Group 5: Major amputation (n=2)
Final outcome per episode in patients with a single DFU episode in 2013/2014 (n=49) (n)	22	15	7	3	2
Final outcome per episode in patients with multiple DFU episodes in 2013/2014 (n=7) (n)	9	7	4	0	0
No. of DFUs observed per episode (n)					
One DFU	21	16	8	1	0
Two DFU	8	3	3	1	2
Three DFU	2	2	0	0	0
Four DFU	0	1	0	1	0
DFU locations (n)					
Hallux	9	4	3	3	2
Digit II – V	16	9	6	1	0
Plantar side					
Metatarsophalangeal joint	16	12	5	3	1
Midfoot	2	2	0	0	1
Heel	0	5	0	0	0
Texas wound classification staging (n)					
A – No infection or ischemia	18	15	6	2	1
B – Infection present	20	15	4	1	1
C – Ischemia present	0	0	0	1	0
D – Infection and ischemia present	5	2	4	3	2
Texas wound classification grading (n)					
0 – Epithelialized wound	1	0	0	1	0
1 – Superficial wound	35	26	7	4	1
2 – Wound penetrates to tendon or capsule	2	5	0	1	1
3 – Wound penetrates to bone or joint	5	1	7	1	1
Ulcer size (median (cm ²), IQR)	1.0 (3.0)	1.0 (1.0)	2.0 (1.4)	2.0 (0.8)	3.5 (3.7)
Deceased (n (%))†	2	3	1	0	0

Abbreviations: M, male; F, female; y, year; IQR, interquartile range; SD, standard deviation; n, number; †, as of April 2017.

In-hospital costs of care

Average in-hospital costs were US\$ 10,827 (range: 702 – 82,880) per DFU episode. Due to the skewness of cost data, Box-Whisker diagrams with median costs, quartiles and range per group were plotted (Figure 2). The average costs for primary healed DFUs (group 1) were US\$ 4,830 per episode, with a median duration of 17 weeks (IQR: 7-30). When the patient visited the rehabilitation specialist for further preventive measures to prevent recurrence (e.g. total contact casts, orthotics), an average of US\$ 9,310 per episode, with a median time to heal of 12 weeks (IQR: 4-20) was observed (group 2). For single minor amputations, the costs were on average US\$ 13,580 per episode, with a median duration of 26 weeks (IQR: 16-41) until healing (group 3). When multiple minor amputations in an episode were necessary, the average costs were US\$ 31,835 per episode, with a median duration of 68 weeks (IQR: 42-71) until healing (group 4). Two participants underwent, after one and two minor amputations, respectively, a major amputation averaging US\$ 73,813, with a median duration of 63 weeks (IQR: 63-64) until healing (group 5). Costs differed significantly between groups, $H(4) = 18.428$, $p < 0.001$.

Minor discrepancies existed between observed and declared resource use (average of US\$ 222 (range: 49 – 767), in 25 of 69 cases). In-hospital patient days (days on the ward) in the 69 DFU episodes constituted 41.2% of total costs and were followed by consultancy costs (25.8%) and costs of interventions (19.9%) as main cost drivers. The most frequent consulted specialist was the rehabilitation specialist, accounting for 44.7% of the total consultancy costs, followed by the vascular surgeon (23.2%), internist (11.1%), dermatologist (10.0%) and orthopedic surgeon (9.2%). Costs of surgery accounted for 47.6% of the total intervention costs, followed by plaster casts (20.8%) and other interventions (10.5%), like injections. Percutaneous revascularization procedures accounted for 9.7% of the costs of interventions, see Table 3 for further details. Figure 3 gives an overview on the distribution of costs per group.

There was a positive trend between the severity of the ulcer at presentation and the total costs, $r_s = .232$, $p = 0.055$. No correlation was found between the number of prior ulcers (or having a prior Charcot foot) and total costs, $r_s = .002$, $p = .987$, nor between age and total costs, $r_s = .003$, $p = 0.979$ or duration of diabetes and total costs, $r_s = -.103$, $p = 0.409$. A significant weak to moderate correlation was found between the number of ulcers per DFU episode and total costs, $r_s = .397$, $p < 0.001$, and the number of amputations and total costs, $r_s = .525$, $p < 0.001$. The duration of in-hospital care and total costs were more strongly related, $r_s = .620$, $p < 0.001$.

Figure 2 Box-and-Whisker plots of in-hospital costs per group in US dollars. *In-hospital cumulative costs over time*

Figure 4 shows the cumulative costs over time (days), per group. The minor amputation group (group 3, n=11) and multiple minor amputation group (group 4, n=3) compared to primary healed persons (group 1, n=31) and primary healed with prolonged rehabilitation (group 2, n=22) showed the sharpest increase in the first 30 days of in-hospital care. The increase in costs stabilized earlier when minor amputation(s) were carried out (group 3 and 4), compared to primary healing (group 1 and 2). The incremental costs of group 5 (n=2) increased relative slowly, with sharp increases in costs when minor amputations (n=3) were carried out, before the final major amputations were necessary. Figure 5 (supplemental material) shows the differences in cumulative costs over time (days) between first and new (recurrent) DFU episodes. In the first 60 days of ulcer treatment, no differences are observed. After this period, new onset ulcers become more expensive compared to recurrent DFU episodes.

Figure 3 Distribution of DFU episode costs per group in US dollars.
Y-axis: Cumulative costs in US dollars. X-axis: days.

Domains	Group 1: Primary healed, n. of DFU = 31	Group 2: Primary healed with prolonged rehabilitation, n. of DFU = 22	Group 3: Minor amputation, n. of DFU = 11	Group 4: Multiple minor amputations, n. of DFU = 3	Group 5: Major amputation, n. of DFU = 2
	Mean costs (US dollar)	Mean costs (US dollar)	Mean costs (US dollar)	Mean costs (US dollar)	Mean costs (US dollar)
Consultancy	2020	2910	2880	4028	11041
Radiology	217	199	302	628	835
Clinical chemistry	129	317	405	1448	6468
Bacteriology	289	453	775	983	1974
Pathology	0	131	0	0	0
Interventional	1038	2316	3166	6755	16251
Patient day (ward)	3666	10055	6484	15863	35466
Drugs	203	420	368	2131	2197
	% of total	% of total	% of total	% of total	% of total
Consultancy	27%	17%	20%	13%	15%
Radiology	3%	1%	2%	2%	1%
Clinical chemistry	2%	2%	3%	5%	9%
Bacteriology	4%	3%	5%	3%	3%
Pathology	0%	1%	0%	0%	0%
Interventional	14%	14%	22%	21%	22%
Patient day (ward)	48%	60%	45%	50%	48%
Drugs	3%	3%	3%	7%	3%

Abbreviations: n., number. Medians, quartiles and ranges per group are displayed in Figure 1.

Table 3 Total costs and costs per DFU episode in US dollars (n=69).

Costs per domain (% of total)	Total costs	Mean cost (SD), range
Consultation costs (25.8)	192.498	2.789 (2.769), 242 – 20.232
Vascular surgeon	44.644	
Internist	21.451	
Orthopedic surgeon	17.662	
Dermatologists	19.297	
Rehabilitation specialist	86.019	
Other	3.425	
Radiology (2.2)	16.125	252 (299), 18 – 1.293
Clinical chemistry (4.0)	30.027	509 (1.384), 18 – 9.633
Microbiology (4.3)	31.900	491 (592), 53 – 2.593
Pathology (0.02)	131	131
Interventions (19.9)	155.040	2.755 (4.021), 12.2 – 23.233
Surgery	70.865	
Radiologic intervention	14.472	
Plaster casts	40.971	
Vacuum assisted therapy	4.321	
Intensive Care	4.642	
Physiotherapy	4.138	
Others	15.631	
In-hospital patient days (41.2)	307.797	8.795 (11.069), 550 – 43.888
Drugs (2.7)	19.835	525.6 (583.4), 10.0 – 3132
Total	753.353	10.827 (16.067), 702 – 82.880*

Abbreviations: *, medians, quartiles and ranges per group are given in Figure 2.

Figure 4 Cumulative costs over time per group in US dollars.

(supplemental) Figure 5 Cumulative costs over time between first and new (recurrent) DFU episodes in US dollars.

Y-axis: Cumulative costs in US dollars. X-axis: days. Green line: new-onset DFU. Blue line: recurrent DFU.

Discussion

In this study, we followed persons presenting with a new onset diabetic foot ulcer to make an overview of direct costs of clinical practice in a large Dutch nonacademic center. Costs are high, with an average of US\$ 10,827 (range: 702 – 82,880) per DFU episode, based on 69 DFU episodes in 59 patients. Between the different outcome groups, resource utilization and costs varied considerably.

Due to the long follow up period, nearly all currently available treatments were included in our analysis. Our calculations are relevant for several reasons. First, it was not known what the average costs are of treating the diabetic foot nowadays. Second, it was not known how

the costs across the domains are distributed within groups of varying natural history of DFU. Third, it was not clear if the moment of a necessary amputation influences the total costs per ulcer, including rehabilitation. The results of our study give insights in the development of total costs during the natural course of DFU disease and are especially important in combination with utility values to evaluate cost-effectiveness of new therapies.

The average costs for primary healed DFUs were on average half as much as single minor amputations and when multiple minor amputations in an episode were necessary, the average costs rose to thrice that of a primary healed DFU. Only two participants underwent a major amputation averaging US\$ 73,813. A minor amputation did not result in lower total costs or a shorter time of increments in average costs compared to primary healing. (Recurrent) ulcers of patients with multiple DFU episodes in the period of observation did not cost more, compared to the previous episode (Figure 5). Factors of influence might include better follow-up of patients with previous ulcers, treated peripheral artery disease and patient education. The main determinants of length of stay were infection and the presence of peripheral artery disease. The main cost drivers per group were patient days on the ward (48 to 60%) and consultancy costs (17 to 27%), of which the latter constituted 27% of the total costs in primary healed persons (group 1) and 15% in the major amputation group (group 4). Reducing total costs when an ulcer is already present could presumably be more easily accomplished when concentrating cost-saving strategies on those domains. It should be noted that podiatry contribution to the diabetic foot team were calculated on an hourly basis, charged to the hospital.

Several caveats relating to our study are important to highlight. The first is the use of partial prospective/retrospective, single center data which might reduce the external validity of our findings. Much effort has gone into reviewing resource use during DFU treatment. Observed resource use and data from the financial department on resource use was compared, to reduce study design associated bias. As this study is on resource of DFUs treated by a multidisciplinary team, data was not limited to a single discipline or treatment only. Moreover, we evaluated full length follow-up of all ulcers, until discharge. The provided care by the multidisciplinary team is in line with DFU care in equivalent centers in the Netherlands and Western Europe and treats sufficient patients per annum²⁴. National and international multidisciplinary diabetic foot teams are composed of the same specialists as our team, providing care according to national and international guidelines, what might justify extrapolating our results to other hospitals and therefore generalize our results to an international level¹⁴. The second caveat is that the grading and staging were done at presentation only and ulcer characteristics show a relatively low grading and staging in this population, in comparison with other diabetic foot studies²⁵⁻²⁸. Some persons had multiple

wounds or recurrent wound infection, which prolonged wound healing. Several participants had revascularization procedures, which enhance wound healing and therefore probably reduce wound-healing time. These confounding factors may have altered or undermined the expected effects of wound classification at baseline to total costs, as was assessed using correlation coefficients ($r_s = .232$, $p=0.055$). It has recently been suggested and confirmed in our data that resource use in ulceration is affected by the presence of peripheral artery disease and infection²⁹. Future larger studies should use more advanced statistical methods to determine factors associated with total costs³⁰. Third, only low numbers of participants were studied in the minor and major amputation groups. Moreover, the major amputations were preceded by minor amputations, making it difficult to estimate the total costs of only a major amputation. The costs of these episodes must be interpreted with caution, although the costs seem to be in line with other countries¹⁴. Our data have the virtues of extensive follow-up of in-hospital care with various important clinical end-points. We experienced low loss of follow-up, good alignment between observed and declared costs and had a reasonable number of primary healed ulcers. Moreover, patients were referred to the multidisciplinary in-hospital team rather quickly, with a median ulcer duration of two weeks prior to in-hospital care.

The cost of DFU disease and therapies is increasingly studied over the last decades⁶⁻⁸. It has been suggested that the costs of these lower extremity complications make up to 0.6% of total health care expenditure in the United Kingdom and costs the United States between 27.8 and 36.0 billion US dollars a year^{6,13}. However, most cost-of-illness studies used estimates of resource use and clinical opinion based on assumptions of annual incidence, prevalence, recurrence rates and healing time^{2,10,31,32}. Relatively few studies have analyzed the impact of DFUs on healthcare costs using patient-level data. Micro-costing methods are preferred in costs studies, which assess the resource use and expenditure on person level. When comparing the patient-level costs from our study to the literature, we found a recent systematic review on the subject, including studies from both the developed and developing world¹⁸. Studies were categorized in data originating from Europe, the US/Canada/Australia and developing countries. It is important to interpret these reported numbers considering differences in health care systems, with costs being generally higher in, for example, the United States. The reported average costs of DFUs per admission from a study performed in the United States were US\$ 9,661 (95% CI, 9,605 – 9,716) and when infected US\$ 12,608 (12,501 – 12,714). A minor amputation costs US\$ 11,117 (11,001 – 11,233) and major amputation US\$ 16,927 (16,370 – 17,485). When infected the associated costs were on average US\$ 3,350 higher per episode³³. A study from Canada reported the average costs for admission and emergency department and clinic visits related to DFU to be US\$ 12,411. However, it was not clear if these were the total costs for healing per DFU episode³⁴. A

Swedish study from 1994 estimated an average of US\$ 10,209 per DFU when an amputation was not required, US\$ 51,646 when a minor lower extremity amputation was carried out and US\$ 78,069 when a major lower extremity amputation was needed⁸. A Dutch study from 1993 did not differentiate between minor or major amputation, but estimated the two-year total impact on hospital care for 3,707 and 3,790 DFU related hospitalizations to costs between 38,556.960 and 37,720.020 European Currency Units. A Belgian study estimated the costs to be US\$ 8,111 per DFU episode, US\$ 7,242 to US\$ 8,966 per minor amputation and US\$ 7,058 to US\$ 51,957 per major amputation³⁵. The costs for DFU disease and lower extremity amputation are difficult to compare with the results of the important EURODIALE study²⁹. The costs reported in this European study are restricted to one-year follow-up only, with 104 out of 821 of patients not being healed within 12 months. Moreover, patients in need of an amputation were followed until this operation was performed, whereas in our study patients were followed and costs calculated until the foot or leg completely healed and the patient was discharged from follow-up. The patients who healed within 12 months, were unknown to have suffered from single or multiple ulcers and included minor amputations below the ankle. Therefore, the total average costs for patients classified in our study as primary healed (group 1) are probably lower than the EURODIALE reported total direct costs of € 7,147 (2005 price level). Our findings suggest a slight increase in DFU costs, compared with these older studies, but definite comparisons are difficult because of differences in study design, protocol and lack of standardized reporting. Eleven studies originating from several developing countries showed that costs are substantially lower. However, in the Caribbean the mean costs were closer to European countries¹⁸.

In addition to direct in-hospital costs, a considerable amount of money is related to indirect costs due to loss of productivity, reduced quality of life and costs individual persons and family members make in dealing with DFU disease^{10,36}. Studies based on North American and European data estimated that between 7 and 20% of total expenditures on diabetes is related to non in-hospital (out-patient) costs⁵. Our study concentrated on better measureable in-hospital costs, where loss of productivity is less of issue regarding the age of the studied population. It would be interesting to investigate resource use in primary care, out of hospital costs related to productivity loss and the costs associated with health-related quality of life in future studies^{37,38}. It has been estimated that in 2030 the number of people with diabetes is comparable in age distribution, therefore the contribution of indirect costs to the total costs will probably not change in the following decades³⁹. Further research on factors influencing the total costs and duration of DFU disease would be of value, particularly in larger datasets⁴⁰.

Conclusion

Despite the cost-effectiveness of the multidisciplinary foot team, DFUs still place a significant financial burden to our healthcare system, individual patients and therefore society. Economic factors of new therapies will play a more important role since not all emerging therapies can be reimbursed. The results of this study can be combined with information on life expectancy and utility values to express the health benefits of new therapies for DFU disease, in terms of quality adjusted life years. This should be of value to health care researches and policymakers investigating cost-effectiveness of interventions that prevent these costly complications.

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Chapter XVI

Cost-effectiveness of lower extremity nerve decompression surgery in the prevention of ulcers and amputations: a Markov analysis

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Abstract

Background

The costs and health effects associated with lower extremity complications in diabetes mellitus are an increasing burden to society. In selected patients, lower extremity nerve decompression (LEND) is able to reduce symptoms of neuropathy and the concomitant risks of diabetic foot ulcers and lowers the risk of amputations. To estimate the health and economic effects of this type of surgery, cost-effectiveness of this intervention compared to current non-surgical care was studied.

Methods

To estimate the incremental cost-effectiveness of LEND over a 10 year period, a Markov model was developed to simulate the onset and progression of diabetic foot disease in patients with diabetes and neuropathy who underwent LEND surgery, compared to a group receiving current non-surgical care. Mean survival time, health-related quality of life, (risk of) lower extremity complications and in-hospital costs were the outcome measures assessed. Data from the Rotterdam Diabetic Foot Study were used as current care, complemented with information from international studies on the epidemiology of diabetic foot disease, resource use and costs, to feed the model.

Results

LEND surgery resulted in improved life expectancy (88,369.5 vs. 86,513.6 life-years), gain of quality-adjusted life-years (QALYs) (67,652.5 vs. 64,082.3) and reduced incidence of foot complications compared to current care (490 vs. 1,087). The incremental cost-effectiveness analysis was -€59,279.6 per QALY gained, which is below the Dutch critical threshold of <€80,000 per QALY.

Conclusions

Decompression surgery of lower extremity nerves improves survival, reduces diabetic foot complications, is cost saving and cost-effective compared with current care, suggesting considerable social-economic benefit for society.

Introduction

The prevalence of diabetes mellitus has quadrupled since 1980, accounting for 422 million of cases in 2014, with the majority of the rise explained by increasing rates of diabetes in developing countries¹. This number is expected to increase further in the years to come, which is directly related to the rising prevalence of obesity, sedentary lifestyle and unhealthy diet, on top of the continuous expanding and ageing global population². Therefore, the number of complications of diabetes is also expected to increase, posing a worrisome burden of disease, treatment and costs for society. The burden of lower-extremity complications as seen in diabetes mellitus is worrisome and expensive at both patient and society level. The costs of diabetic neuropathy, foot ulceration (DFU) and lower extremity amputation (LEA) are already immense, with reports of burden on public and private payers ranging from US\$ 9 to 13 billion in addition to the costs of diabetes itself^{3,4}.

To diminish the burden to society, various strategies have been implemented to reduce the incidence of new DFU or deterioration into LEA^{5,6}. Regrettably, symptoms of neuropathy have proven to be tenacious, with few convincing long-term solutions available tackling the symptoms of neuropathy and its consequent fearsome sensory loss⁷. Yet, emerging evidence reveals that entrapped lower extremity nerves are frequently observed in patients with diabetes, with increasing prevalence in patients reporting symptoms of neuropathy^{8,9}. Therefore, the so-called stocking and glove distribution of neuropathy might be explained by multiple compressed nerves in both the upper and lower extremity¹⁰. A potential cost-effective intervention is the surgical decompression of entrapped lower extremity nerves (LEND surgery), of which health benefits and significant supportive clinical evidence has been previously reported¹¹⁻¹³. More specifically, improvements in pain and sensation after LEND surgery resulted in fewer observed DFUs and LEAs, compared to non-operated subjects with diabetes^{12,14}. These findings may eventually save lives, since ulceration is independently associated with death¹⁵. Despite these promising results, the long-term costs, the health gains and the cost-effectiveness of LEND surgery have not been determined in a clinical study. A cost-effectiveness analysis is useful to evaluate the gain in health benefits for patients of a new treatment strategy compared to current care, to assess its 'value for money' and to support health care policy decisions regarding insurance package coverage and reimbursement¹⁶.

The aim of our study is to assess the long-term health benefits, the cost consequences and incremental cost-effectiveness of LEND surgery relative to current care, in a group of diabetic patients with neuropathy at risk for lower extremity complications.

Methods

Markov model

A Markov model is a statistical technique to analyze uncertain processes over time. It is particularly useful when there is an ongoing risk over a longer time and when important events might happen more than once, as in diabetic foot complications. Therefore, Markov models are particularly suited to model the course of disease when events are likely to recur over time and the resulting consequences, such as long-term outcomes, costs and effects¹⁷. A Markov model consists of two or more health states. The number and nature of the states are chosen regarding the health or decision problem¹⁸, that is, each health state is thought to be homogeneous in terms of resource use (costs) and health outcomes (effectiveness). Between two cycles, time progresses with one unit, and patients can transit between health states, stay in a health state, or die. The probability to stay in that state or move to another state is expressed as transition probabilities. Through the cycles, the patients are followed individually over their lifetime.

