



Clinical Diagnosis of Diabetic Peripheral Neuropathy

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1 Introduction and Context

The variability in clinical presentation and complexities in measurement of diabetic neuropathy have not only challenged the clear understanding of epidemiology, impact, and the clinical trial development of therapies, but these often complicate the diagnostic process. However, with a clear understanding of these obstacles and the relevant clinical tools, clinicians from all fields of specialty can develop an efficient approach to diagnosis. This includes more simplified approaches suitable to primary care and diabetes management clinics that screen for and diagnose diabetic neuropathy, to the specialty neurology clinics that may use more refined diagnostic methods required for confirmation of neuropathy and the evaluation of more atypical cases. Certainly, the vast majority of cases of diabetic neuropathy do not require referral to a neurology specialist for confirmation. This places a responsibility on the diabetes care clinician to be able to confidently make a working diagnosis on clinical evidence and to initiate man-

agement, consider other causes of polyneuropathy, while identifying atypical features that warrant specialist referral. This chapter discusses these considerations and the approaches to the clinical diagnosis of diabetic neuropathy, while chapter “Clinical Features Diabetic Neuropathies” details clinical features, and chapter “Diagnostic Techniques for Diabetic Peripheral Neuropathy” details specialized diagnostic techniques.

1.1 Diabetic Distal Symmetric Polyneuropathy (Diabetic DSP): A Brief Overview

The most common form—and the one usually referred to as “diabetic peripheral neuropathy” or even more simply as “diabetic neuropathy”—is the diffuse, symmetrical, slowly-progressive length-dependent damage to the peripheral and autonomic nervous system classified technically by the term “diabetic distal symmetrical polyneuropathy” (diabetic DSP) [1]. It typically remains asymptomatic for years, may first present clinically with symptoms of abnormal sensation symmetrically at the tips of the toes and may over time spread to the stocking-and-glove distribution. It involves injury to different anatomical nerve types that show variable clinical manifestations between individuals. These can be classified as small fibers (thinly-myelinated autonomic B-fibers, and thinly- or un- myelinated autonomic

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and sensory C-fibers) that make up autonomic and pain and temperature sensory fibers. Damage to large fibers (myelinated $A\alpha$, $A\beta$, $A\delta$ sensory, and $A\gamma$ motor) are responsible for other sensory and skeletal muscle impairments [2, 3]. At the symptomatic stages, some have a large fiber-predominant pattern and experience numbness, tingling, or imbalance owing to sensory ataxia, while others have small fiber-predominant symptoms that may instead present with burning and stabbing pain, impairment in sensing heat and cold, or a propensity to clinical autonomic abnormalities like postural hypotension and gastroparesis [1]. Some experience combined manifestations of large and small fiber types, and, regardless of pattern, people with diabetes can be asymptomatic for extended periods even though their physical examination or specialized testing can reveal subtle or even marked impairments in nerve structure and function. With progression to foot muscle weakness (motor weakness represents another large fiber dysfunction), or clinical autonomic manifestations like dry feet from limited sweat production (sudomotor dysfunction),

the subsequent risk of ulcer, infection, and amputation intensify. Complications like these are feared more than death itself [4], and of great concern is the recent evidence in certain parts of the world of a resurgence in the risk of amputations [5–7].

1.2 Staging of Diabetic DSP

For the purpose of understanding the face value of symptoms and signs and their measurement scales, we center the discussion of clinical diagnosis in this chapter around the conventional staging system described in Table 1 [9]. In simple terms, in practice diabetic DSP (Stage 1b or higher) is identified through two possible points in clinical care: Asymptomatic screening, leading to a clinical diagnostic workup if screening physical examination results are abnormal, or alternatively through complaints of neuropathic symptoms on a clinical encounter, leading similarly to a clinical workup involving history, physical examination, simple laboratory tests, and

Table 1 Conventional diabetic distal symmetric polyneuropathy (diabetic DSP) staging system with notes on diagnostic considerations

Stage	Description and considerations
Stage 0	No diabetic DSP Absence of neuropathic symptoms, signs, and normal NCS. In clinical practice, such patients would not be evaluated by NCS, and thus Stage 0 would rarely be confirmed. This is more relevant to clinical research. May be associated with dysfunction in objective tests other than NCS: Small fiber morphology tests: Examples include intra-epidermal nerve fiber density or other parameters, subtle abnormalities in corneal nerve fiber density Small fiber function tests: heart rate variability, sudomotor dysfunction, abnormal vascular reactivity to heating or other stimuli Large Fiber function tests: subtle abnormalities in monofilament sensitivity Large Function morphology tests: Subtle abnormalities in sural nerve biopsy Measureable subtle dysfunction in these tests could serve as predictive index tests during Stage 0 for future onset of diabetic DSP. Proof-of-concept exists for the 8-point distal monofilament examination and for corneal nerve fiber density [8] (CNFL in press)
Stage 1	Asymptomatic diabetic DSP
Stage 1a	Absence of neuropathic symptoms, signs, but with abnormal NCS In clinical practice, such patients would not be evaluated by NCS and thus this stage would rarely be identified. This is more relevant to clinical research
Stage 1b	Abnormality in nerve conduction studies and neuropathic signs, but absence of neuropathic symptoms In clinical practice, such patients would be identified by asymptomatic screening as recommended by guidelines These subclinical stages 1a and 1b could similarly be associated with abnormalities in other large fiber morphology and function measures, or in small fiber measures as outlined for Stage 0

Table 1 (continued)

Stage	Description and considerations
Stage 2	Clinical diabetic DSP
Stage 2a	Criteria for subclinical neuropathy have been met and there are neuropathic symptoms with or without neuropathic signs In clinical practice, such people would be identified based on symptomatic complaints leading to a history and physical examination At this stage, neuropathy is sufficient for complications including neuropathic pain and sensory ataxia (imbalance)
Stage 2b	Criteria for subclinical neuropathy have been met and there is unequivocal weakness of ankle dorsiflexion Beyond this initial motor manifestation change, later stages (undefined by this classification scheme) include progressive motor dysfunction and the presence of foot complications such as ulceration, infection, amputation, and the Charcot deformity

DSP distal symmetric polyneuropathy, NCS nerve conduction studies
Table modified on content in Dyck et al. [9]

consideration in a small subset of people for neurologist referral for specialized testing and evaluation.

type 2 diabetes, the existence of pre-diabetes may lead to polyneuropathy and therefore it may be present at diagnosis even without substantial elevations in glycemic exposure [17].