Figure 1 shows our Markov model. It shows eight possible health states a diabetic subject may be confronted with during life including neuropathy, DFUs (uncomplicated, infected or ischemic), primarily healed after ulceration, minor amputation, major amputation and death. All patients start their course of disease in the state 'Diabetes with neuropathy'. We assumed that all lower extremity amputations (LEAs) are preceded by DFUs, since diabetes underlies up to 8 of 10 non-traumatic amputations, of which 85% are preceded by a DFU¹⁹. Neuropathy symptoms are partially explained by the existence of multiple compression neuropathies²⁰. We assume for this study that diabetic sensorimotor polyneuropathy and compression neuropathies do not render patients differently at risk regarding ulceration and consequent amputation²¹. Table 1 displays the 6-months transition probabilities used. The time horizon was 10-year or 20 cycles of 6 months. The 6 month cycle length corresponds to wound healing times, being between two to eight months²².

Table 1 Transition probabilities between health states in current care and after LEND surgery (cycle length a half year).

Transitions			Transition probability	
Health states			Current care	After LEND surgery
Diabetes with neuropathy	>	Diabetes with neuropathy	.95(1)	.971*
	>	Uncomplicated DFU	.022(1)	.001(2)
	>	Infected DFU	.014(1)	.014(1)
	>	DFU with ischemia	0(1)	0
Uncomplicated DFU	>	Death	.014*	.014^
	>	Primary healed	.9825(1)	.983(1)
	>	Death	.0175(1)	.018^
Infected DFU	>	Primary healed	.4(1)	.4*
	>	Minor amputation [#]	.35(1)	.35(1)^
	>	Major amputation [#]	.09(1)	.09(1)^
	>	Death	.16(1)	.16^
DFU with ischemia	>	Primary healed	.38(1)	.779^
	>	Minor amputation [#]	.13(1)	.001(2)
	>	Major amputation [#]	.27(1)	0(2)
	>	Death	.22(1)	.22
Primary healed	>	Primary healed	.803(1)	.933*
	>	Uncomplicated DFU	.097(1)	.019(2)
	>	Infected DFU	.044(1)	.002(2)
	>	DFU with ischemia	.029(1)	.019(2)
	>	Death	.027(1)*	.027^
Minor amputation [#]	>	Minor amputation	.76(3)	.76(3)
	>	Uncomplicated DFU	.013(3)	.013(3)
	>	Infected DFU	.044(1)	.044(1)
	>	DFU with ischaemia	.029(1)	.029(1)
	>	Major amputation	.127*	.127*
Major amputation [#]	>	Death	.027(1)	.027^
	>	Major amputation [#]	.88(1)	.88^
	>	Death	.12(1)	.12^

Abbreviations: LEND, lower extremity nerve decompression; DFU, diabetic foot ulcer; *, cumulative transition probability; ^, same as current care transition probability; #, an amputation could only be preceded by an infected or ischemic DFU.

Figure 1 Transition probabilities between health states in current care and after LEND surgery (cycle length a half year).

Legend: health states a diabetic subject with neuropathy may reside in ('death' is not displayed as balloon).

Modeling LEND surgery and current care

The model simulated two hypothetical cohorts of diabetic patients. The first cohort was modeled as patients with diabetes and neuropathy receiving LEND surgery and the second as diabetic patients with neuropathy receiving current (non-decompression) care. For both cohorts it was assumed that they received care for their feet according to international guidelines²³, including prescription of analgesic drugs, mechanical offloading when necessary, treatment of peripheral artery disorders, and amputations when necessary.

For the current care cohort, data were obtained from the Rotterdam Diabetic Foot Study (RDF Study), a prospective cohort study of unselected diabetic patients followed at the outpatient Diabetes Clinic of Franciscus Gasthuis & Vlietland hospital, Rotterdam, the Netherlands. Aim of the RDF Study is to investigate the natural history of (compression) neuropathy, including deterioration of sensation of the feet. The RDF Study design and methods have been described in detail^{9, 24-26}. Two hundred forty-one diabetic males and

175 females (42.1%) were included (mean (SD) age 61.8 years (12.4), range 21.6 – 90.2), of whom 44.0% (95%CI: 38.8-49.2%) had symptoms of neuropathy at baseline (Michigan Neuropathy Symptom Score ≥ 4). This studied cohort had varying sensory loss, as indicated by the Rotterdam Diabetic Foot Study Test Battery score²⁴. A positive Tinel sign at the tarsal tunnel was found in 44.9% (95%CI: 40.1-49.7%) of patients, which increased to 50.3% (95%CI: 41.5-58.5%) when reporting more symptoms of diabetic neuropathy⁹.

The model was illustrated using a base case of a 62-year-old diabetic patient with neuropathy due to super-imposed compression neuropathies of the lower extremities. The mean age of diagnosis of diabetes corresponds to the mean age of RDF Study patients; all patients of both cohorts were assumed to start in their 62nd life year. To ensure consistency, data from comparable populations were preferred to feed the model^{17, 27}.

Data on effects and effectiveness of LEND surgery were retrieved from the literature¹². LEND surgery is carried out in patients with signs of superimposed nerve compression of the tibial nerve at the tarsal tunnel, common fibular nerve near the head of the fibula, deep peroneal nerve at the dorsum of the foot and superficial peroneal nerve just proximal of the ankle. The major indication of this intervention is relief of symptoms of neuropathy. The consequent gain in sensation at the feet, caused by tibial neurolysis, results in a lower likelihood of plantar DFU and consequent LEA²⁸⁻³¹. Literature data from the literature were used to obtain incidence and prevalence rates of lower extremity complications for both cohorts (Table 1). Table 1 displays the consequent reduction in 6-month risks of for lower extremity complications for the LEND surgery and current care cohorts.

Cost-utility analysis

After running, the Markov model reveals how many patients from the LEND surgery and current care cohorts have spent time in each health state. The main outcome measures were cumulative incidences of foot ulcers, minor and major amputations, and death after 10 years. Moreover, the cumulative (total) costs and quality-adjusted life years (QALYs) after 10-years of treatment, and incremental cost-utility of LEND surgery versus current care can be estimated once the costs and utilities of each health state have been added. Cost utility analysis (CUA) was considered the appropriate framework because of the differences in health-related quality of life across the health states.

Costs

The CUA took a hospital perspective, i.e., only included direct in-hospital costs. Considered were costs on in-hospital stay, consultancy costs, (surgical) interventions, microbiology and clinical laboratory tests, drugs, radiology and pathology²². Costs were expressed in Euros

and whenever necessary adjusted to the 2015 price level using the consumer price index and discounted by 4%, in accordance to the Dutch guidelines for pharmacoeconomic research³². Annual costs were transformed to half-year values in agreement with the 6-month cycle in the Markov model. Table 2 displays an overview of the estimated resource use and costs per unit. The costs associated with the treatment of neuropathy was retrieved from the literature³³. Costs of LEND surgery were derived from the financial department of University Medical Center Utrecht (mean: €1435). Surgical site infection associated with LEND surgery was accounted for, since this is reported to occur in 5.9% of diabetic patients¹². Costs of surgical site complications were derived from literature (mean: €400)³⁴.

Table 2 Health utility parameters per health state.

Health state	Utilities (QALYs)	
	<i>Base case</i>	<i>95%CI for sensitivity analyses</i>
Diabetes with neuropathy	.84	.81 to .87
Uncomplicated DFU	.75	.71 to .79
Infected DFU	.70	.66 to .75
DFU with ischemia	.59	.53 to .65
Primary healed	.60	.51 to .69
Minor amputation	.68	.63 to .72
Major amputation	.62	.57 to .67

Abbreviations: QALYs, quality adjusted life years.

Utilities

QALY is the universal outcome measure in healthcare and the method of choice in cost-effectiveness studies. A QALY is a combined measure of quality of life (life expectancy) and health-related quality of life. A QALY is calculated as time spent in a health state times the utility or the valuation of that health state³⁵. The utility score ranges from 0 (death) to 1 (perfect health); a higher utility score represents a better health state. QALYs were transformed to 6 months values in agreement with the 6-month cycle length. Utility values were derived from literature. QALYs were discounted by 1.5%, following Dutch guidelines for pharmacoeconomic research (Table 3)^{17, 36, 37}.

ICUR

The outcome of the cost-effectiveness study is the incremental cost-utility ratio (ICUR), defined as the difference in (discounted) cumulative costs between LEND surgery and current care, divided by the difference in (discounted) cumulative QALYs between these strategies, and depicted in the Cost-Effectiveness plane. We also calculated the absolute cost-utility ratio of each strategy, the course of the ICUR over time, the net-monetary benefit (the linear combination of costs and effects (expressed in Euros) and the net-health benefit (expressed in QALYs).

Table 3 Cost estimates per health state.

6 month average (Euros)		
Health state	Base case	Interquartile range for sensitivity analyses
Diabetes with neuropathy	574	115-746
Uncomplicated DFU	10,145	2102-12,949
Infected DFU	9545	1722-12,408
DFU with ischemia	34,939	12,958-46,560
Primary healed	10,145	2102-12,949
Minor amputation	10,968	2194-14,259
Major amputation	27,444	5489-35,677
Transition costs		
Minor amputation	4107	821-5339
Major amputation	7900	1580-10,270

Legend: costs are in Euro's (2015) and rounded. Costs for LEND surgery were €1435 plus €400 for surgical site infections, which occur in 5.9% of operations.

To support decision making, a willingness-to-pay (WTP) threshold of €80,000 extra per QALY gained was used, which represents the maximum amount the Dutch society is willing to spend to prolong life with one year of perfect health (i.e., €20,000 to €80,000 per QALY gained, depending on the burden of disease)³⁸. We added a cost-effectiveness acceptability curve (CEAC), which depicts the probability that a specific strategy is cost-effective at different thresholds of willingness-to-pay per QALY.

Statistical analyses

Absolute risk reduction and number needed to treat were calculated. Sensitivity analyses are an important part of cost-effectiveness analysis, since the method is based primarily on assumptions. Varying the model parameters is used to assess the robustness and validity of the ICUR (point estimate) and other outcomes³⁹. Probabilistic sensitivity analyses were performed on the effectiveness of LEND-surgery, transition probabilities, (transition) costs and utility weights, using 10,000 Monte Carlo simulations. Values were varied according to published data. The Beta distribution was used for transition probabilities, the Gaussian distribution for utility weights and the Gamma distribution for costs. Microsoft Excel 15.14 (Microsoft Corp., Redmond, Washington, USA) and the R software (2019) with package markovchain (R Foundation for Statistical Computing, Vienna, Austria) were used for building the model.

Results

Base case analysis

Table 4 shows the impact of LEND surgery on the incidence of DFU, minor amputations, major amputations and death at 10-years follow-up (10,000 Monte Carlo simulations) for a 62-year-old diabetic patient with lower extremity compression neuropathies who is at risk for lower extremity complications. With LEND surgery, about 55.7% of the simulated cohort remained in the health state 'diabetes with neuropathy' (i.e., after surgery, thus with symptom relief), about 60% higher than current care (relative risk (RR): 1.6). Moreover, with LEND surgery, a simulated 312 DFUs (risk difference (RD): 3.1, RR: 0.3) and 285 amputations (RD: 2.9, RR: 0.6) could be prevented compared to current care. The number needed to treat (with LEND surgery) to reverse risk for DFU and amputations was 32.0 and 35.1, respectively.

Table 4 also shows that with LEND surgery fewer patients will die within 10 years (RD: 5.0, RR: 0.9). The fewer observed lower extremity complications in the LEND surgery cohort resulted in less mortality and more lives saved compared to current care strategies (6335 versus 6840, respectively; or 505 lives saved in favor of LEND surgery) and, consequently, more (discounted) life-years saved (88,369.5 vs. 86,513.6; or 1855.9 life-years gained in favor of LEND surgery), and more discounted QALYs (67,652.5 vs. 64,082.3; or 3570.2 QALYs gained with LEND surgery), at lower discounted costs (€46,973 vs. €68,172; or €21,199 saved with LEND surgery). Costs are initially higher for LEND surgery due the costs of surgery and surgical site infections in the first cycle but are surpassed by the costs of current care from 19 months onwards.

Cost-utility analysis

Figure 2 shows the results of the probabilistic sensitivity analysis on the absolute and incremental cost-utility ratio (ICUR) when the parameter values are varied (Tables 1-3). Figure 3 shows the cost-effectiveness plane, visualizing the variation in incremental health effects and incremental costs for 10,000 iterations. LEND surgery is likely to be less costly and more effective compared to current care (89.69% of iterations result in a position in the southeastern plane).

Table 4 10-year cohort stimulation results comparing the incidence of lower extremity complications between the two strategies.

Health state	Current care (n=10.000)		LEND surgery (n=10.000)		Risk calculations			
	Patients (n)	Absolute risk (%)	Patients (n)	Absolute risk (%)	Absolute risk (%)	Absolute risk reduction (%)	Relative risk	Relative risk reduction (%)
Diabetes with neuropathy ^Δ 3585*								
Uncomplicated DFU	248	2.5	21	0.2	2.8	0.1	91.5	44.1
Infected DFU	137	1.4	88	0.9	0.5	0.7	35.5	206.2
DFU with ischemia	55	0.6	19	0.2	0.4	0.3	66.5	271.9
Primary healed	1663	16.6	780	7.8	8.8	0.5	53.1	11.3
Minor amputation	239	2.4	144	1.4	1.0	0.6	39.9	104.8
Major amputation	408	4.1	218	2.2	1.9	0.5	46.5	52.7
Death	3665	36.6	3160	31.6	5.0	0.9	13.8	19.8
Total DFUs[*]	440		128		4.4	0.3	70.9	32.0
Total amputations[#]	647		362		1.3	0.6	44.1	35.1

Legend: LEND, lower extremity complications; *, aggregated numbers from the health states 'Uncomplicated DFU', 'Infected DFU' and 'DFU with ischemia'; #, aggregated numbers from the health states 'Minor amputation' and 'Major amputation'; Δ, not progressed to another health state.

Figure 2 Cost-effectiveness plane.

Legend: costs in Euros (€); QALY, quality adjusted life year; LEND, lower extremity nerve decompression surgery.

The ICUR (point estimate) was -€59,279.6 per QALY gained. The ICUR is not only lower than the threshold of €80,000 per QALY gained for societal decision-making, but is also negative, implying that with LEND surgery instead of current care, costs on average are lower (€21,199) and QALYs on average are gained (3507.2). LEND surgery is therefore the dominant strategy. Figure 4, shows the ICUR over time, indicating that LEND surgery is the preferred option after 18 months.

Figure 3 Incremental cost-effectiveness plane.

Legend: costs in Euros (€); QALY, quality adjusted life year.

Figure 5, the acceptability curve (CEAC), indicates that the probability for LEND to be cost-effective is over 90% for any positive maximum amount that society is willing to pay for a QALY. At a societal WTP of €80,000, the net monetary benefit for current care was €444,486.3 and for LEND surgery €494,246.9. The net health benefit was 6.4 vs. 6.8. Both indicate that LEND surgery is the preferred strategy.

Figure 4 Incremental cost-effectiveness ratio over time.

Legend: ICER, incremental cost-effectiveness ratio; LEND, lower extremity nerve decompression surgery.

Discussion

This study used a Markov decision model to project the epidemiological outcomes and cost-effectiveness of two cohorts of diabetic subjects with nerve compressions in the lower extremities, receiving either LEND surgery or current care. Our results suggest that LEND surgery is superior in relieving neuropathy symptoms and avoiding lower extremity complications, thereby saving life years and improving quality of life, at lower costs. Both Dutch and US health technology assessment criteria suggest that LEND surgery is a cost-effective strategy compared to the current care of diabetic subjects with neuropathy.

Figure 5 Cost-Effectiveness Acceptability Curve.

Currently, the only viable treatment of neuropathy symptoms include analgesic drugs (e.g. anticonvulsants and tricyclic antidepressants), but these are not very effective and associated with serious risks, and do not improve sensation in the insensate foot⁴⁰. Yet, the high prevalence of treatable nerve entrapments in the lower extremity of diabetic subjects gave rise to a surgical approach to these refractory symptoms^{29, 41}. Despite being still controversial, cumulative data suggests an important role for the peripheral nerve surgeon in identifying the patient at risk, with consequent treatment recommendations^{20, 42, 43}. The positive effects of LEND surgery are underscored by other studies from different research groups, on various outcome parameters^{44, 45}, including sensibility tests, balance, pain, nerve conduction studies, tibial nerve ultrasound and electromyographic recordings.

Moreover, these studies suggest that LEND surgery is safe with respect to risk of surgical site infection (5.9 vs. 9.5% in other types of lower extremity surgery, and infections that do occur are usually straightforwardly treated^{12, 46}. We included surgical site infections in our model and LEND surgery was cost-effective after month 18. Given this key-result, we argue that a broader implementation of LEND surgery is possible. Multidisciplinary foot teams have proven to be cost-effective and are broadly available these days^{16, 17, 27, 47}; as are plastic surgeons and podiatrists with expertise in peripheral nerve surgery. Moreover, an epidemiological study on the prevalence of tibial nerve compression showed that this condition is up to 61% more prevalent in diabetic subjects compared to non-diabetic controls^{9, 21}. Beyond the favorable cost-effectiveness of LEND surgery, out-of-hospital factors such as caregiver relief are probably significant.

Several caveats of our study are important to highlight. Firstly, like any model, the validity of the results depends on the validity of the input data and the Markov model structure. The majority of the transition probabilities were derived from Swedish data, which roughly matched our population data, but was perhaps somewhat dated (years 2001 and 2004)^{17, 27, 29}. Moreover, only patients with neuropathy were modeled to undergo LEND surgery, since previous research suggested that only patients with mild to moderate nerve damage would benefit most from this type of surgery¹³. However, recent studies report on decompression surgery in patients with a history of DFU, although an indicator of end-stage nerve function, show that the recurrence risk of ipsilateral DFU is lowered to 1.6% per year^{24, 25, 48}. Treating this vulnerable group with LEND surgery could lead to an extra health gain. Larger prospective studies should investigate these effects to corroborate (or redesign) the Markov model structure and its input data⁴⁹. Treating this vulnerable group with LEND surgery could lead to an extra health gain.

Secondly, we did not include the costs and health effects of accidental falls in our analysis, which is an important source of disease burden and costs⁵⁰. A previous report suggests an improvement of balance parameters to return to normal ranges after bilateral LEND surgery, which in turn could lower the risk of falls⁵¹. The improvement of LEND surgery on reinnervating the insensate foot likely has big potential to avoid falls. Unfortunately, we could not include this effect in our model because sensation was not measured in a uniform way, nor was this study prospective and did not report fall occurrence.

Finally, we only included the hospital-based costs, thereby disregarding medical costs outside hospitals, non-medical patient-related costs, costs related to sick leave, and medical costs made during the life years gained⁵². In part, we addressed this in the sensitivity analysis. We acknowledge that these costs can be considerable, but also more difficult to

estimate⁵³. However, non-medical costs, such as patient time and transportation costs are likely to be higher in the current care group, since the complications requiring hospital visits occur more frequently in this group. Medical costs during life years gained are probably higher in the LEND surgery group. On balance, it is unclear whether the inclusion of these costs would have changed the overall cost difference.

In conclusion, LEND surgery is highly effective and cost-effective in avoiding serious adverse events and is associated with a greater survival over time and less morbidity (better quality of life) on the long-term. Large prospective studies can help to improve the model, especially the transition probabilities and utilities of the associated health states specific for lower extremity nerve entrapments. The overall conclusion that diabetic patients with neuropathy frequently have treatable nerve compression syndromes eligible for surgery provides guidance to the clinician. By examining the patient for nerve entrapments, a treatment option that affects long-term prognosis becomes available.

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The future

PART VI

Chapter XVII

(Cost-)Effectiveness of lower extremity nerve decompression surgery in diabetic subjects: the DeCompression (DECO) trial. Study protocol for a randomized controlled trial

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Abstract

Introduction

The peripheral nerves of patients with diabetes are often pathologically swollen, which results in entrapment at places of anatomical narrowing. This results in nerve dysfunction. Surgical treatment of compression neuropathies in the lower extremities (LEND) results in relief of symptoms and gain in peripheral nerve function, which may lead to less sensory loss (short term) and less associated detrimental effects including foot ulceration and amputations, and lower costs (long term). The aim of the DeCompression (DECO) trial is to evaluate the effectiveness and (cost-)effectiveness of surgical decompression of compressed lower extremity nerves (LEND surgery) compared to patients treated with conventional (non-surgical) care.

Methods and analysis

A stratified randomized (1 to 1) controlled trial comparing LEND surgery (intervention) with conventional non-surgical care (control strategy) in diabetic subjects with complaints of neuropathy due to compression neuropathies in the lower extremity. Randomization is stratified for participating hospital (n=11) and number of nerves involved. Patients and controls have the same follow-up at 1.5, 3, 6, 9, 12, 18, 24 and 48 months. Participants (n=344) will be recruited in 12 months and enrolled in all affiliated hospitals in which they receive both the intervention or conventional non-surgical care and follow-up. Outcome assessors are blinded to group assignment. Primary outcome: disease-specific quality of life (Norfolk QoL-DN). Secondary outcomes: health-related quality of life (EQ-5D5L, SF-36), plantar sensation (RDF Test Battery), incidence of ulcerations/amputations, resource use and productivity loss (iMCQ, iPCQ) during follow-up. The incremental cost-effectiveness ratio will be estimated on the basis of the collected empirical data and a cost-utility model.

Ethics and dissemination

Ethics approval has been granted by the Medical Research Ethics Committee of Utrecht University Medical Center (reference: NL68312.041.19v5, protocol number: 19-335/M). Dissemination of results will be via journal articles and presentations at national and international conferences.

Trial registration number

NL7664 (Netherlands Trial Register)

Strengths and limitations of this study

- First randomized controlled trial on bilateral lower extremity nerve decompression surgery with proper control group
- Substantial four years of follow-up to study long-term outcomes (i.e. ulcer and amputation incidence)
- First randomized controlled trial using cost-effectiveness as endpoint
- It is not feasible to blind the patients for the allocated treatment. Sham surgery is considered unethical.

Introduction

Current non-surgical care does not have satisfying treatments for the tingling, burning, electrical and painful symptoms of neuropathy and patients have nowhere to go when seeking treatment for the concomitant numbness in their feet. Refractory to therapies like antidepressants and anticonvulsants, symptoms are not treated to satisfaction and the numbness is sadly observed. Neuropathy lowers the quality of life and precedes diabetic foot disease¹⁻³. Up to 60% of patients with diabetes will be confronted with neuropathy. It has been estimated that the incidence of diabetic foot ulcers (DFUs) at some point during the disease is about 15%⁴. DFUs precede eight out of 10 non-traumatic amputations and the all-cause mortality rate after five years is 39-80%⁵⁻⁷! This is equivalent to the mortality rates of lung and colorectal cancers⁸!

The costs for society are sizeable: the average cost for a DFU episode is US\$ 10,827⁹⁻¹⁰. In the Netherlands, over one million people have diabetes and the incidence (2.8-3.5/1000 inhabitants) is still rising. In line with aims and priorities defined by the International Working Group on the Diabetic Foot (IWGDF), more effective treatments for our diabetic population are urgently needed. It is now acknowledged that many patients with symptoms of neuropathy, also have localized nerve compressions, which contribute to the symptoms¹¹. Nerves in the legs and feet also suffer from this phenomenon, which are treated surgically by releasing the nerve from the site of compression. In this way, blood flow in the nerve is restored and processes of nerve regeneration are allowed, which relieves symptoms and may consequently result in gain of sensory function¹². It is assumed that these patients have a lower risk of falls, foot ulceration and consequent lower extremity amputations. Current series report considerable pain relief of >4 points (0-10 on a visual analogue scale), occurring in 91% of patients and sensibility improvement in 69% of patients. Health-related quality of life (HRQoL) was still significantly improved in six out of eight SF-36 domains at 24

months and low peri- and post-operative complication rates are reported (pooled wound dehiscence rate of 15%)^{13 14}.

However, no high-quality real-world data exist in which lower extremity nerve decompression (LEND) surgery is compared to conventional, non-surgical care in the diabetic neuropathy population¹⁵⁻¹⁷. Since conventional non-surgical care for the patient with neuropathy outnumbers current practices compared to surgical management of entrapped lower extremity nerves, but the latter having increasingly positive evidence, it is meaningful to further investigate differences in outcomes in a randomized controlled setting.

Research aim and objectives

The aim of the DeCompression (DECO) study is to further investigate the effectiveness and cost-effectiveness of LEND surgery.

Methods and Analysis

Patient and public involvement

Both a patient panel and patient federation (Patienten Vereniging Nederland) were involved in the design of the study.

Study design and settings

This study is a multicenter, randomized controlled trial in which patients with symptomatic neuropathy and bilateral compression neuropathies of the posterior tibial nerve at the tarsal tunnel will be allocated into decompression surgery versus non-surgical follow-up. Additional compression neuropathies of the lower extremity will also be assessed (tibial nerve at soleal sling, common peroneal nerve at the fibular head, superficial peroneal nerve and deep peroneal nerve) and decompressed when in the surgical group.

The study will be performed in 11 centers in the Netherlands: Utrecht Medical University Center, Utrecht; Diaconessen Hospital, Utrecht; Franciscus Gasthuis & Vlietland Hospital, Rotterdam; Maastad Hospital, Rotterdam; Jeroen Bosch Hospital, 's Hertogenbosch; Isala Hospital, Zwolle; OLVG Hospital, Amsterdam; Amsterdam University Medical Center, AMC, Amsterdam; Amsterdam University Medical Center, VUmc, Amsterdam; Antonius Hospital, Nieuwegein and Meander Medical Center, Amersfoort.

Patient selection

Eligible for participation are all adult diabetic patients with symptoms of neuropathy in the lower extremities who are visiting the outpatient clinics of the participating hospitals (Figure 1, 2, 3 and 4). The study population concerns patients with type 1 or 2 diabetes with neuropathy symptoms (30 to 60% of diabetes patients) and with signs of super-imposed nerve compressions in the leg (up to 35%)¹⁸. Of paramount importance is to define how severe the degree of sensory loss is, as measure of peripheral nerve function and to estimate the likelihood of successful surgery^{17 19 20}. Additional inclusion and exclusion criteria are shown in the Table 1.

Table 1 Inclusion and exclusion criteria.

Inclusion criteria
In order to be eligible to participate in this study, a subject must meet all of the following criteria:
· Having diabetes mellitus (type 1 or 2)
· Patients (> 17 and < 76 years old)
· Symptoms of neuropathy (assessed with the MNSI, scoring > 3)
· A bilateral Tinel sign at the tarsal tunnel (posterior tibial nerve) and fibular neck (common peroneal nerve)
· Sufficient circulation to heal lower-extremity incisions (by palpating the peripheral arteries of the foot: a palpable dorsal pedis artery or posterior tibial artery is needed). In case of non-palpable arteries a pedal Doppler arterial waveform is evaluated. A toe brachial index (≥ 0.75) is performed when the Doppler signal is not triphasic
· Minimal or controlled pedal oedema (assessed with inspection and physical examination)
· Being fit for surgery
· Compliant with instructions for their own care
· Intact protective sensation (cutaneous threshold <10 g monofilament) at the plantar side of the foot (plantar hallux and fifth toe)
· Written informed consent
Exclusion criteria
A potential subject who meets any of the following criteria will be excluded from participation in this study:
· DFU(s) or amputation(s) in history, active radicular syndrome or neurological disease interfering with sensation of the feet, as assessed in the interview and screening questionnaire (e.g. HIV and chemotherapy induced neuropathy)
· Previous surgery at lower extremity nerve compression sites
· Active Charcot foot
· Not able to understand written and oral instructions (i.e. insufficient command of Dutch language)
· Being incompetent (incapacitated)
· Current enrollment in a clinical trial which involves surgery of the lower extremity or medical drug trials investigating the effects on neuropathy symptoms.
· Glycated hemoglobin (HbA1c) level > 11% at baseline
· Pregnant women

Figure legends Study flow charts (Figure 1-4).

Legend: LEND, lower extremity nerve decompression; MNSI, Michigan Neuropathy Screening Instrument; ADP, a. dorsalis pedis; ATP, a. tibialis posterior; +, positive.

Patients with symptoms of neuropathy have to be examined regarding the presence of compression neuropathies in the lower extremity, using the physical examination (Tinel's sign) as recommended by the American Association of Neuromuscular and Electrodiagnostic Medicine^{21 22}. Patients will undergo a thorough screening of their lower extremities (sensory tests, vascular status). The instruments of the Rotterdam Diabetic Foot (RDF) Study Test Battery will categorize each patient in their sensory loss, thereby determining whether they will be eligible for LEND surgery^{17 21}. The RDF Test Battery is used as a measure of nerve function and likelihood of nerve regeneration after surgery^{17 23}. The investigator assesses foot morphology.

Surgical intervention

Interventions will take place in all affiliated hospitals, in which both plastic- and neurosurgeons will perform LEND surgery. The aim is to operate patients within three months after randomization. A surgical release of up to four nerves in one leg will be carried out (the common-, superficial-, and deep peroneal nerves and tibial nerve at the soleal sling and tarsal tunnel). After release of the flexor retinaculum at the tarsal tunnel, the calcaneal branch and medial and lateral plantar nerves will be released via the same incision²⁴. Post-operatively, patients will be allowed to use the operated leg full weight bearing immediately and will use a walker for three weeks when necessary. In the patient who did not have pre-operative pain and who experiences pain due to nerve regeneration, a regimen of neuropathic pain medication may be started, according to the current national protocols on neuropathic pain²⁵. The contralateral leg will be operated three months later, with similar follow-up accordingly. Participating surgeons are trained to standardize the method of treatment and number of patients treated is recorded.

The following post- operative instructions are given to the subjects in the surgical group:

- The wound has to stay dry for 7 days
- The patient should keep the operated leg elevated when resting
- The patient is allowed to walk small distances the next days after the operation
- Long distance walking, running or walking the dog is not recommended and is allowed 3 weeks after surgery in case of normal wound healing
- Swimming and bathing is allowed after 14 days
- Performing sports is allowed after 3-6 weeks
- Patients will be instructed about wound problems
- Patients need to be instructed when he/she needs to contact the hospital

Conventional non-surgical care

The control group is treated to care as usual, being conventional non-surgical care, and is defined as care in line with national and international guidelines for the treatment of neuropathy and diabetic foot disease. Non-surgical care includes the treatment with analgesics, according to the national guideline on painful neuropathy, preventive measures and education for patients at risk for diabetic foot ulceration. Biomechanical offloading and foot infection treatments are provided in both groups, when required during follow-up.

Randomization

Patients will be randomized (1:1, stratified for hospital) to LEND surgery (intervention group) or current conventional non-surgical care (control group), using a web-based randomization system (Castor Electronic Data Capture). Randomization is stratified for center and number of nerves involved, implying that approximately the same numbers of LEND and control patients are treated in each center. We acknowledge that practice variation across centers may exist, but this will not bias the overall estimated effect size of LEND vs. control treatment. Patients who decline randomization will be treated to care as usual. After the end of the study, control subjects have the possibility to undergo surgery, if the surgery is proven to be superior.

Outcome measurements

Primary objective

Primary outcome: to study the influence of LEND surgery on disease-specific quality of life as measured on the Norfolk-QoL-DN questionnaire, at 48 months follow-up.

Description: The Norfolk-QoL-DN questionnaire is developed to assess patients' subjective perceptions of symptoms associated with specific nerve fiber damage occurring in diabetes and is validated in other populations^{26 27}. Questions relate to physical functioning, large

fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy and autonomic neuropathy and are summed into a total score. The questionnaire is administered at different time points during follow-up (Table 2).

Secondary objectives are (short term):

1) To study the influence of LEND surgery on balance and gait parameters at 24 months.
Secondary outcome: the difference between pedobarographic and pedothermographic imaging results between the intervention and control group.

Description: Pedobarographic imaging will be used to assess differences in plantar pressure distributions during standing and gait. Pedothermographic imaging will assess differences in vascular supply at the foot sole. Increased plantar pressure relates to the development of DFUs²⁸. Temperature measurements are shown to be of value in the prediction of tissue breakdown²⁹⁻³¹. The before mentioned measurements are carried out at baseline and 12 and 24 months of follow-up (Table 2).

2) To study to what extent pre-operative electrodiagnostic studies (used to grade the severeness of diabetic sensorimotor polyneuropathy (DSP)) account for the variation in surgical outcome (HRQoL: Norfolk-QoL-DN, SF-36, EQ-5D) at 24 months.

Secondary outcome: the influence of electrodiagnostic parameters (CMAP, DML, SNAP) on the difference in scores of HRQoL between the intervention and control group.

Table 2 Visit plan of the DECO trial.

	Baseline measurement	1.5 months (6 weeks)	3 months (12 weeks)	6 months	9 months	12 months	18 months	24 months	48 months
LEND (n=172)	Start intervention (LEND surgery)	First follow-up after operation*	Second follow-up + operation contralateral side*	Third follow-up	Fourth follow-up	Fifth follow-up	Sixth follow-up	Seventh follow-up	Eighth follow-up
Current conventional non-surgical care (n=172)	Start follow-up	First follow-up	Second follow-up	Third follow-up	Fourth follow-up	Fifth follow-up	Sixth follow-up	Seventh follow-up	Eighth follow-up
Informed consent									
Questionnaires	Norfolk-QoL-DN EQ-5D5L SF-36	Norfolk-QoL-DN	Norfolk-QoL-DN EQ-5D5L iMCQ / IPCQ	Norfolk-QoL-DN EQ-5D5L iMCQ / IPCQ	Norfolk-QoL-DN EQ-5D5L iMCQ / IPCQ	Norfolk-QoL-DN EQ-5D5L SF-36 iMCQ / IPCQ	Norfolk-QoL-DN EQ-5D5L SF-36 iMCQ / IPCQ	Norfolk-QoL-DN EQ-5D5L SF-36 iMCQ / IPCQ	Norfolk-QoL-DN EQ-5D5L SF-36 iMCQ / IPCQ
Physical assessment	RDF Tests (n=344)			RDF Tests (n=344)	RDF Tests (n=344)	RDF Tests (n=344)	RDF Tests (n=344)	RDF Tests (n=344)	RDF Tests (n=344)
Venipuncture	N=344					n=344	n=344	n=344	n=344
Electrodiagnostic testing	n=80					n=80	n=80	n=80	n=80
Quantitative sensory testing	n=80			n=80		n=80	n=80	n=80	n=80
Balance & Gait	n=80					n=80	n=80	n=80	n=80

Legend: LEND, lower extremity nerve decompression; RDF, Rotterdam Diabetic Foot Study Test Battery; AEs, Adverse Events; SAEs, Serious Adverse Events; iMCQ, Medical Consumption Questionnaire; IPCQ, Productivity Costs Questionnaire; QoL, Quality of Life; DN, diabetic neuropathy; *, when wound problems are assessed.

Description: Since diabetes induces nerve damage, surgical outcome after LEND is presumably related to the degree of pre-operative nerve functioning. To assess this relationship, validated electrodiagnostic parameters are used to grade nerve functioning, as well to monitor nerve parameters during follow-up, according to an established protocol from the Rotterdam Study³².

3) To study to what extent pre-operative nerve damage influences the results of LEND surgery on balance and gait parameters, Visual Analogue Scale (VAS) neuropathy scores, HRQoL and symptoms at 24 months.

Secondary outcome: the influence of RDF Test Battery/QST scores on the difference in balance and gait parameters, VAS neuropathy scores, HRQoL and symptoms (Michigan Neuropathy Screening Instrument (MNSI)) between the intervention and control group.

Description: The relationship between the degree of pre-operative diabetes induced nerve damage and surgical results of LEND on before mentioned outcomes will be assessed¹⁷.

Secondary objectives are (long term):

1) To study if LEND surgery is cost-effective, compared to conventional non-surgical care (HRQoL, resource use, productivity loss), at 48 months.

Secondary outcome: the difference between HRQoL, resource use (based on data from hospital financial systems, general practitioner, national databases) and productivity loss (Medical Cost Questionnaire (iMCQ) and Productivity Cost Questionnaire (iPCQ)) between the intervention and control group. Cost-effectiveness will be evaluated as the incremental cost-utility ratio (ICUR/ICER) of LEND surgery compared to conventional non-surgical care.

Description: Cost-effectiveness of LEND compared to conventional care is estimated by comparing HRQoL, medical costs (resource use due to DFUs, amputations, falls) and productivity loss between the two strategies at 48 months of follow-up (Table 2).

2) The influence of LEND surgery on gain in sensory function at 48 months.

Secondary outcome: the difference in RDF Test Battery scores and QST between the intervention and control group.

Description: Since the compression component in neuropathy of peripheral nerves is released with LEND surgery, processes of remyelination and axon outgrowth are allowed. To study these processes over time, somatosensory testing of the (foot) skin is conducted at different time-points during follow-up (Table 2)^{17 20 33}.

3) To study to what extent this surgical procedure results in lower risk of diabetic foot ulceration, amputation and falls at 48 months.

Secondary outcome: the difference in incident diabetic foot ulceration, amputation and falls between the intervention and control group.

Description: Reinnervation of the skin presumably relates to lower odds of lower extremity complications and falls during follow-up. To study this, besides quantification of skin sensation, incident ulceration, amputations and falls are monitored during the total duration of the study (Table 2).

4) To study to what extent pre-operative nerve damage influences the results of LEND surgery (i.e. HRQoL, sensory function and the incidence of ulceration, amputation and falls) at 48 months.

Secondary outcome: the influence of baseline nerve function, as assessed with the RDF Test Battery and QST instruments, on HRQoL, RDF Test Battery scores, QST, incident ulceration, amputation and falls.

Description: It is expected that the degree of pre-operative nerve damage serves as an effect modifier on these outcomes^{17 20 33}.

Study procedures

Utrecht Medical University Center is the coordinating center and responsible for training the participating surgeons in both the anatomy lab and during live surgery demonstrations. Outcomes will be evaluated in terms of HRQoL (Norfolk QoL-DN, EQ-5D-5L, SF-36), balance and gait parameters, sensory function, incident ulceration, amputation and falls, resource use and productivity loss (Table 2). The follow-up moments are at 1.5, 3, 6, 9, 12, 18, 24 and 48 months and include clinical checkups and wound checkups. Outcome assessors are blinded to group assignment (locations of incisions are blinded, and patients are instructed before the assessment). Patients will be asked regarding their resource use according to the intervals.

All participants are treated according to current standards of diabetic foot care, according to national and international (International Working Group on the Diabetic Foot (IWGDF)) guidelines. The duration of the study is 5 years in total. Inclusion of participants is expected to last 12 months in total. The follow-up period is 48 months.

Laboratory results and relevant data on the medical history will be retrieved from the patient file. In screening patients on neuropathy symptoms the MNSI will be used. Degree of neuropathy symptoms will also be evaluated with the Visual Analogue Scale and will be used for both legs and feet separately. The VAS is a straight line, the ends of which are the extreme limits of the sensation being assessed. The line is 10 cm in length, using a 10-point scale ranging from 1 to 10, with 1 being barely perceptible and 10 being intolerable. All patients are given questionnaires to assess baseline neuropathy symptoms (Norfolk QoL-DN) and quality of life (SF-36, EQ-5D5L).

Sensory status

The RDF Study Test Battery consists of monofilament testing, two-point discrimination, vibration sense testing and questions on previous ulcers/amputations and its clinical utility has been validated^{19,20}. The RDF Study Test Battery instruments (tuning fork, monofilament) are validated and part of both the neuropathy and diabetic foot care guidelines³⁴. The total time needed to execute the tests of the RDF Study Test Battery is approximately 30 minutes.

Quantitative Sensory Testing (QST)

To study the effects of LEND surgery on sensory loss (small and large fiber functions) and sensory gain (hyperalgesia, allodynia, hyperpathia), we combine the instruments of the RDF Test Battery with the instruments used in the battery of the German Research Network on Neuropathic Pain (DFNS). In two centers (in total 80 patients, 40 in each arm) the QST measurements will be carried out. The DFNS instruments measure thermal detection thresholds for the perception of cold, warm and paradoxical heat sensations, thermal pain thresholds for cold and hot stimuli, mechanical pain sensitivity including thresholds for pinprick and blunt pressure, a stimulus-response function for pinprick sensitivity and dynamic mechanical allodynia and pain summation to repetitive pinprick stimuli. The procedures described below are derived from and according to the QST protocol for clinical trials of the DFNS and are applied at the plantar side of the foot³⁵.

Thermal detection, thermal pain thresholds and paradoxical heat sensations

The tests for thermal sensation are performed using a TSA (MEDOC, Israel) thermal sensory testing device. Cold detection threshold (CDT) and warm detection threshold (WDT) are measured first. The number of paradoxical heat sensations (PHS) is determined during the thermal sensory limen procedure (TSL, the difference limen for alternating cold and warm stimuli), followed by cold pain threshold (CPT), and heat pain threshold (HPT). Of three consecutive measurements, the mean threshold temperature is calculated. All thresholds are obtained with ramped stimuli (1 °C/s) that are terminated when the subject presses a button. Cut-off temperatures are 0 and 50 °C. The baseline temperature is 32 °C (center of

neutral range) and the contact area of the thermode is 7.84 cm². During the session, subjects are not able to watch the computer screen. All tests are first demonstrated over an area that is not tested in the session.

Mechanical pain threshold for pinprick stimuli

Mechanical pain threshold (MPT) is measured using a set of seven custom-made weighted pinprick stimulators that exert forces between 8 and 512 mN. Using the method of limits, the final threshold is the geometric mean of five series of ascending and descending stimulus intensities.

Stimulus-response-functions: mechanical pain sensitivity for pinprick stimuli and dynamic mechanical allodynia for stroking light touch

Mechanical pain sensitivity (MPS) is tested using the same weighted pinprick stimulators as for MPT. To obtain a stimulus-response-function, these seven pinprick stimuli are applied in a balanced order, five times each, and the subject is asked to give a pain rating for each stimulus on a 0-100 numerical rating scale ('0' indicating 'no pain', and '100' indicating 'most intense pain imaginable'). Stimulus-response-functions for dynamic mechanical allodynia (ALL) are determined using a set of three light tactile stimulators: a cotton wisp exerting a force of ± 3 mN, a cotton wool tip fixed to an elastic strip exerting a force of ± 100 mN and a standardized brush (Somedic, Sweden) exerting a force of ± 200 -400 mN. The three tactile stimuli are applied five times each with a single stroke of approximately 1-2 cm in length over the skin. They are intermingled with the pinprick stimuli in balanced order and subjects are asked to give a rating on the same scale as for pinprick stimuli.