2 Key Clinical Considerations FOR Diabetic DSP Diagnosis

2.1 Clinical Risk Factors for Diabetic DSP Are Typically Present

Elevated cumulative glycemic exposure is the fundamental risk factor for diabetic DSP onset [10–12]. As such, age, diabetes duration, and glycemic exposure measured by an inability to maintain glycated hemoglobin A1c at target levels, generally considered to be 7.0% or less, are related risk factors [13]. Additionally, cardiovascular metabolic risk factors including presence of hypertension, abdominal obesity, hypertriglyceridemia, and low high-density lipoprotein, as well as taller height, alcohol abuse, and chronic kidney disease have been identified, in addition to putative racial and genetic factors that may be clinically identifiable in future [13–16]. However, specific threshold levels of risk factors and their duration have not been proposed. Generally, an individual with short duration of type 1 diabetes is extremely unlikely to have diabetic DSP unless exceedingly high glycemic exposure has occurred and other risk factors are present. However, in

2.2 The Impaired Protective Sensation of Diabetic DSP Represents Only One Component Cause of Foot Complications

While diabetic DSP itself is sufficient to cause pain and imbalance as complications, it represents only a component cause, neither necessary nor sufficient, to cause ulcer, infection, the Charcot deformity, or amputation. Tissue ischemia from peripheral vascular disease, and foot deformity or the minor trauma to skin that incites ulceration and infection induced by inadequacies in footwear and general foot care represent the other component causes. The implication is that if a clinician is to meaningfully help to prevent foot complications, the annual foot evaluation must not focus only on the identification of the loss of protective sensation representing diabetic DSP alone. It must include evaluation for arterial patency (pedal pulses and skin changes), and foot inspection for presence of abnormalities such as callouses or deformity that may indicate the presence of repetitive minor trauma (Fig. 1 and Table 2).

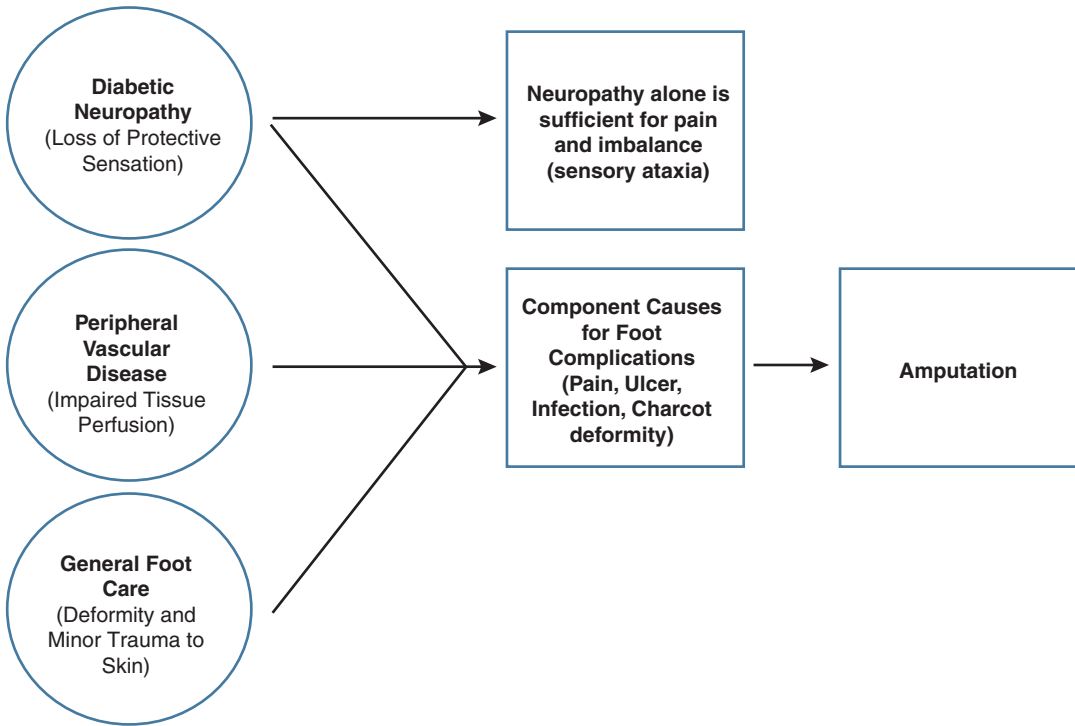


Fig. 1 A simplified view of the core component causes of foot complications and amputation. While sufficient for pain and sensory ataxia, the presence of loss of protective sensation from diabetic neuropathy alone is not considered sufficient for advanced foot complications without

the presence of peripheral vascular disease or minor trauma to skin. The implication is that clinical evaluation focused only on diabetic neuropathy, without consideration of the other component causes through simple inspection and palpation for pulses, is insufficient

Table 2 Clinical manifestations according to fiber classification and other key clinical features of diabetic DSP