Wind-up ratio – the perceptual correlate of temporal pain summation for repetitive pinprick stimuli

In this test of temporal summation, the perceived magnitude of a single pinprick stimulus was compared with that of a train of 10 pinprick stimuli of the same force repeated at a 1/s rate (256 mN). The train of pinprick stimuli is given within a small area of 1 cm² and the subject is asked to give a pain rating representing the pain at the end of the train using a numerical rating scale. Single pinprick stimuli are alternated with a train of 10 stimuli until both are done five times at five different skin sites. The mean pain rating of trains divided by the mean pain rating to single stimuli is calculated as wind-up ratio (WUR).

Pressure pain threshold

The pressure pain threshold (PPT) is determined with three series of ascending stimulus intensities, each applied as a slowly increasing ramp of 50 kPa/s, using a pressure gauge device (FDN200, Wagner Instruments, USA).

The total time needed to execute the tests of the DFNS protocol is approximately 20 minutes.

Electrodiagnostic tests

In two centers (in total 80 patients, 40 in each arm) the electrodiagnostic tests will be carried out, according to the protocol of the Rotterdam Study³². The sural sensory nerve will be measured bilaterally and the peroneal motor nerve unilaterally, since these nerves are considered the most sensitive to detect DSP. The distal peroneal nerve compound muscle action potential (CMAP) amplitude and distal motor latency (DML) are recorded at the extensor digitorum brevis muscle. Stimulation is applied to the anterior side of the ankle, 8 centimeters proximal to the recording electrode. CMAP baseline peak amplitudes below 1.1 millivolts and DML values above 6.5 milliseconds were considered abnormal. Sural sensory nerve action potential (SNAP) amplitudes are measured bilaterally with a standard recording electrode placed behind the lateral malleolus. Stimulation is applied on the posterior side of the calf, 14 cm proximal to the recording electrode. SNAP baseline peak amplitudes below 4.0 mV are considered abnormal. Electrophysiology is performed using standard techniques of percutaneous supramaximal stimulation.

Balance and gait

In two centers (in total 80 patients, 40 in each arm), balance and gait parameters will be obtained. A pedobarographic and pedothermographic image will be made of both feet of each patient. The pedobarographic image will be made using a platform with pressure sensors measurement system (Tekscan Matscan™, MA, USA or similar) and a pedothermographic image of the microvasculature will be made using an infrared camera (FLIR ONE Pro®, FLIR Systems, OR, USA). Both pedobarographic and pedothermographic images will be made of both feet of each patient. The pedothermographic image will be obtained after a 15-minute acclimatization period in an air-conditioned room (i.e. constant temperature and humidity). The plantar surface of both feet will be recorded during unloaded conditions. Next, patients will be asked to stand for 3 min on a dedicated polyethylene thermographic 'foot mirror', while recording the dynamic change of the pedothermographic image. For the pedobarographic measurements, patients will be asked to walk barefooted 5 times over a measurement system using a 2-step protocol with a self-selected, but constant walking speed.

Incidence of falls, ulcers and amputations

The incidence of falls, ulcers and amputations will be assessed at six-month intervals. Ulcer characteristics will be determined using the IWGDF Perfusion, Extent, Depth, Infection and Sensation (PEDIS) and Society for Vascular Surgery Wound, Ischemia and foot infection (WIFI) classification systems^{36 37}.

Sample size calculation

Sample size was calculated as a difference in quality of life of the total Norfolk-QoL-DN score at 48 months (primary outcome), based on our own RDF Study cohort data and the literature on LEND surgery³⁵. The sample size calculation was based on the natural logarithm-transformed Norfolk QoL scores, given the skewness of these data. The mean of the ln-transformed scores is 2.46. The SD is 1.058. For this superiority study question, we used the usual parameters: type I error=5% (2-sided) and type II error=20% (power=80%). A minimal 15% reduction of symptoms is anticipated after LEND surgery, which resulted in a total sample size of 129 per group, ratio = 1:1). Adjusting for an anticipated 25% lost to follow-up renders our total study size to be 344 patients ($129 \times 100/75 = 172$ patients per group (± 32 patients per center ($n=11$)). These numbers are also sufficient to demonstrate a reduction in the other outcome measures between the groups, such as ulceration rates: 2% vs. 15% at 48 months ($\alpha = 0.05$ (two-sided), $\beta = 0.20$ (power 80%), ratio = 1:1, corrected for multiple testing¹⁴.

Data collection, management and analysis

All patients will be analyzed according to the schedule in Table 2. Data from initial visits, hospitalization and follow-up visits will be entered into a database via an electronic data capture system (Castor EDC). Data will be recorded and analyzed without any personal identifiers by using coded information. Source documents and identifiers will be archived. All analysis will be performed on the basis of intention to treat. Reporting of this randomized controlled trial (RCT) will be performed according to the CONSORT/CHEERS (EQUATOR) guidelines. Missing data will be reported and handled with depending on the mechanism of missingness within the DECO-trial dataset.

Statistical analyses

The difference between groups in change between baseline and follow-up in QoL will be used as primary outcome. Baseline characteristics will be described with conventional statistics: means (95% confidence interval) for continuous variables with normal distributions, medians (inter-quartile range) for variables with skewed distributions and the Chi-square test (or Fisher's Exact test, if appropriate) for discrete variables. Between-group comparison of the primary end-point (Norfolk QoL-DN score) will be performed using repeated measurements analysis with time, allocated group and time * allocated group as determinants. Stratified for randomization are hospital and number of nerves involved. Basically, the same method will be followed for analysis of EQ5D5L and SF-36 profiles, over time (a different method may be selected, depending on the precise shape of the distributions). Between groups comparisons of sensory function will be performed using Wilcoxon rank-sum test repeated measurement analysis. The Between-group cumulative incidence of DFU, amputations and falls will be

tested using the Chi-square test. Between groups comparison of the time to these events will be estimated using Kaplan-Meier analysis. The role of pre-operative loss of sensation (nerve damage) as a possible effect modifier of effectiveness will be studied by adding this variable to the repeated measurements and the Kaplan-Meier analysis. Differences in surgical outcome are investigated by assessing possible effect modifiers like hospital, surgeon's experience and patient factors. Between group comparisons of balance and gait parameters will be performed using Wilcoxon rank-sum test repeated measurement analysis. Regression analysis will be used to study the influence of pre-operative electrodiagnostic parameters on Norfolk QoL-DN symptom scores at 24 months. Regression analysis will be used to study the influence of pre-operative RDF Test Battery scores on balance and gait parameters, VAS pain scores, HRQoL and symptoms at 24 months. Parameters on pre-operative nerve damage as possible effect modifier of effectiveness will also be studied by adding this variable to the repeated measurements and the Kaplan-Meier analysis.

Cost-effectiveness analyses

We will assess the cost-effectiveness of LEND surgery versus conventional non-surgical care over a period of 48 months. We will perform a cost-utility analysis using a disease progression model, quality of life and costs data. Cost-effectiveness will be evaluated as the incremental cost-utility ratio (ICUR/ICER) of LEND surgery compared to conventional non-surgical care. The confidence interval of the ICUR point estimate will be obtained with bootstrapping. Data from the DECO-study will be used to quantify length of life (survival), quality of life (based on the EQ5D5L utility scores for which 'Dutch tariffs' are available) and costs. In the view of the long-term study perspective, estimated costs are adjusted for inflation (Gross Domestic Product (GDP) index) as well as for societal time preference (discounting). Uncertainty of the estimated ICUR will be quantified using univariate sensitivity analysis ('tornado' plots) and probabilistic sensitivity analysis, depicted as cost-effectiveness plane and acceptability curves. Heterogeneity will be studied in subgroup analyses, in order to resolve uncertainty and guide subgroup-specific treatment decisions^{38 39}. Examples of subgroups include age, duration of diabetes, metabolic control, socio-economic status (level of education and current activities of daily life) and degree of nerve damage at study entry. Estimating the cost-utility acceptability curves of both treatment strategies and Value of Information Analysis will support decision-making. The economic analysis will be based on the societal perspective and on the healthcare perspective in which the direct medical and productivity costs in both groups will be compared. The friction cost method will be used to estimate the indirect costs of disease, which explicitly considers economic circumstances that limit production losses due to disease, according to recent Dutch guidelines. The costs per unit of medical consumption will be estimated, using the methods from the most recent Dutch Manual for Costing in Economic Evaluations. The biggest gain in lowering costs is

expected from the long-term prevention of diabetic ulcers and amputations. Other factors include time to ulcer and remaining life expectancy. Hospital data will be used to estimate the costs of surgery. Implementation costs of training surgeons will be considered.

The study will be monitored by Julius Center, Zeist, the Netherlands. At least one monitoring visit per year per center will be conducted. During the complete study period, all adverse events will be reported (Table 2).

Ethics and dissemination

The study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO) and General Data Protection Regulation (GDPR). Previous studies have proven that LEND surgery has beneficial effects on the pain and restoration of sensation in patients with neuropathy symptoms. However, the long-term effects of LEND surgery are not yet known regarding restoration of sensation, prevention of ulceration and amputations and cost-effectiveness, compared to conventional non-surgical care. Recruitment of patients starts in November 2019 and will be finished when all 344 patients have been followed up for 4 years, which is expected at the end of 2024.

Discussion

A proper RCT, designed and based on thorough knowledge of peripheral nerve pathology, it's associated surgical treatments and patient selection, does not yet exist in the current literature and is much needed to breach this status quo. Since current care does not provide a solution to the refractory problems of neuropathy, and the incidence of diabetes is still rising, new treatments like LEND surgery might give solutions regarding efficacy and expediency. RCTs on LEND surgery are pled for in the medical community and our previous work, the RDF-study, forms the perfect precursor of the DECO trial^{40 41}.

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General discussion

General discussion

The results of the research are discussed in five parts, from assessing the feet of the patient to future perspectives, resembling the separate parts of this thesis. The questions asked in the general introduction are answered with the results of the respective studies and more elaborated on in this part of the thesis. Furthermore, limitations of this thesis are discussed, and each part finishes with recommendations for future research.

Part I & II: 'The first order' and 'Assessing the feet of the (diabetic) patient'

To this day, tests to evaluate sensibility in the feet are not standardized. Current international guidelines on the (prevention of) diabetic foot syndrome recommends testing for loss of protective sensation and loss of vibratory sense with the 10 g monofilament or tuning fork, respectively¹. However, the number of, or which test sites to use, or how these instruments compare in identifying the at-risk foot is unclear.

In this thesis the use of objective measures of peripheral nerve function versus subjective measures of symptoms is advocated for, which enabled us to answer these long-standing questions, improving outcome measurement and advancing future (prediction) research.

Monofilament testing

What is actually tested with the monofilament? What is the neurophysiologic base and what does it mean when the test is abnormal? Monofilament testing (static one-point discrimination (S1PD)) tests the cutaneous threshold, which is the amount of force applied to the skin to elicit a response (**Chapter I**)². In normal circumstances, when a pressure is applied to the skin, the Merkel cell neurite complex is stimulated. It responds to the vertical skin displacement by the monofilament, a constant 'touch', by firing neural impulses throughout the duration of the stimulus. The fire frequency diminishes with prolonged duration but increases with increased stimulus intensity (i.e., skin indentation). These properties classify this receptor/fiber system in 'slowly adapting'. Usually 1 to 5 Merkel cells connect per axon, which are grouped in myelinated A β fibers. Damage to axons or structures connected to axons (e.g. Merkel cells) due to the pathological processes seen in diabetes result in fewer neural afferent impulses. To stimulate the remaining Merkel cells, increasing pressures are needed with, for example, thicker monofilaments, which in turn reflect increased cutaneous thresholds. Monofilament testing was found to be predictive of diabetic sensorimotor polyneuropathy (DSP), compared to nerve conduction studies, biothesiometer or neurological assessment³. One or more insensate sites is associated with prediabetes (RR 1.11 (95% CI 0.92 to 1.34), undiagnosed diabetes (RR 1.08 (0.73 to 1.61)) and diabetes (RR 1.74 (1.50 to 2.01))⁴.

Historically, doctors Semmes and Weinstein developed the monofilament (i.e., pressure aesthesiometer) as measure of skin's sensitivity to touch in order to evaluate somatosensory changes in patients who had penetrating brain injuries⁵. In 1898, Von Frey had started developing precursors of monofilament testing, which were thorns glued to the end of a hair, calibrated on a balance, determining pressure sensitivity by noting whether the bended hair produced a response. Semmes and Weinstein presented a set of 20 nylon monofilaments, which range in diameter from 0.0635 to 1.1430 mm, with a cross-sectional area of 0.0032 to 1.0261 mm². The force produced when the filament bows ranges from 0.0045 to 447 g, and when cross-sectional diameter is taken into account the stress (i.e., pressure: bowing force divided by cross-sectional area) is 1.4063 to 435.6301 g/mm². The monofilaments are usually equipped with a number (M), representing the decimal logarithm of 10 times the bowing force in milligrams: $M = \log_{10} (10 * \text{bowing force in mg})$. In clinical practice, the forces produced differ slightly from theoretical numbers⁶. The commonly used 5.07 monofilament produces a force ranging from 8.5 to 10.2 grams, for example. This is therefore the biggest criticism, that the monofilament tests a range and not the exact cutaneous threshold, influenced by manufacturing processes, age of the monofilament and conditions such as temperature and humidity⁷⁻⁹. Moreover, higher pressures applied may be associated with pain, masking the measurement of the sensory modality of interest. Nonetheless, monofilament testing has proven to be of value in different settings, in both the developed and developing world and reproducibility in the lower extremity has been found good, with high inter-observer (0.92) and intra-observer reliability (0.63 to 1.00)^{10,11}.

Since long, sensory loss has been shown prospectively to be predictive of ulceration and much lessons are learned from seminal work in leprosy¹². Several instruments were used, including vibratory (biothesiometer) and pain measurements, but since the eighties of the twentieth century the monofilament got into vogue for its use in the lower extremity¹³. Much expertise in somatosensory testing comes from evaluating pathologies seen in the upper extremity (i.e., nerve compressions, nerve regeneration after transection), in which the monofilament has had a long-standing place⁸. The lowest threshold of sensation surrounding ulcers of both leprosy and diabetic patients was found to be the 6.10 monofilament (force: 75 g)¹⁴. It was therefore concluded that the next monofilament of the set of three, the 5.07 (10 g), would be a good indicator of intact 'protective sensation', protecting these patients from neuropathic foot ulceration when sensate to that stimulus. Although the term 'protective sensation' was never officially related to the 10 g monofilament test at the feet, prospective studies have since then shown that inability to feel the 10 g monofilament was predictive of ulceration and the phrase became associated with the 5.07 marking, and was adapted in international guidelines on the prevention of the diabetic foot^{1,15,16}.

In the studies reviewed by Feng et al., diabetic patients were categorized according to the number of sites insensate to the monofilament, ranging from one to nine on both feet¹⁵. Insensate at one test site is associated with an increased risk for diabetic foot ulceration (DFU). However, the problem when comparing these studies lies in the differences in the number of test sites used and that there is no standardization in how and where to test at the feet. As advocated in **Chapter II**, we propose to assess sensation at places of the foot that exhibit less callous formation: hallux, fifth toe, medial heel, first dorsal web and lateral foot¹⁷. In this way, the true threshold is more adequately estimated, making test results more valid and reproducible. Moreover, different peripheral nerves are thereby tested. According to the presented normative threshold data, the cutaneous threshold has quite a range, especially in higher age categories. One explanation is the logarithmic character of the 20-piece monofilament set, with greater 'steps' in amount of force with increasing monofilament marking and thereby losing sensitivity. Another explanation is the fact that a monofilament tests a range (between monofilaments) and not the true threshold. Since age is associated with declining sensibility, we advocate using multiple monofilaments in a screening setting (e.g. 1.0, 4.0, 10 and 60 g) to get a better estimate of pedal cutaneous thresholds¹⁸. In assessing S1PD at the feet of diabetic patients, the 10 g monofilament is sufficient since it is predictive for lower extremity complications when not felt and is cheap and fast to conduct. Categorizing (plantar) thresholds at the feet in 'normal', 'diminished light touch', 'diminished protective sensation', 'loss of protective sensation' and 'deep pressure sensation' are only used by manufacturers of monofilaments and are surprisingly not based on normative data. Yet, from the results of **Chapter II** we suggest to use 'normal' for plantar cutaneous thresholds up to 4 gram at the hallux and fifth toe, 'diminished light touch' for up to 10 gram, and 'loss of protective sensation' for >10 gram. For cutaneous thresholds at the medial heel, first dorsal web and lateral foot we propose to use 'normal' when the cutaneous threshold is ≤ 2 gram, 'diminished light touch' for >2 g and ≤ 10 gram and 'loss of protective sensation' for >10 gram¹⁷.

Since sensory loss due to DSP is generally symmetrical in nature, few test sites are needed to estimate overall sensory status (**Chapter VI**)¹⁹. Recommended from the results of this thesis is testing sensibility at the hallux, fifth toe, medial heel, first dorsal web and lateral foot and abandoning the metatarsal heads or plantar heel as test sites, since much more information is derived from the before mentioned locations compared to the latter two, of which there is no evidence nor added value.

Two-point discrimination

Originally developed by Ernst Heinrich Weber (1795-1878), the two-point threshold technique or the Weber test is now known as the classical (static) two-point discrimination (S2PD)

test. Measuring innervation density of the slowly-adapting fiber/receptor population, it has an important place in both neurological and peripheral nerve surgery practices. Since it represents axonal decline when aberrant, it represents end-stage nerve compression^{20,21}. On the other hand, when used to follow the process of nerve regeneration, it detects re-innervation of peripheral sensory receptors, with values decreasing (i.e., a better spatial acuity) during regeneration over time²².

The moving two-point discrimination test (M2PD) was developed by A. Lee Dellon (1944) and measures the peripheral innervation density of the rapidly-adapting receptor/fiber system²³. It is an important aspect of touch, correlating highly with hand function²⁴. M2PD also has a certain place in the evaluation of both peripheral nerve compression and regeneration and is regarded to functional recover before S2PD and vibration sense in the process of nerve regeneration⁸.

The RDF Study was commenced to evaluate sensibility in the lower extremity of diabetic subjects, but with a peripheral nerve surgeon's perspective. Therefore, S2PD and M2PD were introduced in evaluating the feet, next to guideline recommended monofilament and vibratory testing. The resultant RDF Study Test Battery covers the most important sensory modalities.

As demonstrated in **Chapter II**, S2PD and M2PD were shown to be valid measures of sensibility, as was its reliability, measured with the Pressure-Specified Sensory Device (PSSD) (**Chapter III**)^{17,25}. An age dependent increase in S2PD and M2PD values was seen at the majority of test locations. No significant differences between men and women were observed. Although no formal reliability studies were carried out as part of the normative data study, we recommend testing S2PD at hallux and fifth toe and M2PD at hallux and lateral foot since these test sites showed less scatter compared to other test sites. A study in leprosy patients on inter- and intrarater reliability of M2PD at the big toe showed good results (weighted kappa (CI: 95%): 0.74 (0.63 to 0.84) and 0.82 (0.66-0.97)), respectively¹¹. Clinical experience taught us that in patients with symptoms of neuropathy, S2PD and M2PD measurements are more difficult to conduct. Patients with positive symptoms sometimes perceive one-point stimuli as two points or get hypersensitized during testing. Insensitivity to the varying interprong distance may result in reduced reliability. Hence, normal S2PD and M2PD values at the feet translate to intact axons conveying those stimuli, suggesting a high negative predictive value (i.e., being disease free).

Vibration sense

For long, sensibility is assessed with vibratory instruments. Diabetes was one of the first diseases in which impaired vibratory sense was quantified²⁶. The most frequent studied instruments are the tuning fork and biothesiometer, which are readily available and easy to use. No specific somatosensory end organ for vibratory sense exists. Vibratory stimuli are picked-up by rapidly-adapting Meissner (30-50 Hz) and Pacinian (200-300 Hz) corpuscles in glabrous skin or hair follicle lanceolate endings in hairy skin (**Chapter I**)². The clinical evaluation of both vibratory sense and S2PD tests the same neural pathways, however, have a different meaning in the clinical examination of patients with peripheral neuropathy. The vibration threshold at a certain piece of skin tells the clinician something about the function of the rapidly-adapting receptor/fiber system or its peripheral receptive field. Yet, spatial acuity requires a large number of overlapping receptive fields, which is tested with M2PD. Vibratory testing is especially of use in the longitudinal follow-up of peripheral nerve compression syndromes, peripheral (diabetic) neuropathy and the evaluation of surgical outcome after peripheral nerve repair and nerve decompression²⁷.

As demonstrated in **Chapter III**, vibration sense was seen to decline in groups of incremental neuropathy severity²⁵. An age dependent decline in sensory end organ density lies at root of the gradual lessening of vibratory sense, which was confirmed in our data (**Chapter II**)^{17,28-30}. Vibratory thresholds are easily established with graded tuning forks in the outpatient clinic. They are reliable, with good inter- and intraobserver agreement reported (weighted kappa: 0.83 and 0.79) and also responsive to change³¹. Sometimes a patient with neuropathic symptoms continuously perceives the vibratory stimulus, although the stimulus itself had already been taken away (≤ 0 with a Rydel-Seiffer tuning fork). In such case, a test that examines the same receptor/fiber system could be of use (e.g. M2PD) in determining the integrity or functional status of the nerve.

Quantitative Sensory Testing

To overcome the disadvantages of before mentioned test instruments and evaluate in more quantitative ways somatosensory function, quantitative sensory tests (QST) were developed. The workhorse of assessing large-fiber sensory function, next to the clinical examination, has always been electro diagnostic testing. Yet, with nerve conduction studies small and unmyelinated fibers are not evaluated. QST allows non-invasive testing of sensory nerve function, ranging from A-alpha fibers to C fibers³². In this way, pain, heat-pain and cold-pain thresholds are quantified, which correlate to the clinical picture of painful diabetic neuropathy^{33,34}. Several systems and protocols were developed, of which we used the PSSD in the RDF Study (**Chapter III**), although the PSSD is only able to quantify large-fiber sensorimotor function^{25,35,36}.

One of the unique abilities of the PSSD is the quantification of the pressure applied during S2PD and M2PD testing³⁷. Moreover, S1PD is measured with a hemispherical prong of 1 mm² attached to a single hand-held tool, in contrast to the 20-piece monofilament set, that have variable contact areas⁷. The PSSD assesses the majority of large-fiber sensorimotor functions, seen to deteriorate in the natural history of peripheral (diabetic) neuropathies and entrapment neuropathies (i.e., S1PD, S2PD and M2PD) but to revert after decompression or nerve regeneration (**General introduction**). Our study focused on the psychometric measurement properties of the PSSD and was found to be both valid and reliable in assessing sensibility in the feet of diabetic subjects (**Chapter III**)²⁵. Pressure thresholds were observed to increase before two-point discrimination widens, in line with previous reports on various neuropathies, but for the first time validated in a large group of diabetic subjects^{38,39}. PSSD measurements were able to allocate patients to different categories of sensory loss, which relates to the risk of ulceration (**Chapter XI**)⁴⁰. A downside of PSSD testing is the difficulty of testing in the lower extremities of diabetic subjects, who are generally older and have concomitant neuropathic symptoms, blurring especially S2PD and M2PD measurements. Future follow-up of the RDF Study cohort will relate PSSD measurements with the incidence of ulceration. Furthermore, PSSD measurements will be subjected to in-depth psychometric analysis, in order to validate the by dr. Dellon postulated rank-order of somatosensory functions lost in the natural history of neuropathy⁴¹.

Zhang et al. reported significant improvements in cold, warmth and vibratory perception thresholds in patients that underwent lower extremity nerve decompression (LEND) surgery⁴². The same group investigated the influence of diabetes duration on these QST parameters after LEND surgery, showing significant improvements from pre-operative values although a slower recovery in patients with longer disease duration was observed⁴³. The DeCompression (DECO)-trial will include the assessment of all QST parameters, according to the protocol of the German Research Network on Neuropathic Pain³⁵. In this way, both the natural history of lower extremity entrapment neuropathy and outcomes on these nerve parameters after LEND surgery are investigated (**Chapter XVII**)⁴⁴. Moreover, since only 20% of a peripheral nerve is made of large myelinated fibers and new evidence suggests that mild nerve compression preferentially degenerates small fibers, QST could potentially give an answer on the discrepancy between electro diagnostic sensitivity versus reported symptoms⁴⁵⁻⁴⁷. Future studies could also use the QST derived sensory profile in patient stratification in regard to therapy⁴⁸.

Grading lower extremity sensory loss: a theory of everything, for everyone?

The standard model of current clinical sensibility testing depends on the practice where you were raised. Is it in a podiatry or endocrinologist practice, sensory status is assessed

with the 10 g monofilament or tuning fork. In the neurological practice, sensory status will be assessed with the clinical examination including tuning fork, S2PD or cotton wasp, supplemented with electro diagnostic techniques or, but rarely, with skin- or nerve biopsies. In the peripheral nerve surgeon's practice, sensory status will be assessed with S2PD, M2PD, vibration sense and a wide range of monofilaments, substituted with electro diagnostic studies and/or QST when necessary and available.

As theoretical physicists are in search for the unification of the four fundamental forces using string theory, the in this thesis presented clinical grading of lower extremity sensory function may unify the before mentioned practices. By giving answers on how the different common somatosensory tests compare and where to apply them at the feet, long standing discussions on validity and reproducibility may be settled.

The most important findings of this thesis are the result of combining the classical works by dr. A. Lee Dellon with the International Working Group on the Diabetic Foot (IWGDF) guideline recommended test instruments. In **Chapter IV** we presented the resultant grading scales of sensory loss in the lower extremity, unifying the by dr. Dellon advocated S2PD and M2PD tests with 10 g monofilament and vibratory testing, as proposed by the IWGDF guidelines for the assessment of the foot at risk⁴⁹. Several answers were thereby given on the validity of the sensory tests used, as well as the diagnostic performance of the Tinel sign. Moreover, by using those grading scales the test site at the foot was shown to be predictive of overall sensory loss, uncovering new dimensions of somatosensory testing (**Chapter IV, VI and VIII**)^{19,49,50}.

Dr. Dellon's clinical grading scales of peripheral nerve problems have not been validated previously in other populations⁴¹. By then, the scales were developed based on own experience and empirical data, with the suggestion to do a psychometrical validation study in the future. Using modern statistical techniques on scale development we were able to do so. In **Chapter IV** we firstly confirmed that sensory loss is gradable⁴⁹. We established that the loss of protective sensation is preceded by the loss of S2PD, M2PD and vibration sense on all test locations, for every nerve involved. Secondly, by combining certain test instruments with test sites, an overall estimate of pedal sensory status is derived⁴⁹. Thirdly, we illustrated that a history of DFU is equivalent to end-stage sensory loss, preceded by aberrancy on a majority of the tests previously mentioned. Finally, we demonstrated that the Tinel sign, as indicator of tibial neuropathy at the tarsal tunnel, could vary from positive to negative during all degrees of nerve damage, which aids the discussion on its validity and diagnostic accuracy (i.e., sensitivity and specificity). These conclusions will now be further discussed.

Test instruments included in the presented RDF Study Test Battery are currently used in clinical practice and broadly available. The novelty of the 39-, 31- and 13-item RDF Test Batteries lies in the fact that with these instruments a precise estimate of sensory status is possible, when testing is done at specific test sites. Sum scores can be used to get an appraisal of overall degree of sensory loss and site-specific somatosensory function is graded when using the full test battery, without the need of expensive test instruments. The short-form versions were developed for screening purposes, to which diabetic patients are subjected to annually and are suggested to be implemented in prediction models of DFU development^{51,52}. Another considerable advantage of the RDF Test Battery is its objective outcome assessment, in contrast to subjective scoring of neuropathy symptoms as is done with the Michigan Neuropathy Screening Instrument (MNSI)⁵³. Moreover, the grading is non-invasive and fast to carry out⁵⁴. Since neuropathy symptoms do not necessarily mean large-fiber sensory loss, and thereby DFU risk, we advocate for distinguishing these when the risk for foot ulceration, imbalance and falls is the outcome of interest. RDF-39 scores were compared to data from non-diabetic controls that were measured for the normative data study (**Chapter II**)¹⁷. Clear differences were seen in sum scores (median: 5.5 (IQR: 3.0-10.8) vs. median 17.0 (IQR: 9.0-22.0), respectively, suggesting its validity in sensory status assessment (**Chapter IV**)⁴⁹. In controls, some aberrancy was seen in the first 11 items on S2PD and M2PD, due to the rather low threshold of 9 mm used for dichotomizing both S2PD and M2PD tests^{17,55}.

As already proposed by Dellon et al., reviewed in the **General Introduction** and now validated in RDF Study data, the pathophysiology of neuropathy (either DSP or entrapment) results in elevations of cutaneous threshold, axonal density decline, loss of vibration sense and loss of protective sensation^{41,49}. Since Mokken Scale Analysis requires a sample size >250 subjects, RDF Study PSSD data (n=155 patients measured) could not be used for such an analysis⁵⁶. Therefore, the test instruments included in the RDF grading scales do not completely resemble the clinical grading scales as developed by dr. Dellon. Yet, the subtle differences (e.g. increasing pressure before two-point discrimination decreases, which is not assessed with the RDF-39, -31 and -13) are probably more clinically relevant in upper extremity peripheral nerve assessment.

Psychometric characteristics of the instruments included in the RDF Study Test Battery have been previously reported^{3,30,31,57}. However, since the RDF-39 is a new diagnostic tool combining different instruments, its measurement properties need to be evaluated. Responsiveness of the RDF-39, i.e., the sensitivity of the instrument to detect change of the construct measured, was assessed during RDF Study follow-up (**Chapter IV**)⁴⁹. Median RDF-39 scores did not significantly change over a median period of observation 955.5

days (IQR, 841.5-1121), which was anticipated in regard to the slow progressive nature of neuropathy over time. One has to bear in mind that the RDF-39 is a dichotomized version of the full test battery. In that sense, it probably lost some of its sensitivity to change. Moreover, in that study only 135 patients were measured at the second follow-up due to constraints in availability of test personnel at that time. Currently, third follow-up data is available for 180 patients, though these data has not been published yet. Future studies should assess how sensitive to change the RDF-39, -31 and -13 are compared to the full RDF Study Test Battery. Yet, we do think that the measurements included in the battery are likely to detect change after LEND surgery, since previous studies report dramatic improvements of spatial discrimination and S1PD after this type of surgery^{39,41,58}.

It is debated that in contrast to the ordinal nature of the Mokken Scale Analysis derived RDF-39 sum score it should be better to use interval (i.e., continuous) measurements for a more precise estimate of the trait of interest ('theta', i.e., sensory status),^{59,60}. To derive such an outcome, a parametric item response theory model was fitted to RDF Study data (**Chapter V**)⁶¹. For each patient an interval value of theta was obtained, which differed significantly from non-diabetic controls, confirming its discriminative ability^{49,61}. In future studies the added value of such an estimate should be compared with non-parametric derived (ordinal) sum scores, with the latter more easily interpreted and calculated without the need of a computerized model.

Measures of reliability (test-retest, inter-rater, intra-rater) have not been studied yet for the RDF Test Batteries (i.e. RDF-39, -31 and -13) and will be subject of future studies. External validity is currently investigated in another cohort of diabetic patients with varying degrees of neuropathy, but could also been done in other populations where sensation at the feet is at stake⁶². Examples include diseases like chronic idiopathic axonal polyneuropathy, thyroid dysfunction, chemotherapy-induced neuropathy, kidney disease or deficiencies in vitamins^{63,64}.

Validity and applicability of the Tinel sign

First described by dr. Paul Hoffmann (1884-1962), but shortly followed by dr. Jules Tinel's (1879-1952) publications, the (Hoffmann)-Tinel sign was originally described as diagnostic maneuver to localize nerve damage and assess the presence and course of nerve regeneration after traumatic peripheral nerve injury⁶⁵. Much later it also came in vogue to assess the presence of peripheral nerve compression⁶⁶. For long, a lot of discussion focused on the intra- and inter-examiner variability, validity and thereby usefulness of the Tinel sign and therefore abandoned by many, but cherished by others^{58,67-69}. In the research carried out for this thesis we focused on the Tinel sign in relation to peripheral nerve entrapment.

With the Tinel sign in relation to carpal tunnel syndrome most frequently studied, the test is often compared to nerve conduction studies as golden standard, for which variable values of diagnostic accuracy were found (sensitivity: 38-100%, specificity: 55-100%)⁷⁰. Since the electro diagnosis of tibial nerve entrapment in patients with DSP is not reported in the literature and hampered with several difficulties as outlined in the **General introduction**, we evaluated the current physical examination (i.e., the Tinel sign) in diagnosing tibial nerve entrapment⁷¹⁻⁷³.

In **Chapter VII** we determined the validity of the Tinel sign by comparing diabetic subjects with and without a Tinel sign at the tarsal tunnel⁷⁴. The study showed that diabetic subjects with a Tinel sign, indicative of tibial neuropathy, reported significantly more neuropathic symptoms and had significantly more sensory deficit in the distribution of the tibial nerve and was therefore found to be valid⁷⁴. In the same study the prevalence of tibial nerve entrapment (i.e., a positive Tinel sign at the tarsal tunnel) and tarsal tunnel syndrome (TTS; i.e., a positive Tinel sign at the tarsal tunnel and sensory symptoms) were investigated. It was shown that tibial nerve entrapment was 1.73 times (73%) more frequently observed in diabetic subjects compared to controls and that TTS was present in up to 29.9% (95%CI: 25.2 to 34.5) of diabetic subjects. These findings have important consequences, since a diagnosis of entrapment neuropathy makes prognostication and treatment possible (**Chapter X**)⁷⁵.

In current peripheral nerve surgery practice and research, a person who has both diabetes mellitus, symptoms of neuropathy and a positive Tinel sign at a given peripheral nerve is considered to have an entrapment neuropathy of the nerve (or nerves) involved, irrespective of the presence of DSP^{58,76}. A diagnosis of super-imposed nerve compression is thereby made, regardless the fact that some patients with diabetes develop an entrapment neuropathy not caused by diabetes or that patients with diabetes may require other (component) causes leading to peripheral nerve entrapment^{69,77}. This may also explain the observed heterogeneity in reported surgical outcomes, understanding of relationships, etiology and selection of the appropriate treatments⁷⁸⁻⁸¹. Neuropathy in diabetes is diverse and therefore challenging, with both the central and peripheral nervous systems involved^{82,83}. In **Chapter VII** we reported functional anomalies of the tibial nerve in both controls and diabetic subjects⁷⁴. Since the control group was selected on having no sensory symptoms in the feet, a diagnosis of TTS was not made in these healthy volunteers. However, the Tinel sign was prevalent, making it possible to calculate adjusted prevalence estimates. In future (population-based) studies the 'population attributable fraction' may serve as measure to elucidate the proportion of TTS that can be truly related to a certain risk factor⁸⁴. Given the worldwide increase in the prevalence and incidence of risk factors for diabetes and neuropathy, it is likely that the future disease-burden of neuropathy will increase⁸⁵⁻⁸⁷.

How is the Tinel sign becoming positive in entrapment neuropathies? It is believed that a patient's positive response to percussion is indicative of mild demyelination and regenerating axonal sprouting⁸⁸⁻⁹². When the compression has caused too much damage (resulting in extensive demyelination and loss of large myelinated nerve fibers), a positive response is no more elicited⁷¹. However, as discussed in **Chapter IV and V**, we observed in our data that the Tinel sign does not have a robust position in the natural course of overall sensory loss at the feet^{49,61}. Otherwise stated, the Tinel sign was not observed to become positive when certain sensory tests had become aberrant, in a pre-defined rank-order. Nor is it likely that a certain degree of sensibility loss (i.e., nerve damage) predicts the presence of a Tinel sign. We did observe, however, that the proportion positive Tinel sign per RDF-39 sum score did correlate weakly positively, but not significantly, with the total RDF-39 sum score ($r_s = 0.21$ to 0.32 , unpublished data).

The before mentioned natural history of a positive Tinel sign during nerve compression has not been prospectively investigated and is based on theoretical assumptions, although based on histopathologic examinations⁹⁰⁻⁹². A previous study combining stages of regeneration with grading the Tinel sign is an interesting effort to standardization⁹³. In the Mokken Scale Analysis on RDF Study data (**Chapter IV**) the items 'Tinel left (tarsal tunnel)' and 'Tinel right (tarsal tunnel)', along with an item on 'positive neuropathy symptoms' were dropped out by the automatic item selection procedure, as first step in the analysis⁴⁹. This means that those items do not have a fixed position in the hierarchy of test items. For the item on positive neuropathy symptoms this is straightforwardly explained, since people with all stages of nerve damage (i.e., sensory loss) can report positive symptoms: patients with minor sensory loss and patients with previous foot ulceration can have these aching symptoms. This in contrast to the only subjective item included in the test battery, on 'numbness' at the feet. Numbness is reported after loosing two-point discrimination and vibration sense. The Mokken Scale Analysis included that item since it becomes aberrant in a relative fixed position amongst other (hierarchically ordered) items. Numbness is therefore a better predictor of sensory status compared to positive symptoms, as suggested in previous studies investigating the sensitivity of symptoms for the diagnosis of (diabetic) polyneuropathy^{94,95}. We do think, however, that the finding that patients can have a positive Tinel sign even in severe stages of neuropathy has important consequences for patient selection in LEND surgery.

All studies on LEND surgery used the Tinel sign as divining rod in determining eligibility for surgery^{58,69,96,97}. Significant long-term pain reduction is reported, with return of sensibility after this type of surgery. One study investigated the outcome of surgical decompression of the tibial nerve in patients with diabetic neuropathy but with a negative Tinel sign and

reported a lower likelihood of a successful outcome compared to Tinel positive subjects (33% vs. 92%)⁶⁹. We expect somatosensory function to correlate with surgical outcome, as explored in **Chapter XII**⁹⁸. Future studies should relate to which degree nerve functioning predicts surgical outcome, together with factors such as age, duration of diabetes etcetera. The presented scales could aid this debate. Previous studies reported on LEND surgery in patients with a positive Tinel sign and prior DFUs, reverting annual recurrence risk dramatically (1.6% vs. 7.0%)^{99,100}. In this way, other patient populations for implementing LEND surgery are explored.

On the contrary, other medical practices refute the applicability of the Tinel sign^{67,101-103}. Datema et al. found that a Tinel sign was not associated with nerve entrapment in DSP; however, nerve conduction studies were used as golden standard. As outlined in the **General introduction** this hinders validity and generates considerable controversy. A high specificity (i.e. true negatives) was found for the Tinel sign in ruling out nerve entrapment, but patient numbers were small (n=27). An interesting study by Melenhorst et al. showed that a minority of medical professionals is aware of the theory of super-imposed nerve entrapment, let alone refer to a surgeon, but a considerable percentage thinks it might play a role in the pathogenesis of neuropathy symptoms¹⁰⁴. In **Part IV** of this thesis the utility of the Tinel sign in LEND surgery decision-making is further discussed.

RDF Study follow-up and future studies will make clear what the natural history is of a positive Tinel sign at the tarsal tunnel. How long is it elicited over time and are certain factors associated with it? What is its incidence? Are the (cardiovascular) risk factors for DSP also associated with peripheral nerve entrapment?^{85,105-108}. What happens at the molecular level^{109,110}? What is the relationship between the dimensions of the tarsal tunnel and the likelihood of entrapment?⁸⁰. May inching techniques by electrodiagnostic studies aid diagnosis and prognostication?^{111,112}. What about the other lower extremity peripheral nerves? Prospective, observational cohort data enables us to answer these questions in research to come.

Part III: Prediction of adverse events

Prediction research can be executed in several steps of increasing difficulty, but beauty. In its most simple form, univariable analysis, a single predictor is related to the outcome of interest. It is of limited value since other factors of influence on the outcome are not controlled for. Adjustment of confounders (i.e., multivariable analysis) allows the assessment of relative risks. Other statistical approaches in prediction research include recursive partitioning (decision trees) and neural network analysis. Combining predictors to estimate the outcome of interest for individual patients is the ultimate goal of prediction models, although large

data sets for development and validation are needed to assess its performance. In this part of the thesis the predictive value of sensory testing on overall pedal sensory status, imbalance, risk of falls and risk for ulceration are discussed.

In **Chapter VIII** we used decision tree analysis to derive what test site in monofilament and/or vibratory testing is most informative in estimating one-year ulcer-free survival⁵⁰. In this way, new dimensions to the 'classical' tests were explored, by appreciating the predictive value of the test site. Patients with prior DFU were distinguished, since they fall in a different risk category of re-ulceration. The decision trees should be seen in light of the Person-Item Map presented in **Chapter IV**⁴⁹. The item with the largest discriminative ability (in this case vibratory testing at the medial malleolus) is the first step (split) in the separate trees and positioned in the middle of the x-axis of the Person-Item Map. The next step is testing protective sensation at the heel, which is indeed the middle of the previous split, and so forth. In this way, a quick estimate of the chance of one-year ulcer-survival is possible, aiding medical decision-making. The decision trees were proven to be more accurate compared to a composite score of monofilament or tuning fork testing^{113,114}.

Since the first dorsal web and lateral foot have lower normative cutaneous thresholds compared to plantar test sites (**Chapter II**), protective sensation is later lost in the natural course of sensory loss at the former test sites (**Chapter IV and V**)^{17,49,61}. This has predictive value and was visualized in the Person-Item Map (**Chapter IV**), but also apparent in the decision tree that was developed to predict the RDF-39 sum score (**Chapter VI**)¹⁹. By using only three tests, seven categories of sensory loss could reliably be distinguished. Predicted RDF-39 mean (SD) values per category were: 5.4 (3.7), 8.7 (4.3), 15.3 (4.1), 16.3 (3.7), 21.4 (3.8), 24.8 (4.1), and 33.2 (4.3), in which loss of protective sensation at the first dorsal web equaled severe sensory loss (33.2 (4.3)). This information could directly be implemented in a variety of clinical practices, such as of general practitioners, podiatrist and endocrinologists, since the sum score is predictive in the likelihood for complications as will be further discussed.