Fiber classification	Large fibers: myelinated A δ sensory, A γ motor, and A α and A β mixed motor and sensory	Small fibers: thinly-myelinated autonomic B-fibers, and thinly- or un- myelinated autonomic and sensory C-fibers
Function	Touch, pressure, vibration, proprioception/ balance, somatic motor	Pain sensation, temperature sensation, autonomic
Symptoms	Numbness, tingling, unsteadiness	Pain, discrimination of hot and cold
Signs	Impairments in ankle reflexes, vibration, light touch, 10-g monofilament, proprioception, sensory ataxia (positive Romberg test) [18]	Impairments in thermal discrimination, pinprick sensation
“Red Flags” that are inconsistent with diabetic DSP	Asymmetry Nonlength dependence Acute or subacute rather than insidious, chronic onset and progression Motor predominance [19] Also consider Family history of sensory and motor symptoms Sensory neuropathies causing gait ataxia and proprioceptive dysfunction Severe dysautonomia [20]	
Late stage findings	Dry skin (sudomotor neuropathy), callus, fissures, ulcerations, cellulitis Charcot deformity	
Physical examination for other foot complication component causes	Inspection for deformity Callus, abrasions, hallux valgus Vascular Pallor, cyanosis, capillary refill, pedal pulses (posterior tibial and dorsalis pedis)	

Diabetic DSP diabetic distal symmetric polyneuropathy
Adapted from concepts introduced by Pop-Busui et al. [1]

2.3 Impaired Protective Sensation Shows Heterogeneity Between People with Diabetes

Impaired protective sensation may occur asymptotically (in approximately half of those with objective evidence of diabetic DSP) [21] or symptomatically. Whether symptomatic or not, the symptoms and signs may represent small or large fiber sensory modalities, as well as autonomic and motor modalities. Severity can be determined by the extent of sensory modality impairment, and by the presence and extent of motor weakness in the muscles of the feet. Furthermore, while autonomic dysfunction can be observed at early stages by specialized testing, clinical autonomic manifestations generally occur at more advanced stages. Finally, many may present with mixed findings representing both small- and large-fiber modalities [1, 11]. The implication of this heterogeneity of clinical presentation is that the evaluating clinician must consider these varied attributes, that theoretically the selection of individual screening tests may not be sufficient, and that scales that consider multiple attributes may have advantages over other investigative tests.

In summary, evaluation of the feet in people with diabetes represents consideration of risk factors for diabetic DSP, evaluation of a composite of the varied components of diabetic DSP, as well as a composite of the features of neuropathy, peripheral vascular disease, and foot deformity and foot care. The diagnosis of diabetic DSP itself requires a process of clinical assessment, either initiated by asymptomatic screening or in response to a symptomatic complaint, that considers the results of various clinical history and examination tests. As in any process of diagnostic medicine, each symptom or sign incrementally revises the clinician's estimates of disease probability and reduces clinical uncertainty [22].

3 Asymptomatic Clinical Presentation: Screening for Diabetic DSP

It is estimated that approximately half of people with objective evidence by physical examination or specialized testing have no symptoms of neuropathy [1, 21]. Asymptomatic screening for neuropathy has therefore generally been justified based on “disease principles” criteria for screening [23]. For example, the epidemiology of diabetic DSP is generally understood, its natural history includes a latent phase, and the target population for screening—including type 2 diabetes at diagnosis and type 1 diabetes with 5 or more years of diabetes duration—is well defined [1]. Screening is also supported by “test principles.” For example, screening test performance characteristics and their interpretation and thresholds are generally well understood [23]. This justification exists even if “system principles” are not uniformly met. While a diabetes multiprofessional care infrastructure exists, screening is acceptable to people with diabetes and carries little harm, some aspects are not yet well understood. These include how valid specific tests are when implemented in different settings, the economic evaluation of screening, the lack of neuropathy-specific, and the implications of misclassifying neuropathy as present when it is not (false positive) or falsely negative. Despite these limitations, the diabetes community has consistently supported screening for diabetic DSP [1, 24, 25].

In practice, the annual screening examination recommended by diabetes organizations can be accomplished by way of very simple tests for loss of protective sensation. Examples include testing pressure sensation with a monofilament, testing vibration sensation with a tuning fork, or frankly an even simpler “Touch the Toes” approach adopted by Diabetes UK in which the feet are simply exposed, inspected, and touched

with the fingertip [24, 26, 27]. Some organizations, like the American Diabetes Association through its neuropathy position statement, recommend a more extensive evaluation. This recommendation calls for an annual careful neuropathic history, along with a small fiber function test (such as temperature or pinprick sensation), a large fiber test (vibration sensation using a 128-Hz tuning fork), as well as a simplified version of the 10 g monofilament test to assess for feet at risk of ulceration or non-traumatic amputation [1].

While we discuss physical examination maneuvers below under Neuropathic Signs, we wish to discuss a particular aspect of screening for impaired protective sensation using common maneuvers. Most maneuvers have been justified by their *face validity*: They make sense, they are available in clinical practice, they are well recognized by diverse clinicians, and represent a key attribute of diabetic DSP. Several common examples exist that have more extensive research evidence in that they not only have demonstrated face validity and reasonable test reproducibility, but also intrinsic diagnostic accuracy for concurrent validity [28, 29]. Concurrent validity represents the ability of a test to reasonably classify, in a cross-sectional study design, who in the study sample has neuropathy defined by a reference standard test (including nerve conduction studies) and who does not. Several examples of tests with this level of evidence exist [28, 29]. However, we highlight a particular quantitative variation of the 10 g-monofilament examination that has even further evidence as a screening test for the prediction of future onset of diabetic DSP. This scoring system has been created in order to measure more subtle degrees of abnormality in protective sensation [8, 24]. First, it is applied only to a distal, non-callousing site (proximal to the nail bed as shown in Fig. 2) in order to identify earlier, distal length-dependent sensory impairment as compared to the more traditional multi-site testing that includes more proximal sites on the soles of the feet. Second, rather than simply grading a 10g monofilament test as a binary “normal” or “abnormal” result as in the tradi-

tional multi-site testing, in the test variation the monofilament is applied four times to each great toe in a random, arrhythmic manner to generate a quantitative score. For each stimulus, a score of 0 is assigned if it is not perceived, 0.5 if it is substantially less than that perceived on the forehead or sternum, and 1 if it is perceived normally, resulting in a total score from 0 (completely insensate) to 8 (completely sensate). Unlike the binary score, this allowed determination of two specific thresholds: The concurrent validity threshold for identifying the presence of neuropathy in cross-sectional study (this was determined to be a score of 0–3 out of 8), as well as a predictive validity threshold not associated with the current presence of neuropathy but instead with future onset in a 4-year longitudinal cohort structure (this was determined in a longitudinal cohort to be a score of 3.5–5.5). A score of 6–8 is interpreted as ruling out current neuropathy and extremely low 4-year risk of onset [8, 24]. In summary, while frank loss of sensation to the 10g monofilament helps to predict future ulcer and amputation risk among those with neuropathy, a quantitative variation of this examination seeking more subtle changes in sensation that would otherwise be called “normal” can be used as a screening tool, such that asymptomatic individuals (Stage 0 and 1a) can be reasonably stratified into those at low and high future risk. This, after all, is the intention of asymptomatic screening for disease: to identify at the earliest stages when interventions, such as improvement in glycemic control, are more likely to be effective. The identification of other tests, including objective measures, that could have sensitive thresholds to identify individuals at future risk of neuropathy onset represents an urgent clinical research need [30]. While the more sensitive, quantitative variation of the monofilament examination provides an approach to screening for protective sensation that has been evaluated in meta-analysis [28], we readily acknowledge that the predictive validity findings arise from a single-center longitudinal cohort and that it is not known with certainty if there are advantages over other simple [27] or complex [1] screening approaches.



Fig. 2 Quantitative variation of the 10 g monofilament test suitable for diabetic dsp screening for the presence of neuropathy (impaired protective sensation) or its future risk. The 10g monofilament is also known as the 10 g Semmes-Weinstein monofilament. Adapted from Brill et al. [24] The testing procedure: (1) Show the 10 g monofilament to the person with diabetes. (2) Touch it first to the person's forehead or sternum so that the sensation is understood. (3) Instruct the person to say "less" or "same" every time the monofilament stimulus is perceived. (4) With the person's eyes closed, apply the monofilament to the dorsum of the great toe proximal to the nail bed as shown in the illustration. Use a smooth motion to touch

the skin, bend the filament for a full second, then lift from the skin. (5) Perform this stimulus four times per foot in an arrhythmic manner so the person does not anticipate when the stimulus is to be applied. (6) For each of the 8 stimuli, assign a score of 0 if it is not perceived, 0.5 if it is substantially less than that perceived on the forehead or sternum, and 1 if it is perceived the same. A score of 3 out of 8 correct responses means that the presence of neuropathy is likely. A score of 3.5–5 means that the risk of new-onset neuropathy in the next 4 years is high. A score of 5.5 or greater indicates that there is a low risk of neuropathy onset in the next 4 years

4 Neuropathic Symptoms

The common symptoms of diabetic DSP are the large and small fiber sensory manifestations. Historically classified as "positive" symptoms, indicating nerve hyper-function creating a sensation normally absent, or "negative" symptoms, that represent hypo-function creating loss of a sensation normally present, this distinction is not

clinically informative as there is a subtlety to the lived experience of polyneuropathy [31, 32]. Some recommend classification by small and large fiber sensory modalities [1], and we describe clinical features according to this classification throughout this chapter (summarized in Table 2). Regardless of classification, common symptoms are pain, tingling, numbness, unsteadiness, and a feeling of weakness. Symptoms typically have a

slow, insidious progression, beginning bilaterally at the tips of the toes moving proximally over months or years to involve the lower thighs at which point the hands may become involved. This “stocking and glove” distribution of sensory symptoms can even progress to involve the midline of the abdomen, and symptom descriptions are variable between people. Unequivocally, symptoms present in the hands that are not accompanied by clinical features first in the lower limbs at or below the knee are not consistent with a diagnosis of diabetic DSP. Among the small fiber symptoms, common pain descriptors are “burning,” “stinging,” “shock-like,” lancinating pain [33]. Less common descriptors are a “squeezing,” pressure sensation. Pain can be present during the daytime or nighttime, and often have paroxysmal patterns. Small fiber dysfunction also includes impaired temperature discrimination, often described as a loss of ability to identify hot or cold water with one’s feet in the bathtub. Large fiber sensory symptoms include tingling, “pins and needles,” or numbness. Numbness can represent a lack of sensation, and is often used variably by people with diabetes to describe lack of thermal sensitivity, light touch, lack of pain sensation from minor traumas that would normally be present, such as the finding of a stone in one’s shoe or a cut to the skin without feeling pain or discomfort. People frequently describe a relative feeling of unsteadiness, which can be a manifestation of pain, tingling, numbness, or instead from a sensory ataxia in which either foot proprioception is affected or the stabilizing effect of feeling the ground. Similarly, a nonspecific feeling of weakness is a very common descriptor, likely as a consequence of abnormal sensory symptoms, as frequently this is described even when motor testing is completely normal. Motor symptoms resulting from muscle weakness can occur in more advanced diabetic DSP with impairment of foot dorsiflexion and plantar flexion that may be described as an inability to perform activities that require standing on the forefoot or on extended toes or heel-walking. Hyperalgesia and allodynia as manifestations of abnormal sensory processing are less common. Hyperalgesia refers to a painful stimulus that

feels exaggerated, while allodynia refers to a normal stimulus that is perceived as painful such as severe pain induced by rubbing the toes along the bedsheets. While uncommon in diabetic DSP without first experiencing sensory symptoms, symptoms of autonomic dysfunction such as dryness of skin from sudomotor neuropathy, or the symptoms of gastroparesis, enteropathy, or clinical cardiac autonomic neuropathy with postural lightheadedness and syncope may occur. Finally the symptoms of foot complications like infection, ulceration and Charcot deformity may be present symptoms in advanced neuropathy.