Predicting imbalance, falls and diabetic foot ulceration

The finding that sensory loss can be graded has important consequences, since decreased foot sensation is a causative factor for various adverse events. Two of such were explored in this thesis: the relationship between pedal sensation, balance and falls (**Chapter IX**) and the relationship between pedal sensation and risk for ulceration (**Chapter XI**)^{40,115}. Previous studies investigated the relationship between neuropathy and balance, but did not use uniform measures of sensibility¹¹⁶⁻¹¹⁸. The studies confirmed the importance of cutaneous sensation in maintaining postural and gait stability, which was assessed in our study with the valid and reliable Brief-BESTest^{119,120}. Compared to traditional screening instruments

alone (i.e., monofilaments and tuning fork), the degree of sensory loss is more precisely estimated by including measures of early sensory loss (S2PD, M2PD) and appreciation of the predictive value of test locations. The RDF-39 was primarily developed as a screening tool on sensory loss at the feet of diabetic subjects. The current study adds the prediction of balance impairment, as a new dimension of the RDF-39, distinguishing patients with intact protective sensation already being at risk. The prospective nature of the RDF Study made it also possible to relate the RDF-39 baseline score to recurrent falls during follow-up. In multivariable analysis, the sum score indeed appeared to be the strongest predictor of both imbalance and recurrent falls. Underlying mechanisms are not totally unraveled yet, but plantar pressure distribution is probably changed due to reduced cutaneous sensation, which in turn is important for proprioception and maintaining standing balance^{8,121-123}.

Although we reported more sensory deficits in diabetic subjects with tibial neuropathy, it was not analyzed if these patients had worse outcomes on the Brief-BESTest or were at greater risk for falls compared to those without tibial nerve entrapment⁷⁴. A promising study reported the effects of bilateral tibial neurolysis on balance parameters in patients with peripheral neuropathy¹²⁴. A significant reduction of sway was observed, suggesting improved balance and thereby a lower risk for falls. Since tibial neuropathy is highly prevalent in diabetic subjects, this might be an important indication for surgery, even if no aching sensory symptoms exist (**Chapter VII**)⁷⁴. The RDF-39 sum score could aid shared decision-making on this topic, but is also recommended to be included in multifactorial risk assessment in the older patient at risk for falls¹²⁵. Since falls account for approximately 10% of emergency department visits among elderly persons, with considerable resultant morbidity, mortality and costs, this type of surgery might be important in reversing the chance on these outcomes¹²⁶.

The fact that degree of sensory loss relates to the risk for foot ulceration is another outcome that was associated with the baseline RDF-39 sum score (**Chapter XI**)⁴⁰. In earlier studies it was shown that vibratory thresholds were clinical useful predictors for foot ulceration^{127,128}. Previous studies did relate the number of insensate (to the 10 g monofilament) test sites to the risk of ulceration, but this was not assessed in a prospective study^{113,114}. A study by Boyko et al. considered being insensate at one or more sites representing peripheral sensory neuropathy⁵². However, the added value of a multitude of test sites was not corroborated by a meta-analysis on prognostic factors for foot ulceration¹²⁹. The IWGDF guidelines recommend random testing at the feet, defining loss of protective sensation when insensate to the 10 g monofilament at ≥ 2 test sites¹. From our study results it is now concluded that the combination of test and test site has predictive value.

The long-term results of the RDF Study showed that the incidence of DFUs in this cohort was comparable with international studies (4.5 vs. 2.2 to 6.8 per 100-person-years)^{52,130,131}. By categorizing each patient according to the degree of sensory loss, relative risks were observed to significantly differ between RDF-39 sum scores. In line with expectations, the lower the degree of sensory loss, the lesser the risks for foot ulceration. Patient with intact sensation were at no risk. Patients that lost S2PD, M2PD and/or vibration sense were at relatively low risk (ulcer incidence rate of <3.00 per 100 person-years). As anticipated, ulcer risk was significant in patients who lost protective sensation at the plantar side of the foot (ulcer incidence rate of 10.0 per 100 person-years). The highest risk for an adverse event was observed in patients with aberrant Romberg tests, and, not surprisingly, prior DFU or amputation (36.33 and 67.70 per 100 person-years). In adjusted analysis, sensory loss was the most important driver to DFU development. Renal function was also shown to be a significant predictor for DFU occurrence. The resultant models adequately predicted ulceration (positive likelihood ratio of 4.44) or ulcer-free survival in patients without previous DFU (positive likelihood ratio of 3.77). Foot ulceration was also associated with mortality in the follow-up of RDF Study participants¹³².

Not all known risk factors for DFU were included in our model, such as foot deformities, due to incomplete data¹³³. In line with previous reports, adding palpation of pedal pulses to the risk assessment conferred additional predictive value over the RDF-39¹²⁹. This might be due to the underlying pathophysiology of the majority of DFUs in this cohort being of neurological rather than vascular origin. We advocate the use of the RDF Scales as objective measure of neuropathy, in contrast to symptoms (e.g. MNSI), to include in prediction models for DFU⁵¹.

Since previous DFU is the greatest risk factor for re-ulceration, with recurrence rates of 40% within 1 year, almost 60% within 3 years and 65% within 5 years, the frequency of screening on lower extremity complications is increased when having had DFU^{1,134}. Although sensory loss due to neuropathy is probably the most important factor in the cascade to first DFU, re-ulceration is often associated with other hazards such as pre-ulcerative lesions, peripheral artery disease and osteomyelitis. The healed ulcer should therefore be regarded as in remission, since the recurrence rate is so high¹³⁴. Tailored made recommendations therefore differ in patients with and without prior DFU^{135,136}. From the research presented in this thesis it is recommended that patients without prior DFU should be assessed regarding their sensory status with 'ulcer-free survival' as outcome of interest (**Chapter VIII**)⁵⁰.

Impact of tarsal tunnel syndrome on incident diabetic foot ulceration

To investigate the degree to which sensory deficits observed in uni- and bilateral TTS **(Chapter VII)** result in an increased risk for DFU, RDF Study patients with TTS were compared over time to participants without signs of tibial nerve entrapment **(Chapter X)**^{74,75}. No previous studies reported on the non-surgical natural history of TTS in light of DFU development. This in contrast to a paper that presented the results of unilateral LEND surgery, and thereby 'changing the natural history of diabetic neuropathy' in the operated limb¹³⁷. The contralateral, non-operated limb was regarded as control in which 'the natural history of diabetic neuropathy' was studied, however, patient numbers were low and a proper control group was missing. Nonetheless, it was an interesting study with some important findings, advancing both the clinical and scientific knowledge on lower extremity peripheral nerve disorders in diabetic subjects.

Our paper confirmed the hypothesis that the increased sensory deficit seen in TTS is related to the risk for ulceration. Somatosensory function was an even more important predictor of incident DFU than the Tinel sign alone. This has important consequences regarding selection of the appropriate patient to undergo decompression surgery. A patient is usually operated when having neuropathy symptoms, with signs of nerve compression related to the area of symptoms, together with a somatosensory evaluation. The latter is important for conforming the diagnosis, but should also be regarded as prognosticator for surgical outcome and as predictor for adverse events **(Chapter VII, XII and XI)**^{40,74,98}. Since only patients with superimposed peripheral nerve compressions are eligible for surgery, it is very interesting to see that in those operated patients significant improvements of somatosensory function are reported for tibial nerve innervated areas⁹⁷. Fact is that it remains difficult to differentiate between symptoms of DSP and entrapment, as is the prognosis of the surgical outcome. Although it is estimated that not every diabetic patient will develop entrapment neuropathies, a significant absolute number will **(Chapter VII)**^{74,138}. Assuming the RDF Study cohort to be representative for type 1 and type 2 diabetes patients seen in other teaching hospitals, it is estimated that in those populations 29.9 percent (95%CI: 25.2-34.5) has either uni- or bilateral TTS. With effective surgery, TTS is likely to be an amenable factor to prevent ulcer occurrence and thereby amputation risk in a portion of the diabetic population **(Chapter XI)**⁴⁰.

Part IV: Treatment

Although the majority of studies were derived from the observational RDF Study, some side-projects were included in this thesis. Three resultant chapters elaborate on treatment modalities offered by plastic surgeons to diabetic patients **(Chapter XII, XIII and XIV)**^{98,139,140}. Two studies relate to LEND surgery and one chapter sheds light on the reconstructive

treatment options plastic surgeons could offer, including free flap surgery, to reconstruct a defect in a diabetic foot.

As diabetes is a chronic disease, we thought it would be appropriate to assess the long-term effects of LEND surgery, by follow-up of patients previously participating in the Utrecht based Lower Extremity Nerve Entrapment (LENS) Study^{79-81,141}. The LENS study investigated the effects of LEND surgery in diabetic subjects with compression neuropathies in the lower extremities and painful neuropathy symptoms. Previous long-term outcome studies on LEND surgery predominantly focused on sensation, DFU occurrence and pain perception^{76,137,142-144}. By performing a 5-year LENS study follow-up, we aimed to give insight into factors that influenced surgical outcome, viewed in light of the neurophysiological principles that were outlined in **Part I & II** of this thesis.

The LENS Study was originally designed to randomize treatments between legs, with one extremity receiving either LEND surgery or conservative care. No control group was used. After 12 months of LENS study follow-up the trial ended. However, eight patients underwent additional surgery of the initial non-surgically treated leg, after termination of the study. These patients were satisfied with the initial surgery. For the LENS Follow-Up (LENS-FU) Study, we measured 31 patients available for long-term follow-up, with a mean of 4.6 ± 0.5 years after the first surgery⁹⁸. Eleven of the original 42 patients were lost to follow-up, one patient did complete the questionnaires but sensory status was not assessed at long-term follow-up. Available were data from 23 patients that underwent unilateral surgery and eight patients that underwent bilateral surgery.

Patients who underwent bilateral decompression had significantly lower visual analogue scale (VAS) pain scores at 12 months, were younger, had a lower age when diagnosed with diabetes and had a lower body mass index compared to unilateral decompressed patients. Pain scores decreased similarly in the additional decompressed leg. At 5-year follow-up, patients still experienced pain reduction in the initial surgical leg, compared with the initial control leg (35.5% vs. 12.9%), despite the inherent progression of DSP. Significant improvement in quality of life (EQ-5D) was seen in bilateral operated patients. However, the results of surgery were less profound compared to the literature: these patients were generally younger, had a shorter duration of diabetes and had a better sensory status compared to LENS study participants⁹⁶. On the latter will be more elaborated.

The decision to decompress a peripheral nerve is generally made independent of nerve conduction studies, especially in diabetic subjects with DSP^{73,145}. Since axonopathy with its own demyelination will impede the demonstration, by electro diagnostic studies, of

segmental nerve slowing in fibro osseous tunnels, in LEND surgery the Tinel sign is used as the diagnostic test of choice^{97,145}. Moreover, predicting outcome with nerve conduction studies after carpal tunnel surgery is already difficult, let alone in diabetic patients with superimposed nerve compressions¹¹¹. Kimura inching techniques may aid this debate in the future. The diabetic patients operated in the LENS Study had severe pre-operative sensory loss, indicated by aberrant 10 g monofilament testing and prior ulceration (**Chapter IV and V**)^{49,61}. LENS FU participants available for 5-year follow-up scored a median of 33 points (IQR: 24-34) at the RDF-39 scale, indicative of severe nerve damage when compared to the RDF Study population (n=416) and healthy controls without known neuropathy (n=196), median 17.0 (IQR: 9.0-22.0) vs. median: 5.5 (IQR: 3.0-10.8), respectively. We believe that this degree of nerve damage exerted the odds of a more profound favorable outcome considerably. Bilaterally operated patients had a better sensory status at baseline what may have contributed to their decision to undergo contralateral surgery. Future studies should take the pre-operative degree of nerve damage into account and relate that to surgical outcome (**Chapter XIII**)¹³⁹.

It may have been that LENS Study patients had concomitant proximal tibial nerve entrapment at the soleal sling, which was not investigated, or had recurrent entrapment because of inadequate external neurolysis¹⁴⁶. Currently there is an increasing interest in decompression of the proximal tibial nerve that can become entrapped at the soleal sling. A cadaver study found 8% of specimens studied showed focal narrowing at that location, pinching the nerve¹⁴⁷. Since the double crush hypothesis suggests that proximal nerve compression could result in a distal (dual) nerve disorder, it is interesting to further investigate what remains of TTS symptoms when solely the proximal component is decompressed¹⁴⁸.

Attitudes toward LEND surgery

As earlier briefly touched upon, LEND surgery is surrounded with continuous debate regarding its utility in diabetic patients with symptoms of DSP^{67,101-103}. Skeptic medical professionals continue to question the validity of the Tinel sign, the surgical approach to secondary nerve entrapments in DSP, safety and efficacy of the procedure and regard the positive outcomes biased and the result of placebo effects. These controversies will be briefly discussed. Firstly, the Tinel sign has proven clinically useful as a predictor of a positive outcome of LEND surgery⁵⁸. All studies on LEND surgery in diabetic subjects used the Tinel sign as criterion to undergo surgery, with numerous positive effects on both subjective and objective surgical outcomes^{96,97}. The fact that a positive Tinel sign at a nerve can also be found outside an area of known anatomical narrowing might have been the result of demyelination and axonopathy as seen in DSP or trauma⁶⁷. This does not necessarily lowers its validity and was also observed in our study in asymptomatic healthy

controls (**Chapter VII**)⁷⁴. Moreover, the Tinel sign (i.e., when negative) was able to measure the proportion of actual negatives that were correctly identified as such (electro diagnostic studies were the golden comparator)⁶⁷. Secondly, the surgical procedure is safe to conduct, with respect to the incidence of surgical site infection (5.9%), which is 9.5% in other types of lower extremity surgery in diabetic subjects^{96,149}. Infections that do occur are usually straightforwardly treated and no major complications are reported in current literature. Interestingly, neuropathy seems to increase the risk of surgical site infection even in patients without diabetes¹⁵⁰. Thirdly, in recent years numerous (controlled) prospective studies and two randomized controlled trials externally validated the hypothesis-driven earlier works by dr. Dellon, on which much of the earlier criticism was based^{78,99,151-153}. Lastly, opponents of LEND surgery regard the immediate pain relief observed directly post-operative to be a placebo effect. They support their statement with the observation that after unilateral surgery, patients report symptom improvement in the non-operated extremity¹⁵². However, this phenomenon has already been known in bilateral carpal tunnel syndrome, in which three separate studies reported improvement of symptoms in the non-treated hand after contralateral treatment, both surgical and non-surgical¹⁵⁴⁻¹⁵⁶. Earlier studies showed that a majority of patients with unilateral carpal tunnel syndrome are found to have conduction abnormalities in the contralateral median nerve despite absence of clinical signs, of which 73% of patients developed symptoms over time¹⁵⁷. Since only 5% of cases can be attributed to anatomical abnormalities in the carpal tunnel itself, sensitization and plasticity of the central nervous system is an interesting phenomenon that might explain the variability and outcomes observed¹⁵⁷⁻¹⁶⁰.

An even more interesting demonstration of acute improvement of nerve function after surgical decompression is a study on per-operative electromyography (EMG)¹⁶¹. After external neurolysis of the common peroneal nerve, significant improvements on EMG parameters recorded at the fibularis longus and tibialis anterior muscles were observed, regardless of age, gender, type of diabetes, disease duration, BMI and HbA1c levels. This suggest that motor axons can remain viable during prolonged chronic demyelination, at least in part explained by increased density of voltage-gated potassium and sodium channels in the demyelinated internode and paranode regions of the axon¹⁶¹. Multiple studies showed that after LEND surgery the cross-sectional area of the nerve is decreased, suggesting that the nerve is recovering from entrapment, similar to the median nerve after carpal tunnel release^{42,43,80,144}. This is also implied by the improvements seen in nerve conduction parameters and somatosensory measurements⁹⁷.

In summary, a placebo effect in every surgery is evident and not simply ruled out, but the improvements in objective outcome measures refute most of before mentioned criticisms¹⁶².

The role of the plastic surgeon in the diabetic foot team

The current pillars of diabetic foot management are: 1) treatment of infection, 2) pursuit of adequate arterial blood supply, 3) prescription of therapeutic shoe-wear and 4) with either conventional or surgical methods removal of localized increased pressure¹⁶³. Early and adequate referral is of paramount importance¹⁶⁴. In the Netherlands, the multifactorial problem of the diabetic foot is treated in a multidisciplinary team consisting of internist, podotherapist, vascular surgeon, orthopedic surgeon, dermatologists and rehabilitation specialist (**Chapter XV**)¹⁶⁵. The factors leading to DFU are in this way ascertained and treated accordingly by every specialty involved. Surprisingly, however, the specialist who deals most frequently in clinical practice with wounds and (large) tissue defects is not regularly involved: the plastic surgeon.

Previous paragraphs discussed the possibilities of the plastic surgeon to intervene in the first step to DFU development, that is neuropathy. In the Netherlands, in contrast to other countries, the plastic surgeon is generally not part of the multidisciplinary diabetic foot team. That is interesting, since (chronic) wounds as seen in pressure sores, trauma or oncology are treated with plastic and reconstructive principles that are particularly applicable to diabetic foot syndrome. The arsenal of techniques a reconstructive surgeon can add to the treatments by the diabetic foot team has shown to be of value in covering defects of varying size, resulting in preservation of the foot and thereby prolongation of life^{166,167}.

Two cases were presented in which the ultimate reconstructive technique is applied to salvage the threatened limb: the microvascular free flap. Historically it was thought that increased arteriolar occlusive disease due to endothelial proliferation lead to ischemic lesions and therefore be a contraindication for flap surgery¹⁶⁶. However, this idea was refuted in current series, since survival rates are similar compared to flap surgery in other patient populations¹⁶⁸. Yet, limb salvage in diabetic foot syndrome using free flap surgery is not widespread and technically challenging. Interestingly, in Asian countries a lot of effort is made to preserve limbs, with development of various algorithms and reconstructive techniques over the last two decades¹⁶⁹. Lessons learned show that patient selection and cooperation with the multidisciplinary foot team is of utmost importance. A patient with a lower limb defect eligible for free flap surgery is 1) failing conservative treatment, 2) previously ambulatory and willing to regain a functional limb, 3) engaged in post-operative rehabilitation, 4) has no significant renal impairment and 5) has a local recipient artery with sufficient peak flow (>40 cm/s). Transcutaneous oxygen measurements are used to prognosticate the outcome of the reconstruction¹⁶⁷. Additional nerve coaptation is likely beneficial¹⁷⁰.

Not always a free flap is necessary, but local flaps may breach distal blood flow. Reverse sural or medial plantar flaps have not been as successful as free flap reconstruction¹⁶⁷. An improvement of reported success rates have been reported over the years. A study of 563 free perforator flaps showed that overall success rate was high (96.2%), with total flap loss as low as 3.8%, but successfully reconstructed using a second free flap in 16/22 cases. Partial flap loss occurred in 4.1% of the 563 cases, requiring minor interventions. Two cases of total flap loss required below-knee amputation in the end¹⁷¹. The advantage of perforator flaps over muscle flaps are that they are thin and pliable and do not necessarily need skin grafting or debulking. Moreover, when a thin flap is used the superficial fat can imitate the fibrous septa of the foot sole, minimizing shear forces. Long-term reported outcomes show continued limb preservation with a 5-year survival of 86.8%, which is much higher compared to the natural history of diabetic foot disease¹³⁴.

This brief overview of possible reconstructive techniques gives evidence of the value a plastic surgeon might add to the multidisciplinary diabetic foot team. Future studies should stratify patients in line with IWGDF advised classification systems and outcomes should be both standardized and patient-reported to improve comparability of care and quality of research¹⁷².

Part V: Costs and cost-effectiveness

The rank order of diabetes-related complications by cost is topped by amputations, followed by ischemic heart disease, myocardial infarction and stroke¹⁷³. However, since 8 out of 10 non-traumatic amputations is preceded by DFU, and DFU is induced by neuropathy, it is interesting to look at the whole sequence to lower extremity complications regarding costs¹⁷⁴. In this way, the true economic burden of diabetes-related complications related to the lower extremity is reviewed. Together with health utility values an estimate of cost-effectiveness of (new) interventions is than possible. This is important, since economic evaluations are increasingly desired in medical decision-making, by doctors, but also for funding agencies and policy makers. In the following paragraphs costs associated with lower extremity complications in diabetes are briefly discussed.

When focusing on the costs of treating painful symptoms of neuropathy, literature suggests that the direct costs range from €1,902 to €3,795 annually (2005 price level), depending on pain severity¹⁷⁵. Direct costs are mainly non-drug prescription related, which account for 30-32% of the costs, and relate predominantly to general practitioner contacts and inpatient days. However, since a variety of other disorders are associated with DSP, affecting activities of daily living, the burden is probably much higher but more difficult to differentiate. For example, sleep disturbance due to nocturnal pain is reported by 72-95% of patients

with painful DSP. Moreover, a diagnosis of depression is associated with the disorder. The resultant decline in health-related quality of life results in productivity loss, which was estimated to cost society €5,646 to €16,597 per patient annually (2008 price level)¹⁷⁵. Since balance impairment and falls are associated with neuropathy induced sensory loss, another important factor in the economic burden of neuropathy is acknowledged (**Chapter IX**)^{115,176}. Hence, the consequences and thereby costs of neuropathy are widespread, but also difficult to comprise completely.