5 Neuropathic Signs

A directed neurological examination for diabetic sensorimotor polyneuropathy (DSP) requires examination of the lower limbs starting distally at the toes [33]. As with symptoms and depending on stage and severity, the signs may be a reflexion of small fiber dysfunction, large fiber sensory dysfunction, large fiber motor weakness, presence of clinical autonomic abnormalities such as sudomotor neuropathy, and the manifestations of foot complications (Table 2). Appearance of the skin and feet can reveal dryness and color changes, loss of hair, clawing and deformity of the toes, and ulcerations at late stages. Clinical sensory function is assessed for small (thermal sensitivity, pin prick), large (vibration, proprioception), and mixed (light touch) fiber modalities. These sensory tests are performed by first applying the stimuli to the sternum or forehead so that the person can appreciate the normal sensation, and then distally at the first toe, or adjacent toe, in case of amputation. To determine severity, the stimuli are then moved proximally to provide a level at which the sensory function becomes normal. For vibration, a 128 Hz tuning fork is sufficient and must be applied on bony surfaces. Alternatively, small pocket-sized battery-operated electronic devices that standardize vibration can be used [34]. For proprioception, the distal phalanx is held on the lateral surfaces and moved upwards and downwards in small movements. For pinprick, a disposable sterile

sharp metal tip can be used [35]. For thermal sensitivity, cold sensation can be assessed with a steel tuning fork cooled under running cold water, or alternatively, with a simple pen-like device that has a cool metallic end and a warmer plastic end for comparison [36]. For light touch, a cotton wisp may be used. The 10 g monofilament is a nylon thread affixed to a handle that bends at a standardized pressure of 10 g, representing a combination of touch and pressure sensation. Other physical examination tests such as 2-point discrimination, or the tactile circumferential discriminator to evaluate a person's ability to differentiate stimuli of different diameters, are not commonly used for assessment of diabetic DSP.

Motor function is evaluated by muscle bulk and power of the small foot muscles, and specific strength on foot dorsiflexion and plantarflexion are generally tested. Strength in other lower limb groups should also be assessed (knee and hip movements). The deep tendon reflexes need to be performed with the person fully relaxed and knee and ankle reflexes should be assessed. Gait and ability to perform a tandem gait, Romberg test for sensory ataxia, and also ability to walk on heels and toes would complete the lower limb examination. Upper limbs should be examined depending on lower limb findings [33].

From a diagnostic perspective, the principal purpose of the physical examination is to determine, through the process of clinical assessment, if the various signs are in keeping with the clinical pattern of diabetic DSP through a process, with each finding, of incrementally revising clinical estimates of disease probability. For example, as discussed later, signs such as motor predominance over abnormal sensory tests, asymmetry, and lack of length-dependence are findings that substantially decrease the probability of diabetic DSP. This is of particular importance because it is known that individual physical examination signs are known to have very poor inter- and intra-rater reproducibility, even in the hands of expert neurologists [37]. This can be partially overcome by the clinician having a broad, systematic physical examination including multiple physical examination maneuvers as described, as

well as by the performance of objective confirmatory tests if diagnostic uncertainty remains (chapter "Diagnostic Techniques for Diabetic Peripheral Neuropathy").

Though research into implementation is limited, we make brief mention of certain point-of-care devices, defined as simple, rapid, lab-quality diagnostic devices for use by clinicians at the moment of clinical care for diagnosis. Some are an extension of the physical examination (battery-operated vibrating device in place of a tuning fork, temperature discrimination devices, or the "Neuropad" paper to identify sweat function) [34–36, 38, 39], and, like sensory physical examination, many are heavily dependent on subjective patient responses. Objective sudomotor function assessment by way of electrochemical skin conductance devices have shown conflicting evidence in the literature [40–43], but may be amenable to implementation into practice for screening [44]. Simplified point-of-care nerve conduction devices for sural nerve amplitude and conduction velocity are reproducible and valid, and in future may have impact on clinical decision-making as well as implementation into practice [45–49].

6 Composite Symptom Scales, Sign Scales, and Combined Scales

We have introduced thus far in this chapter the essential components of clinical evaluation, mostly representing symptoms and signs that represent effective clinical practice but that have not individually been evaluated in investigative test research for their diagnostic performance. However, we then introduced some specific screening maneuvers that have concurrent validity for identifying the presence of DSP such as the Ipswich Touch Test adopted by Diabetes UK [27] and versions of pain, vibration, light touch sensation [28, 29], as well as the example of a variation of the 10-g monofilament examination that may permit prediction of future onset of DSP [8]. Investigative test research is broad, though, as these tests can include single symptoms, signs,

laboratory parameters, as well as composite scoring systems [50]. As individual symptoms or signs are likely not sensitive or specific enough to serve as a biomarker response, for example, to a therapeutic intervention in a clinical trial, one strategy is to implement a composite score, such as a self-reported symptom questionnaire or the clinical scales that make up a focus of this Chapter [51]. While these have been developed primarily as a way to summarize the proportions and severity of diabetic DSP in trial or cohort study populations, these composite scales can serve four key purposes to the clinician [22, 50]. First, they incorporate (and remind the clinician of the) multiple aspects of the manifestations of diabetic DSP, rather than focusing on one in isolation. Second, they can provide a diagnostic threshold for concurrent diagnosis, and, though they have not yet been evaluated in this way, for prediction of future onset of diabetic DSP or its related foot complications. Third, the quantitative scores allow a measure of diabetic DSP severity that is typically not conferred by the result of a single symptom or sign. Finally, many identify pain and its severity and can therefore be used to guide therapy for painful diabetic DSP.

7 The Michigan Neuropathy Screening Instrument (MNSI)

First published in 1994 [52], the Michigan Neuropathy Screening Instrument (MNSI) has had major impact on the identification of diabetic DSP, as well as providing a measure of its severity, and, potentially also an ability to track progression and regression in many observational studies and clinical trials [21, 53–56]. The MNSI is, in fact, made up of two separate assessments. First, a questionnaire (symptom scale) component, has major value for screening as it is a self-administered questionnaire made up of 15 items. These include questions such as having received a diagnosis by a physician in the past, or a history of amputation or ulceration, dry skin, but also about neuropathic symptoms such as numbness, pain, temperature sensation, and allodynia. Furthermore, there are two questions that are

unscored, including generalized weakness and cramping, that can help the rater understand other features that may not relate directly or specifically to DSP and foot complications risk factors. The second component is a five-part lower extremity physical examination made up of examination for abnormal appearance including presence of callus or deformity, examination for ulceration, ankle reflexes, and simple 3-level scores using vibration sensation and the monofilament (present, reduced, absent).

7.1 Scale Face Validity

Both the MNSI Questionnaire and MNSI Examination scales incorporate attributes that relate specifically to polyneuropathy, however, they test the presence of other attributes including the presence of foot deformities. Whether the person has polyneuropathy or not, the presence of foot abnormalities such as callus, fissures, ulceration likely places them at high risk of foot complications. Though less specific to diabetic DSP, these features increase its clinical relevance as an outcome measure. For polyneuropathy-specific research, the manifestations especially on foot examination may not be sensitive enough to identify those at earlier stages of polyneuropathy alone, given that the sensory tests are graded in three simple categories.

7.2 Test Quality and Reliability

The MNSI itself has not been tested formally using standard methods and metrics for inter- and intra-rater reproducibility. Studies on variations of the MNSI show suitably high reliability [57, 58].

7.3 Diagnostic Accuracy: Concurrent

The original publication, representing analysis of a small cross-sectional group of type 1 and type 2 participants who had diabetic DSP confirmed by nerve conduction studies, undertook a simple tabulation suggesting that an MNSI Questionnaire score of 7

or greater, and an MNSI Examination score exceeding 2, are associated with extremely high predictive values positive, good sensitivity and extremely high specificity [52]. However, a diagnostic study design conducted in a type 1 diabetes observational cohort that also operationalizing nerve conduction studies to define diabetic DSP cases, suggested that these particular thresholds were associated with substantially lower diagnostic performance, and suggested alternate thresholds [51]. First, a threshold score of 4 or greater on the MNSI Questionnaire, such a test result would carry 40% sensitivity and 92% specificity. Second, an MNSI Examination result exceeding a score of 2 carried 61% sensitivity and 79% specificity. However, on inspection of the receiver operating characteristic curves from this publication, we observe that an MNSI Questionnaire score (such as a score of 1 or greater) could reasonably be chosen to maximize sensitivity to nearly 60%.

7.4 Diagnostic Accuracy: Predictive

While many longitudinal designs have been conducted, and even some cohort designs (in which those with neuropathy at baseline have been excluded), we were unable to find in the literature analyses that explored whether a certain test score could predict future onset of diabetic DSP. While this does not make inherent sense for the MNSI examination scores, which measure manifestations of established diabetic DSP (such as presence of ulcer or complete reduction or abnormality—rather than subtle impairments—of vibration or monofilament sensitivity), such a design could be applied to the MNSI Questionnaire that has components that are suited to earlier, pre-diagnostic stages of diabetic DSP.

7.5 Effect on Treatment Decisions, Impact on Patient Outcomes, Economic Analysis

The results of MNSI testing have not been studied on their effect on the treatment decisions made by clinicians, or whether MNSI testing is associated

with improved outcomes relative to current standards of screening and diagnosis. However, it has been frequently operationalized as a neuropathy outcome in large-scale clinical trials including those evaluating cardiovascular and microvascular outcomes in type 1 and type 2 diabetes [21, 53–56]. As many of these studies required a measure of more advanced diabetic foot disease, the MNSI has provided a successful proof of concept for applying neuropathy scales in trials.

8 Toronto Clinical Neuropathy Score (TCNS)

The Toronto Clinical Neuropathy Score (TCNS), first validated and reported in 2002, was developed specifically for use in a study of simple screening measures for DSP that could be used in the family physician's office or the diabetes clinic [29, 59]. Spectrum bias is a very common design flaw (a source of selection bias) in investigative test research. It represents inappropriate recruitment of many participants for whom there is no diagnostic uncertainty, and recruitment of participants with limited variation in disease characteristic [22]. The original purpose of the TCNS was to create a quantitative score that ranged across all diabetic DSP Stages (Table 1) that would allow for stratified accrual across the full spectrum of neuropathy to appropriately determine the diagnostic performance of simple screening measures [29]. The scale comprises six symptoms (present/absent), knee and ankle reflexes (normal, reduced, or absent scored bilaterally) and sensory tests (normal/abnormal) as shown in Table 3, Panel A and ranges from a perfectly normal score of 0 without clinical evidence of DSP to a maximum abnormal score of 19 points. The symptoms are: foot pain, numbness, tingling, weakness, unsteadiness, weakness, and presence of upper limb symptoms. The sensory signs include sensory tests of pinprick, temperature, light touch, vibration, and proprioception. The deep tendon reflexes include the knee and ankle reflexes. Out of a total score of 19, the grades are defined as follows: 0–5 = no neuropathy; 6–8 = mild neuropathy; 9–11 = moderate neuropathy; ≥ 12 = severe neuropathy.