When reviewing the costs for peripheral artery disease in patients with diabetes, a large Italian study estimated the mean cost per year to be €3,941 (95%CI: 3,881 to 4,001)¹⁷⁷. Revascularization procedures added significantly to the costs, as well as male gender, worse comorbidities and amputations. Again, cost data is predominantly related to inpatient days, followed by outpatient and pharmaceutical care. An American study underscored the impact of diabetes as a comorbid condition, adding significantly both clinically and economically to the cost of peripheral artery disease with an average of US\$1,912 more per episode¹⁷⁸. Although cardiovascular disease is associated with productivity loss, it is difficult to estimate the effect of peripheral artery disease on this outcome¹⁷⁹. In the Italian study, the average diabetic patient with peripheral artery disease was 72 years (SD: 10.1) old, an age generally related to retirement in Western countries. However, this holds not always true for individual patients and is probably different in other parts of the world and should therefore with caution be dealt with¹⁷⁷.

Cost data on diabetic foot care was generally outdated, especially data assessed at person-level, which is a time-consuming method in cost-of-illness studies but approximates the true setting best¹⁸⁰⁻¹⁸³. We therefore chose a micro-costing method to estimate current in-patient costs of diabetic foot care, including revascularization procedures, amputations and rehabilitation trajectories (**Chapter XV**)¹⁶⁵. Cost-data is usually skewed, but we reported averages for readability. In our regional teaching hospital the average costs of a DFU were € 9,754 (2015 price level), for a minor amputation € 12,234 and for a major amputation € 66,498, all with considerable variance. This economic burden is in line with international literature, especially from the Western world, but with considerable differences observed between countries¹⁸⁴. The main driver of cost is in-hospital stay. Non-inpatient costs represent approximately 30% of total costs, and are more difficult to estimate¹⁷³. This is therefore a limitation of our study. Moreover, a minority of patients underwent amputations. Strengths include the full care cycle over which costs were determined, including rehabilitation, and the insight into the evolution of costs over time for the different outcome groups. This in contrast to a one-year follow-up window that was used in the Eurodiale study¹⁸⁵.

Considerable costs are associated with each consecutive step leading to (rehabilitation of) lower extremity amputations, together with detrimental effects on health-related quality of life. Burden to society is substantial, with a study from the United Kingdom estimating an expenditure of 0.6% of National Health Service budget is spent on diabetic foot care¹⁸⁶. By viewing the whole cascade leading to lower extremity amputations, next to each entity apart from each other, insight is given into the magnitude of the problem. This information aids policy makers and future studies on cost-effectiveness analysis.

Cost-effectiveness

Cost-effectiveness analyses are useful to evaluate the gain in health benefits of a new treatment strategy compared to current care, to assess its 'value for money' and to support health care policy decisions (**Chapter XVI**)¹⁸⁷. Cost-effectiveness of interventions can be studied for the different steps in the aforementioned cascade, i.e., diabetes itself, neuropathy, peripheral artery disease, foot deformities leading to localized increased pressure, falls, etcetera, but also on the level of healthcare organization. Examples of the latter include screening and implementation programs¹⁸⁸⁻¹⁹⁰. Most interesting, of course, is to study the effects of interventions on disease entities earlier in the cascade in relation to late onset outcomes (i.e., complications). This requires very large longitudinal (population-based) studies with substantial follow-up, which are expensive and difficult to conduct^{191,192}. The ADDITION-Europe Study, for example, showed that intensive treatment of cardiovascular risk factors in type 2 diabetes was not cost-effective in preventing cardiovascular events, microvascular complications (including neuropathy) and death over a time horizon of 1-5 years¹⁹³. However, modeling a longer horizon is a reasonable and good alternative for 'real-world' trial data to assess long-term outcomes of interventions. This was also done in the before mentioned study and it was shown that the 30-year simulated incremental cost-effectiveness ratio (ICER) was greater than the United Kingdom National Institute for Health and Care Excellence (NICE) recommended threshold of £20,000-30,000 per quality adjusted life year (QALY) and therefore not deemed cost-effective. This study exemplifies the feasibility of a hybrid approach in cost-effectiveness studies, combining real-world and modeled data to estimate long-term outcomes.

Ideally diabetes itself is prevented, for which lifestyle interventions and drug therapies among high-risk individuals and screening for undiagnosed type 2 diabetes were found to be cost-saving and cost-effective strategies¹⁹⁰. Nonetheless, for this part of the thesis a focus is laid on reviewing the cost-effectiveness of interventions that prevent lower extremity complications in type 2 diabetes, starting with neuropathy. No real-data studies assessed cost-effectiveness of screening devices or the screening frequency on neuropathy, and are therefore not further concentrated on in this part of the thesis. When focusing on the

economic evaluation of interventions that tackle painful neuropathy, very few trials provided evidence for superiority of an intervention. A Dutch study on spinal cord stimulation for painful DSP did not show beneficial results at 12 months, compared to conventional care¹⁹⁴. Model-derived evidence was found for the cost-effectiveness of pregabalin, although another study found beneficiary results of desipramine and duloxetine over pregabalin (and gabapentin)^{195,196}. Periodontal treatment seems cost-effective in preventing, amongst others, microvascular diseases including neuropathy¹⁹⁷. Another Markov model showed that smoked cannabis was cost-effective when added to second-line medical treatment for peripheral neuropathy¹⁹⁸.

Model-based studies assessed the effectiveness of prevention strategies for diabetic foot disease, estimating that primary prevention; adequate care and guideline-based care were likely to be cost-effective and even cost-saving¹⁹⁹⁻²⁰¹. The IWGDF guidelines tried to complement their (therapeutic) recommendations with data on economic analyses, however, had to conclude that for only one intervention cost-effectiveness was studied^{1,202}. In that health technology assessment on offloading devices it was concluded that non-removable devices were superior in preventing DFUs with improvement of quality of life, compared to removable devices and therefore deemed cost-effective.

Other economic evaluations on more elusive treatment modalities not part of current Dutch clinical practice are not further reviewed^{203,204}. Cost-effectiveness of multidisciplinary foot teams is cost saving, but cost-effectiveness is often only evident after some years, in both the developed and developing world^{188,189,205}. The current methodologies used in economic evaluations do often not meet International Society for Pharmacoeconomics and Outcomes Research (ISPOR) standards and should be pursued for in future studies²⁰⁶.

(Cost)-effectiveness of LEND surgery compared to conventional, non-surgical care

At first, the reason to surgically treat neuropathy is the patient having symptoms of a compression neuropathy. With effective therapy, the nerves microvascular supply is restored and processes of nerve regeneration are allowed and benefit of therapy starts from there on. As already outlined before, neuropathy induced sensory loss lies at root of many (long-term) clinical outcomes, necessitating a lifetime horizon to capture all impacts on incremental costs and outcomes, including death. A model-based approach to assess these outcomes can overcome the practical issues of a large longitudinal study.

In the past thirty years, the reported outcomes after LEND surgery evolved to also include patient reported outcome measures (PROMs)^{98,141,207}. This is important, since the patient perspective is thereby valued. With this patient perspective, health outcomes achieved

per dollar spent define 'value in health care', what is eventually the outcome of interest of all stakeholders in the healthcare system²⁰⁸. To date, three analyses exist on LEND surgery valuing its effects on quality of life, costs and life-years saved compared to current care strategies²⁰⁹⁻²¹¹. The study by Garrod et al. used decision-tree utility analysis to evaluate the effect of LEND surgery on utilities and concluded that LEND surgery is preferred in avoiding loss of quality of life due to ulceration and amputation²⁰⁹. Costs were not considered and therefore this study is not regarded to be a cost-utility analysis. The study by Rankin et al. illustrated the cost saving implications of LEND surgery in the prevention of DFU recurrence using Markov modeling²¹⁰. A societal perspective, including patient copayments and indirect costs such as lost productivity, was used. However, the authors did not include the long-term additional benefits such as amputation avoidance in their model. The estimated costs of LEND surgery (US\$ 1143/leg * 2) resulted in a return of investment of 2.16 (by preventing DFUs) at year five. The study by Sarmiento et al. also used a Markov model to simulate the effects of tibial neurolysis on incident DFUs and amputations by comparing costs, quality of life and survival to current care, using a 10-year horizon. The resultant ICER was US\$ 31.330,78 per QALY gained and deemed cost-effective to US standards. The three studies were unambiguous in estimating the beneficial effects of LEND surgery compared to current care.

To estimate if similar results in the Dutch healthcare system are likely, LEND surgery was compared to current (non-surgical) neuropathy care using a modeled cost-effectiveness study (i.e., a Markov model) (**Chapter XVI**), partially based on RDF Study and our Dutch in-hospital costs study data^{165,187}. The study projected the epidemiological outcomes and cost-effectiveness of two cohorts of diabetic subjects with nerve compressions in the lower extremity, after 10-years of treatment. The simulated cohorts showed a considerable difference in incident DFUs (risk difference of 3.1) and amputations (risk difference of 2.9), resulting in less mortality and more lives saved with LEND surgery compared to current care strategies (505 lives saved in favor of LEND surgery) at 10-years follow-up. Consequently, 1855.9 discounted life-years and 3507.2 QALYs were gained in favor of LEND surgery, at lower discounted costs. By varying input parameters on effectiveness, transition probabilities, costs and utility weights using simulations (probabilistic sensitivity analysis), LEND surgery was shown to likely be less costly and more effective compared to current care. Costs of surgery and surgical site infections in the first 6 months of the model were surpassed by the costs of current care from 19 months onwards. This means that the combination of effects and costs (ICER) favors LEND surgery from then on. This also translates to beneficial net monetary and health benefits favoring LEND surgery at different willingness-to-pay thresholds. Our study adds to current literature with the use of probabilistic sensitivity analysis and up-to-date data on in-hospital costs of diabetic foot care. Incident DFU and

amputations were taken into account; however, our model did not include the costs and health effects on accidental falls, which is an important source of disease burden and costs, on which LEND surgery could also have a beneficial effect (**Chapter IX**)^{115,124,176}.

Although the Markov model estimated the long-term effects of LEND surgery compared to current care, based on the available literature, only high-quality randomized controlled trial data will give definite answers on the cost-effectiveness of LEND surgery in the prevention of lower extremity complications. The DECO trial is designed to answer these questions and is therefore the next step into the future.

Part VI: The future

The DECO trial is designed to generate high-quality, real-world data on (cost-) effectiveness of LEND surgery, by comparing external neurolysis of lower extremity nerves to conventional, non-surgical care for the diabetic neuropathy population (**Chapter XVII**)⁴⁴. By choosing a substantial follow-up of four years, both quality of life (primary endpoint) and the incidence of DFUs, amputations and falls, resource consumption and productivity loss (secondary endpoints) are investigated on the long-term. With these data, cost-effectiveness analyses are possible, including the estimation of the indirect costs of disease, validating the modeled outcomes of our previously discussed Markov model (**Chapter XVI**)¹⁸⁷. Moreover, with the chosen study design we aim to contribute to the (negative) discussion that has surrounded LEND surgery for the last three decades^{212,213}. Albeit sham surgery is asked for in the medical community, we considered sham surgery unethical in this patient group and not deemed necessary to validly assess the various endpoints^{103,162}.

Several other secondary research aims were formulated based on hypotheses generated from RDF Study data. The majority of the secondary objectives of the DECO study relate to the influence of nerve functioning on health-related quality of life, balance and gait and neuropathy symptoms, sensory status and incident DFU, amputations and falls. To further quantify return of small and large fiber function during follow-up, QST parameters of the protocol by the German Research Network on Neuropathic Pain were included in the study protocol³⁵.

The DECO trial is an ambitious study in which 344 diabetic patients with at least bilateral TTS and sufficient somatosensory function, graded with the RDF Study Test Battery, will be included. Up to four nerves in one leg will be decompressed (the common, superficial and deep peroneal nerves and tibial nerve at the soleal sling and tarsal tunnel), the contralateral leg will be operated 3 months later²¹⁴. Patients will be enrolled in 11 participating centers.

The future of the Rotterdam Diabetic Foot Study

The in this thesis presented longitudinal results of the RDF Study (**Part III**) are supplemented with a third follow-up assessment, after which the physical measurements will be terminated. This third measurement allows us to determine what the natural history is of sensory decline in the feet, in a 6-year time frame (Figure 1). Risk factors for sensory loss will be determined, together with the associated hazards of the gradual insensate feet. The latter can be assessed using joint-models²¹⁵.

Figure 1 Longitudinal follow-up of a RDF Study patient.

Legend: Baseline and first follow-up monofilament measurements at specific test sites. Subject's personal RDF-39 sum score displayed along histogram of all RDF Study participant's sum scores.

In these models, the longitudinal outcome on the RDF Test Battery could be used to estimate the event of interest, for example, DFU occurrence or falls (Figure 2). An individual prognosis is profiled to detect disease progression based on baseline and follow-up information²¹⁶. Since disease can differ between patients and within the same patient over time, individual patient data are preferred and, using these models, risk is assessed dynamically on a patient level, aiding personalized medical decision-making.

Figure 2 Longitudinal follow-up of a RDF Study patient with joint modeling applied.

Legend: Longitudinal and time-to-event data (DFU occurrence as event of interest). Y-axis: RDF-39 sum score; X-axis: time of follow-up in years.

External validation

The RDF Study Test Battery is currently used in the outpatient clinic of the department of Plastic- and Reconstructive surgery of Utrecht Medical University Center. By evaluating the test results from another populations of diabetic subjects, external validity is assessed. The rank order of somatosensory modalities lost due to neuropathy is likely to be also observed in this population of diabetic patients. Although the RDF Study population received secondary diabetes care in a regional teaching hospital, and may probably differ from populations seen in primary or tertiary healthcare institutions, external validity of the results is likely since the risk of floor and ceiling effects was observed to be low (**Chapter IV and V**)^{49,61}.

When the RDF Study Test Battery is found to be valid in other populations, future trials investigating interventions that reduce the risk of DSP may implement this diagnostic tool. This is especially the case for studies on multiple risk factor-lowering interventions that previously failed to show reduction in DSP with conventional measurements, due to low sensitivity²¹⁷.

Screening

The aim of screening is to detect a disease, condition or abnormality at a stage in which treatment can halt or delay progression. This treatment is usually an intervention offered at an earlier stage than usual. In order to study the effects of early detection and prevention, large population studies are often needed. However, they do not guarantee effective

prediction at the individual level and requires large numbers of individuals to be screened of whom only some will benefit. Several principles should be applied to quantify the positive and negative effects of detection programs on population health²¹⁸.

In this thesis, we described that current lower extremity care in patients with diabetes is stratified according to the risk for complications. However, there is no literature on the effect of screening for preventing DFU¹. Since substantial evidence is available on predictive factors of foot ulceration, and since there are no harms associated with yearly foot screenings, the IWGDF concluded that foot screening is likely beneficial¹²⁹.

Our research provided evidence that a more precise grading of sensory loss results in a better estimation of whom is most likely to suffer from future ulceration, compared to the IWGDF Risk Classification (**Chapter XI**)⁴⁰. Especially ulcer-free survival is a sensible outcome in patients with mild sensory loss and with this information the primary care population is probably more adequately served (**Chapter VI and VIII**)^{19,50}. The RDF Study grading scales could be implemented in a variety of settings, from primary care to tertiary care. Future studies should assess if screening with the RDF Study grading scales result in substantial positive health outcomes in terms of additional years of life, with a higher quality of life, by preventing lower extremity complications. Moreover, optimal time intervals between tests could be determined, in which the long-term RDF Study results discussed in **Chapter XI** may aid⁴⁰. Preferably, this subject is further investigated by means of a randomized controlled trial. Yet, before implementation of a screening program, the anticipated balance between positive health outcomes and side effects must have been made clear.

As shown in **Chapter X**, patients with TTS are at increased risk for DFU occurrence⁷⁵. With the simple Tinel sign, patients with neuropathy symptoms are distinguished for having TTS, and should be referred to a plastic or neurosurgeon with expertise in lower extremity peripheral nerve pathologies. If (adding) screening on lower extremity compression neuropathies yields benefit to the assessment diabetic subjects undergo annually has to be determined. The RDF Study Test Battery may aid this discussion, since patients with minor to moderate sensory loss are more likely to have beneficial results of LEND surgery (**Chapter XII**)⁹⁸. This is further investigated as secondary objective in the DECO trial.

Markov modeling can also be used to give estimates on costs, benefits and cost-effectiveness of screening on lower extremity nerve entrapments when diagnostic randomized controlled trials are not feasible or possible^{219,220}.

Outcome sets in LEND surgery

One can assess outcome at four different levels: the level of pathology, impairment, activity and participation and quality of life²²¹. It is important that outcome measures represent only one of these levels, since items that represent multiple levels may inflate the sum score, leading to false results **(Chapter IV & V)**^{49,59,61}. Outcome measurements encompassing treatment results, complications and quality of life during and following treatment are not standardized for LEND surgery yet. A standard set of patient-centered outcome measurements is already used in diseases like cleft care and breast cancer, aiding monitoring of routine clinical practice, quality of care and outcome comparisons^{222,223}.

To achieve this in the field of LEND surgery, a working group should be assembled representing clinicians, nurses, epidemiologists and patients. The Delphi method could be used to derive relevant clinical and patient related outcome measures, treatment-related complications, survival measures and case-mix factors¹⁴⁸. This thesis may serve as starting point for that endeavor, as were patient perspectives valued using a patient panel in designing the DECO trial. For example, from our studies we concluded that the MNSI questionnaire is probably not specific enough to use in the evaluation of LEND surgery outcomes, since this questionnaire does not specify where in the lower extremity symptoms are felt (leg vs. foot). Therefore, we added the Norfolk QoL-DN questionnaire to RDF Study follow-up assessments and the DECO study protocol, since that PROM distinguishes neuropathy symptoms in hand, arm, leg and foot. Secondly, we advocate for objective and standardized assessment of somatosensory function, as discussed in this thesis and as has been developed for upper extremity nerve repair²²⁴. Third, the RDF Study Test Battery derived scales (RDF-39, -31 and -13) do not include specific testing of common peroneal, superficial peroneal and saphenous nerves, although the same instruments of the full test battery could be used on to be determined test sites. Finally, motor function of lower extremity should be separately assessed and subjected to further psychometric analysis when compared to sensory function **(Chapter IV & V)**^{49,61,225}. These topics, amongst others, should be subject of further (multidisciplinary) debate.

In conclusion

The first reports from the RDF Study described in this thesis show that diabetes-induced sensory loss is gradable with simple to use instruments. This grading allows stratifying those at risk for postural imbalance, recurrent falls and ulceration and is a novel addition to the current literature. Moreover, our studies showed that tibial nerve anomalies are common in diabetic patients compared to the control population, and are accompanied with more neuropathic symptoms and sensory deficit. The latter places the feet with TTS at higher risk for diabetic foot syndrome. Modeled outcomes based on current literature suggest that beneficial long-term effects of decompressing the lower extremity nerves are possible. The DECO study will confirm or refute these estimates, of which the RDF Study was an important predecessor in regard to the epidemiology of lower extremity complications of diabetes. Future studies are necessary to investigate whether optimal prevention, surveillance and treatment of lower extremity neuropathies leads to a reduction in the incidence of its complications, in which the results of the RDF Study may aid.

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Appendices

Valorization

Valorization is the third mission of Dutch universities, after education and research, and is defined as the process of knowledge utilization, by adding academic know-how to society and thereby creating societal or commercial value.

Valorization is important for several reasons, of which knowledge transfer to benefit society is the most important, followed by the utilization of scientific achievements to develop and fund future research. In this section we briefly discuss the added value of the research performed in this thesis and advocate to do this in future theses to come.

Relevance and implementation

Two lines of reasoning are to be distinguished in this thesis. Firstly, new dimensions to current screening instruments are added to the current literature, of which the results should be considered for implementation in both the diabetic sensorimotor polyneuropathy and diabetic foot guidelines. Secondly, tibial nerve entrapment, its diagnosis, functional grading and the potential of lower extremity nerve decompressions (LEND) are discussed. Doctors should be aware of the possible existence of super-imposed nerve compressions in the lower extremity, as well paramedical professionals such as podotherapists, podiatrists and physiotherapists.

To elucidate the promising impact for clinical practice, the effects of LEND surgery on both patient and societal level are further investigated by our team, starting with the DeCompression (DECO) trial. By implementing the results from the ongoing Rotterdam Diabetic Foot Study directly in the DECO trial design, the utilization of our previous works is warranted. A strong collaboration with endocrinologists and plastic surgeons is paramount to make the DECO trial a success. Because endocrinologists see most of patients with diabetes and complaints in the feet, knowledge of this type of surgery is of utmost importance to inform and refer patients. Since plastic surgeons have a lot of expertise in surgery of the peripheral nerve, as it is a subspecialty of hand surgery, LEND surgery can be relatively easily implemented in other hospitals. The team behind the RDF Study has broad experience with the type of surgery itself and has the necessary skills and connections to up scale the intervention to other centers.

Epilogue

What was the natural history of the 75-year old patient' ulcerated right foot? Despite various attempts to recanalize arteries of the right extremity, partial amputations of the second and first toe were necessary during follow-up. A venous femoral-tibial bypass was planned, but a too diseased anterior tibial artery made it impossible to anastomose the bypass.