Table 3 The components of the original Toronto Clinical Neuropathy Score (TCNS) and the modified TCNS (mTCNS)

Symptom scores	Sensory test scores	Reflex scores
A. Scoring of the Toronto clinical neuropathy score (TCNS)		
Foot pain Numbness Tingling Weakness Unsteadiness Upper limb symptoms Symptom scores graded as 0 = absent 1 = present	Pinprick Temperature Light touch Vibration Position sense Sensory test scores graded as 0 = normal 1 = abnormal	Knee reflexes Ankle reflexes Reflexes graded as 0 = normal 1 = reduced 2 = absent Bilaterally
Maximum TCNS Score 19 points		
B. Adaptations in scoring to create the modified TCNS (mTCNS)		
Symptom scores graded as 0 = absent 1 = present without interfering with sense of well-being or activities 2 = present and interfering with well-being but not activities 3 = present and interfering with well-being and activities	Sensory test scores graded as 0 = absent (0) 1 = present at level of the toes 2 = present at level of the ankles 3 = present at a level proximal to the ankles	Not scored
Maximum mTCNS score 33 points		

Adapted from Bril et al. [59, 60]

8.1 Scale Face Validity

The TCNS has attributes that relate specifically to manifestations of small and large fiber dysfunction of polyneuropathy, excluding other components such as foot deformity that raise risk for foot complications. The broad scoring range that includes six points for symptoms and 13 for signs may permit greater sensitivity for earlier stages, though individual test components are assigned binary or three-level ordinal scores (Table 3).

8.2 Test Quality and Reliability

Formal evaluation of reliability reported internal consistency of attributes, and very good to excellent inter- and intra-rater reproducibility [60]. While in opposition to the findings of poor reproducibility of individual physical examination [37], reproducibility is likely greater with investigative tests that make up a composite of multiple individual tests.

8.3 Diagnostic Accuracy: Concurrent

Diagnostic accuracy has been evaluated extensively, including relationship with nerve conduction studies, diabetic DSP classified by signs, symptoms, and nerve conduction studies, and even relative to the results of fiber density on sural nerve biopsies [59, 60]. Furthermore, its validity has been tested in non-diabetic forms of polyneuropathy [61]. In a type 1 diabetes cohort, TCNS had receiver operating characteristic curve area under the curve of 0.86 for identification of Stage 2 diabetic DSP, with an optimal threshold value of 6 or greater identifying DSP with sensitivity and specificity each approximating 80% [51]. Additionally, very good overall accuracy was achieved even for the identification of sub-clinical Stage 1a neuropathy, with an area under the curve of 0.74 [62]. However, its diagnostic performance in type 2 diabetes, along with objective tests, was lower [52].

8.4 Diagnostic Accuracy: Predictive

A pilot longitudinal study that included baseline TCNS indicated subtle baseline differences in scores between those with future incident diabetic DSP and those who remained neuropathy-free, but it did not appear to have diagnostic predictive validity [63]. Though not conclusive, this implies that the main role of the TCNS, like other scales, is optimized for identification rather than on prediction of future neuropathy incidence.

8.5 Effect on Treatment Decisions, Impact on Patient Outcomes, Economic Analysis

Similar to the MNSI, the TCNS has not been studied for effect on the treatment decisions made by clinicians or screening and diagnosis outcomes, but it has frequently been operationalized as a neuropathy outcome in clinical trials and cohort studies [44, 64–68]. The trials, however, are studies of neuropathy therapies as opposed to the large-scale cardiovascular outcome trials that the MNSI has been used as a neuropathy outcome measure.

9 Modified Toronto Clinical Neuropathy Score (mTCNS)

With the intention of creating a scale that is more sensitive for earlier stages of neuropathy, the TCNS has been adapted to the modified TCNS (mTCNS). The modified scale omits the deep tendon reflex assessment, which was a somewhat less reproducible part of the TCNS [60], and that additionally represented later (motor) dysfunction on the spectrum of diabetic DSP severity. The mTCNS also adds greater quantitative levels to both symptoms and sensory signs to create a larger measurement range across the earlier DSP stages, and a more granular scale. The symptoms of the TCNS are graded according to patient-reported outcome principles as absent (0), present but not interfering with activities or sense of well-being (1), present and interfering with sense of well-being but not with activities (2), and present and interfering with activities (3). The signs of the TCNS are graded as absent (0), present at the toes (1), present up to the ankles (2), and present proximal to the ankles (3) in a stocking distribution. The mTCNS score ranges from 0 to 33, as detailed in Table 3, Panel B.

9.1 Scale Face Validity

The mTCNS has modifications that, compared to the TCNS, exclude motor manifestations that con-

fers a measure of earlier stages of diabetic DSP, and expands the scoring of symptoms and sensory signs to include test components that are assigned four-level ordinal scores each (Table 3, Panel B).

9.2 Test Quality, Reliability, and Accuracy

The very good to excellent inter- and intra-rater reproducibility of the mTCNS was formally evaluated and reported along with a new evaluation of the original TCNS in a multicenter study [60]. Furthermore, as hypothesized, scores shared lower correlation with the TCNS as they measure different stages of diabetic DSP (Pearson coefficient 0.56), but validity for identification of Stage 2 neuropathy remains similar [60]. However, a specific threshold has not been independently assessed for the concurrent validity of diabetic DSP, and also ranges of severity have not been assigned as for the TCNS.