The second and third toe healed in a couple of weeks. The hallux, however, remained ulcerative for another four years, but healed in the end. Neuropathic pain remained present, necessitating treatment with tricyclic antidepressants.

What if this patient was timely diagnosed with a lower extremity entrapment neuropathy? Might this have given him an option to choose for a treatment?

Summary

In this thesis, a number of studies were presented with the aim to advance the knowledge on peripheral nerve related consequences of diabetes.

Beside a general introduction and discussion part, this thesis consists of seventeen studies presented over six parts. The majority of the presented studies were the product of the Rotterdam Diabetic Foot (RDF) Study, a longitudinal observational study of 416 diabetic subjects followed at Franciscus Gasthuis & Vlietland hospital in Rotterdam, the Netherlands.

Part I contains a brief overview of normal skin neurosensory physiology, with a focus on touch. The functional organization of mechanosensitive receptors is described, including its somatosensory testing and the anomalies observed in (diabetes) induced neuropathy.

Part II contains the results from six separate studies on different aspects of assessing the feet of (diabetic) patients. The central question for this part was two-fold: first, how do the tests compare to each other in the assessment of somatosensory function, and second, is the Tinel sign valid in diagnosing tibial nerve entrapment at the tarsal tunnel. The Pressure-Specified Sensory Device was found to be valid and reliable in the assessment of sensibility in the feet, and able to differentiate to different categories of sensory loss. Next to the cross-sectional RDF Study baseline data analyses, a separate study in 196 healthy volunteers was conducted to derive normative data of the conventional sensibility tests used. The normative values were subsequently incorporated as part of the dichotomized version of the RDF Study Test Battery (RDF-39). The 39 item RDF-39 was developed using Mokken Scale Analysis, a scaling method related to nonparametric Item Response Theory (IRT). The items of the RDF-39 can be summed to get a total (ordinal) score, with higher scores indicative of more severe sensory deficit. They provide the clinician with a quick screening tool to grade the severeness of neuropathy related sensory loss. Shorter forms are the RDF-31 and RDF-13. Parametric forms of IRT were used to develop the outcome measure from the RDF-39 at an interval scale, aiding further scale development and psychometric analysis. Decision tree analysis showed that as few as three tests are able to reliably estimate the RDF-39 sum score, aiding efficiency in the busy daily practice.

Diabetic patients with a positive Tinel sign were found to have significantly more sensory symptoms and deficit in tibial nerve innervated areas, making the Tinel sign a valid maneuver to diagnose tibial nerve pathology. Consequently, calculation of prevalence estimates was possible, with 29.9% (95%CI: 25.2 to 34.5) of diabetic subjects diagnosed with tarsal tunnel syndrome at either the left or right extremity. That this has important prognostic and therapeutic consequences was shown in **Parts III, IV & V** of this thesis.

In **Part III**, the central aim was to estimate the impact of graded sensory loss on ulcer-free survival, balance, risk of falls and the risk for foot ulceration. Firstly, the discriminative value of test locations was compared to a sum score of monofilaments and vibratory testing in estimating ulcer-free survival, with this sum score currently most often used in clinical practice. Our study showed that specific test sites at the feet have predictive power for overall sensory loss, requiring fewer tests and resulting in greater accuracy in the prediction of one-year ulcer-free survival. Secondly, the RDF-39 was used to relate pedal sensory loss to postural stability and it was shown that loss of sensation predicted imbalance and recurrent falls. Thirdly, the incurred sensory deficit observed in tarsal tunnel syndrome results in a greater risk for diabetic foot ulceration. This is of paramount importance and requires a different mind-set in the medical community: the recognition that sensory disturbances in the feet might be due to the (co-) existence of compression neuropathies. Finally, degree of sensory loss, measured with the RDF-39, was shown to predict the risk for ulceration in long-term RDF Study follow-up. This enables the clinician to better differentiate the patient at risk, with consequent recommendations on follow-up intervals, aiding medical decision making.

Part IV is about two treatment modalities: lower extremity nerve decompression (LEND) surgery and free-flap surgery for diabetic foot reconstruction. By doing a long-term follow-up of the Utrecht based Lower Extremity Nerve Entrapment (LENS) Study, we were able to identify factors influencing the surgical outcome of LEND surgery. It is likely that severe nerve damage, next to higher age, higher body mass index and longer duration of diabetes, exerted the odds for more profound favorable long-term outcomes reported from the LENS Study compared to studies from the literature. However, a considerable number of patients reported significant lower pain scores and higher quality of life at five-year follow-up. A letter to the editor of a major journal commented on a LEND surgery study in which the degree of two-point discrimination was shown to predict pain relief. However, a rather high threshold of 9 mm was chosen (hallux) as inclusion criterion, which was discussed in light of the literature as well as our experience with clinical grading of somatosensory function. Lastly, the arsenal of techniques a reconstructive surgeon can add to the treatments by the diabetic foot team are shown in two successful cases, in which the diabetic foot was reconstructed using free flap surgery. Furthermore, the shiver in regard to using microsurgical techniques in lower limb reconstruction of diabetic subjects is rebutted by evidence from the literature.

In **Part V** we gave an overview of current in-hospital costs of diabetic foot care provided by a multidisciplinary foot team. A micro-costing method was used, giving up-to-date data on current cost-of-illness, aiding research on cost-effectiveness of interventions. In addition, a Markov model was developed to simulate the onset and progression of diabetic foot disease in patients with diabetes induced neuropathy receiving current care, compared to

Summary

a group who were simulated to undergo LEND surgery. Mean survival time, quality of life, foot complications and costs were the outcome measures assessed. Data from the RDF-study were used on the epidemiology of diabetic foot disease, resource use and costs, complemented with information from international studies. Compared to current care, LEND surgery resulted in a reduced incidence of foot complications, improved life expectancy and gain of quality-adjusted life-years (QALYs). The 10-year costs of management of the diabetic after LEND surgery resulted in a beneficial cost per QALY gained. However, since this study was model based, we would like to investigate the cost-effectiveness of the intervention prospectively in the DeCompression (DECO) trial.

The final research part, **Part VI**, the protocol of the DECO trial gives us a look into the near future, in which the (cost-)effectiveness of LEND surgery is compared to conventional non-surgical neuropathy care by means of a randomized controlled trial. Disease-specific quality of life is the primary study end point and secondary objectives include general quality of life, plantar sensation, incidence of ulcerations/amputations, resource use and productivity loss during 48 months of follow-up. The incremental cost-effectiveness ratio will be estimated on the basis of the collected empirical data and a cost-utility model, validating the findings from our Markov model.

The general discussion included an extensive discussion of the main findings of this dissertation, together with several recommendations for future practice and research. This thesis ended on the optimistic notes that with grading sensory loss, a better prognostication regarding various life-changing adverse outcomes is possible and that with LEND surgery the prognosis for diabetic patients will likely improve, of which the chapters of this thesis provided the necessary evidence.

Summary in Dutch [samenvatting in het Nederlands]

In dit proefschrift werden enkele studies gepresenteerd met als doel de kennis over perifere zenuwaandoeningen als gevolg van diabetes te vergroten.

Naast een 'algemene introductie' en 'discussie' bestaat dit proefschrift uit zeventien studies, gepresenteerd in zes delen. Het overgrote deel van de studies waren het resultaat van de Rotterdamse Diabetische Voet Studie [Rotterdam Diabetic Foot (RDF) Study], een longitudinale observationele studie van 416 diabetespatiënten die werden gevolgd in het Franciscus Gasthuis & Vlietland ziekenhuis in Rotterdam, Nederland.

Deel I bestaat uit een overzicht van normale neurosensorische huid fysiologie, met speciale aandacht voor de tastzin. De functionele organisatie van mechanosensitieve receptoren is beschreven, inclusief somatosensorische testen en de afwijkingen die gezien worden in (diabetes geïnduceerde) neuropathie.

Deel II bestaat uit de resultaten van zes separate studies die handelen over diverse aspecten van het voetonderzoek bij (diabetes) patiënten. De centrale vraag van dit deel is tweeledig: ten eerste, hoe verhouden de testen zich tot elkaar in het meten van somatosensorische functie en ten tweede, is het teken van Tinel valide in het diagnosticeren van een beknelling van de nervus tibialis ter plaatse van de tarsale tunnel. De *Pressure-Specified Sensory Device* werd gebruikt om het gevoel in de voeten te meten en werd valide en betrouwbaar gevonden, alsook was het mogelijk om met dit apparaat verschillende groepen diabetespatiënten te onderscheiden met betrekking tot de mate van gevoelsverlies. Naast de transversale analyses op de eerste meetgegevens van de RDF Studie werd een aparte studie verricht om normaalwaarden te verkrijgen van de conventionele sensibiliteitstesten, door 196 gezonde vrijwilligers aan de voeten te meten. Deze normaalwaarden werden vervolgens gebruikt om een gedichotomiseerde versie van de RDF Studie Test Batterij te ontwikkelen, de zogeheten 39-item RDF-39. De RDF-39 werd ontwikkeld middels Mokken Schaal Analyse, een methode gerelateerd aan non-parametrische Item Respons Theorie (IRT). De items van de RDF-39 kunnen worden opgeteld tot een (ordinaire) som score, waarbij hogere scores indicatief zijn voor meer gevoelsverlies. De clinicus kan op deze manier snel tot een gradering van de ernst van het gevoelsverlies komen. Kortere versies zijn de RDF-31 en RDF-13. Parametrische vormen van IRT werden gebruikt om de uitkomstmaat van de RDF-39 op een interval schaal te verkrijgen, nuttig voor verdere schaalontwikkeling en psychometrische analyse. Verdere beslisboom analyse liet zien dat er slechts drie testen nodig zijn om een betrouwbare schatting te maken van de totale RDF-39 score, wat van nut is in de drukke klinische praktijk.

Diabetespatiënten met een positief teken van Tinel hadden significant meer symptomen van neuropathie en gevoelsverlies in tibialis zenuw geïnnerveerde gebieden, waaruit geconcludeerd werd dat het teken van Tinel valide is in het diagnosticeren van tibialis zenuw pathologie. Als gevolg hiervan kon worden geschat wat de prevalentie van deze aandoening is. Tarsaal tunnel syndroom, links of rechts voorkomend, kwam in 29.9% (95% betrouwbaarheidsinterval: 25.2 tot 34.5) van de diabetespatiënten voor. Dat dit belangrijke prognostische en therapeutische gevolgen heeft werd aangetoond in **Deel III, IV & V** van dit proefschrift.

Deel III handelde over de impact van gegradeerd gevoelsverlies op ulcus-vrije overleving, balans, het risico om te vallen en het risico op diabetische voet ulcera. Ten eerste werd de onderscheidende waarde van test locaties vergeleken met een somscore van monofilamenten en stemvork testen, momenteel het meest gebruikt, om ulcus-vrije overleving te schatten. Onze studie liet zien dat specifieke test locaties op de voeten een voorspellende waarde hebben voor het totale gevoelsverlies, waarbij er minder testen nodig zijn en een grotere accuraatheid wordt bereikt in het voorspellen van één jaar ulcus-vrije overleving. Ten tweede werd de RDF-39 gebruikt om gevoelsverlies aan de voeten te relateren aan houdingsafhankelijke stabiliteit (balans) en werd aangetoond dat verlies van voetgevoel disbalans en herhaald vallen voorspelt. Ten derde werd bewezen dat het door tarsaal tunnel syndroom veroorzaakte sensibiliteitsverlies resulteert in een groter risico op de diabetische voet. Dit is zeer belangrijke informatie en vereist een ander denkpatroon in de medische wereld: de herkenning dat symptomen in de voet mogelijksterwijs bestaan door gesuperponeerde zenuwcompressies. Tenslotte, mate van gevoelsverlies, gemeten middels de RDF-39, is voorspellend gebleken voor het risico op ulceratie in de lange termijn resultaten van de RDF Studie. Met deze informatie kan de clinicus beter differentiëren welke patiënt een risico loopt, met daaruit voortvloeiend aanbevelingen tot het volgen van de patiënt (tijdsintervallen), wat de verdere medische besliskunde omtrent gepaste behandelingen bevordert.

Deel IV handelt over twee behandel mogelijkheden: decompressie chirurgie van zenuwen in de onderste extremiteit en vrije lap chirurgie voor reconstructie van de diabetische voet. Door een lange termijn vervolgstudie te doen van de Utrecht gebaseerde *Lower Extremity Nerve Entrapment (LENS)* Studie was het mogelijk om factoren te identificeren die de chirurgische uitkomst na dit type chirurgie beïnvloeden. Het is aannemelijk dat de mate van gevoelsverlies (als maat van zenuwschade), naast een hogere leeftijd, hogere queteletindex en langere duur van diabetes ervoor gezorgd heeft dat de lange termijn uitkomsten van de LENS Studie minder duidelijk waren in vergelijking met andere studies uit de literatuur. Echter, een groot aantal patiënten rapporteerde significant lagere pijn scores en een hogere

kwaliteit van leven bij de vervolg metingen op vijf jaar na start van de studie. Een brief naar de redacteur van ons belangrijkste vaktijdschrift becommentarieerde een studie naar decompressie chirurgie, waarbij werd aangetoond dat twee-punts discriminatie voorspellend is voor pijnverlichting. Echter, als criterium voor studiedeelname was een behoorlijk hoge afkapwaarde van 9 mm gekozen (grote teen), wat werd bediscussieerd in het licht van de literatuur als ook onze eigen ervaringen met het klinisch graderen van somatosensorische functie. Tenslotte werd het arsenaal aan technieken die een reconstructief chirurg kan toevoegen aan de behandelingen door het diabetische voet team geïllustreerd aan de hand van twee casus waarbij de diabetische voet succesvol werd gereconstrueerd middels vrije lap chirurgie. Bovendien werd de huiver met betrekking tot het gebruik van microchirurgische technieken in de onderste extremiteit van diabetespatiënten ontkracht door het opvoeren van bewijs uit de medische literatuur.

In **Deel V** gaven wij een overzicht van de huidige ziekenhuiskosten van diabetische voet zorg door een multidisciplinair team. Een micro kostprijsberekening werd gebruikt, welke actuele gegevens opleverde met betrekking tot kosten van ziekte, wat van belang is bij onderzoek naar kosteneffectiviteit van interventies. Daarnaast werd een Markov model ontwikkeld die de start en progressie van het diabetische voet syndroom simuleerde in patiënten met diabetes geïnduceerde neuropathie. Een groep die decompressiechirurgie voor deze aandoening onderging werd vergeleken met een groep die de huidige, niet-chirurgische zorg voor neuropathie kreeg. De gemiddelde overleving, kwaliteit van leven, voet complicaties en kosten waren de uitkomstmaten. Informatie uit de RDF Studie werd gebruikt met betrekking tot de epidemiologie van het diabetische voet syndroom, middelengebruik en kosten, aangevuld met gegevens uit de internationale literatuur. Vergeleken met de huidige zorg resulteerde decompressie chirurgie in een reductie in de incidentie van voetcomplicaties, een verlengde levensduur en een toename van kwaliteit van leven aangepaste levensjaren. De 10-jaars kosten van zorg voor de diabetespatiënt na decompressie chirurgie resulteerde in een gunstige verhouding van kosten per kwaliteit van leven gecorrigeerd gewonnen levensjaar. Echter, gezien dit een gemodelleerde studie betrof, zouden we graag de daadwerkelijke (kosten-)effectiviteit van decompressie chirurgie onderzoeken in een gerandomiseerd onderzoek, de *DeCompression (DECO)* studie.

In het laatste onderdeel van dit proefschrift, **Deel VI**, geeft het protocol van de DECO studie ons een blik op de nabije toekomst waarin de (kosten-)effectiviteit van decompressie chirurgie wordt vergeleken met conventionele, niet-chirurgische zorg voor neuropathie, middels een gerandomiseerd onderzoek met controlegroep. Ziekte-specifieke kwaliteit van leven is het primaire studie eindpunt en secundaire eindpunten zijn algemene kwaliteit van leven, sensibiteit van de voetzool, incidentie van ulcera en amputaties, middelengebruik

Summary in Dutch

en productiviteitsverlies gedurende een looptijd van 48 maanden. De incrementele kosten-effectiviteits ratio zal worden geschat op basis van de verkregen data en een kosten-utiliteiten model, waarmee de schattingen van het door ons eerder ontwikkelde Markov model kunnen worden gevalideerd.

De 'algemene discussie' behelsde een uitgebreid discours over de belangrijkste bevindingen van deze dissertatie, alsook enkele aanbevelingen voor de klinische praktijk en toekomstig onderzoek. Dit proefschrift eindigde met de optimistische conclusie dat met het graderen van gevoelsverlies een betere voorspelling kan worden gedaan met betrekking tot enkele ongunstige, levensbepalende, uitkomsten en dat met decompressie chirurgie de prognose van diabetespatiënten aannemelijk beter wordt, waar de verschillende hoofdstukken van dit proefschrift met het nodige bewijs hiervoor aan hebben bijgedragen.

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Word of gratitude

‘Never was so much owed by so many to so few’.

Paraphrased from the speech by Winston Churchill to the House of Commons, 20 August 1940.

Curriculum vitae auctoris

Willem Daniël Rinkel was born on the first of May 1987 in Zwijndrecht, the Netherlands. After graduating from higher general secondary education (HAVO) and pre-university education (Atheneum) at Develstein college, Zwijndrecht, he started medical school in 2007 at the Erasmus University Medical Center (Erasmus MC), Rotterdam, the Netherlands. During his study he was involved in numerous extra-curricular activities, which included the legendary peer-to-peer surgical anatomy masterclass *Erasmus Anatomy Research Project*, led by prof. dr. G.J. Kleinrensink (Department of Anatomy), sparking his interest in the surgical specialties. He was founder and chairman of *Anatomie & Zoo*, a seminar on comparative anatomy between humans and animals, in co-operation with Delft University of Technology, Blijdorp Zoo, the veterinary department of Utrecht University, Utrecht, the Netherlands, and the Department of Anatomy of Erasmus MC. In the third year of medical school he became involved in scientific research on the peripheral nerve at the Department of Plastic, Reconstructive- and Handsurgery. He published four peer-reviewed articles in the international literature, co-authored a book chapter and presented the findings of these studies on both national and international congresses before graduating as a medical doctor in 2013.

During medical school, the conducted research and internships strengthened a continued interest in plastic-, reconstructive- and peripheral nerve surgery. It was therefore a great pleasure to start as a doctoral candidate at the same department (supervisors: prof. dr. J.H. Coert and prof. dr. S.E.R. Hovius) directly after receiving his medical degree. The main part of this research included the prospective, observational Rotterdam Diabetic Foot (RDF) Study commenced in Franciscus Gasthuis & Vlietland hospital, Rotterdam, the Netherlands, in close collaboration with the Departments of Internal Medicine (dr. M. Castro Cabezas) and Statistics and Education (dr. E. Birnie). Results of this study, amongst others, were presented on numerous national and international congresses and he has been awarded prizes for both oral presentations and published scientific articles. During his doctoral training he enjoyed ± 250 hours of microsurgery at the Skillslab, supervised workshop participants there, co-organized several Esser courses and Big Hand Events, participated in several courses on epidemiology and methodology at the Netherlands Institute for Health Sciences, the Mokken Scale Analysis workshop at the University of Amsterdam (prof. dr. L.A. van der Ark) and engaged in the 2015 fundamental peripheral nerve course (Association of Extremity Nerve Surgeons (AENS)) and 2017 partial joint denervation course (Mayo Clinic, Rochester, MN, USA), both organized by prof. dr. A. Lee Dellon (Johns Hopkins University, Baltimore, MD, USA). From 2014 till 2018 he supervised more than ten medical students over their master theses.

Much effort has been made to apply sophisticated statistical modelling to data from the RDF Study. His personal goal is to validate and implement the resultant prediction models in current guidelines and clinical practices, together with further investigations on surgical treatments for peripheral neuropathies. By combining clinical expertise with state-of-the-art statistical techniques, he aims to further improve the field of peripheral nerve research and direct patient care. By using large cohort study data, together with statistical modelling and high-quality data from randomized trials he aims to advance patient care for those often neglected. Dr. Rinkel has been granted from Stichting Coolsingel (€ 35k) and the Netherlands Organization for Health Research and Development (ZonMW, € 600k) and awarded numerous personal grants to continue the beforementioned research he started as a doctoral student. The first multicenter randomized controlled trial on lower extremity nerve decompression surgery (DeCompression (DECO) trial) is thereby initiated, for which he is the principal investigator, supervising multiple doctoral students.

In November 2016 he followed prof. dr. J.H. Coert to Utrecht, by then appointed professor at Utrecht University and chairman of the Department of Plastic-, Reconstructive- and Handsurgery, when accepted into the plastic- and reconstructive surgery residency program, which he started a year later at the General Surgery department of Diaconessenziekenhuis Utrecht/Zeist/Doorn (supervisor: dr. T. van Dalen). After completing this start of his residency, he continued training in October 2019 at the University Medical Center Utrecht (supervisor: dr. A.H. Schuurman). Dr. Rinkel is member of the Dutch Society of Plastic Surgery, American Society for the Peripheral Nerve, Association of Extremity Nerve Surgeons, European Association for the Study of Diabetes and Dutch Diabetes Research Association. He lives in Zeist, the Netherlands, and in his spare free time he likes to meet friends and family, to cycle, to read, to sail, to cook and has some bee colonies as beekeeper.