9.3 Effect on Treatment Decisions, Impact on Patient Outcomes, Economic Analysis

Similar to the MNSI and the TCNS, the mTCNS has not been studied for effect on the treatment decisions made by clinicians or screening and diagnosis outcomes, but it has frequently been operationalized as a neuropathy outcome in clinical trials and cohort studies that by design focus on earlier stages of diabetic DSP [69, 70]. Furthermore, it is being implemented in contemporary studies of populations at risk of earlier stages of neuropathy (<https://clinicaltrials.gov/ct2/show/NCT04664426>).

10 Neuropathy Impairment Score of Lower Limbs (NIS-LL)

The NIS-LL is an extensive composite score of neurological signs and objective tests in the lower limbs, excluding symptoms, that was designed

primarily for implementation in clinical trials [71]. This physical examination score was developed by investigators at the Mayo Clinic as a simplification of an even more extensive score, termed the NIS-LL+7 that incorporated the results of seven objective tests including vibration perception testing, heart rate variability with deep breathing as a measure of autonomic dysfunction, and five nerve conduction study parameters. This extensive version is considered to have 100% sensitivity for Stage 1a diabetic DSP [72]. The NIS-LL clinical scale version (excluding the seven additional objective tests) incorporates extensive motor, sensory, and reflex physical examination maneuvers with granular scoring systems. For example, grading of muscle power involves eight discrete levels ranging from 0 to 4, including quarter points. The overall scale is graded from a perfectly normal score of 0 to a maximum of 88 points [71].

10.1 Scale Face Validity

The NIS-LL assigns 64 of the 88 points to muscle strength attributes that are frequently absent when first clinically identified by clinicians, and is therefore at face value a measure of later stage (generally Stage 1b). The potential score for sensory testing is 16/88 points with a maximal loss of sensory modalities of touch pressure, pinprick, vibration (using the 165Hz tuning fork), and joint position. The reflexes at knees and ankles are considered as present, reduced or absent, and defined according to age limits adding potential confusion to non-expert examiners. Both in terms of the later stage diabetic DSP identification and the expertise required for examination, the NIS-LL is not seen as a tool that can be translated to clinical diagnosis, but rather as a specialized tool for interval cohort studies and clinical trials. Given its wide spectrum of motor scores, at face value it might represent a sensitive measure for neuropathic change in clinical trials examining the effect of interventions on more advanced neuropathy stages.

10.2 Test Quality, Reliability, and Accuracy

The NIS-LL has not been evaluated specifically for reproducibility or concurrent validity for a diagnosis of diabetic DSP. However, it was evaluated in a comparative study of neuropathy associated with impaired glucose tolerance subjects and in this setting—as with the other scales evaluated—its overall diagnostic accuracy was excellent [73].

10.3 Effect on Treatment Decisions, Impact on Patient Outcomes, Economic Analysis

Similar to the previous composite scores, the NIS-LL has not been studied for effect on the treatment decisions made by clinicians or screening and diagnosis outcomes as it primarily represents a research tool. However, it has been extensively applied as a neuropathy outcome in clinical trials and cohort studies that by design focus on later stages of diabetic DSP [74–77].

11 Utah Early Neuropathy Scale

This physical examination scale was developed specifically to serve the need for measurement scales that could detect early stages of sensory-predominant polyneuropathies such as DSP at Stage 1b [78]. The scale includes limited scores for motor function (great toe extension and ankle reflexes), and greater proportional contribution to sensation for pin and vibration as well as allodynia. The scale varies from 0 to 42 with 24/42 points for pin sensation, 8/42 for vibration, and 2/42 for allodynia. To demonstrate an example of a score for earlier sensory manifestations and how it is operationalized, we include the scoring for the Utah Early Neuropathy Scale in Fig. 3.

Utah Early Neuropathy Scale

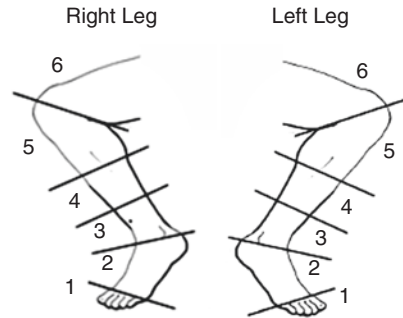
Motor Examination	Right	Left
0 normal		
2 weak		
Great Toe Extension	<input type="text"/>	<input type="text"/>
Total Both Sides (out of 4):	<input type="text"/>	

Pin Sensation:	Right	Left
0 normal		
1 for each segment with reduced sensation	<input type="text"/>	<input type="text"/>
2 for each segment with absent sensation	<input type="text"/>	<input type="text"/>
Total out of both sides: (out of 24):	<input type="text"/>	

Allodynia/Hyperesthesia	Right	Left
0 normal		
1 if present in toes or foot	<input type="text"/>	<input type="text"/>
Total for both sides (out of 2):	<input type="text"/>	

Large Fieber Sensation	Right	Left
0 normal		
1 diminished		
2 absent		
Great toe vibration	<input type="text"/>	<input type="text"/>
Time	s	s
Great toe joint position	<input type="text"/>	<input type="text"/>
Total both sides (out of 8):	<input type="text"/>	

Segments for pin sensation reporting



Deep Tendon Reflex	Right	Left
0 normal		
1 diminished		
2 absent		
Ankle	<input type="text"/>	<input type="text"/>
Total both sides (out of 4):	<input type="text"/>	

Total Score (out of 42)

Fig. 3 Performing the Utah Early Neuropathy Scale (UENS) Examination. The UENS requires a number 2 (13/4 inch) safety pin and a 128 Hz tuning fork. Pin sensation is tested by first reviewing normal sharp sensation to pin on an unaffected portion of the skin. Once this is established, touch the dorsal surface of the foot and leg with the pin, working centripetally from the great toe in 1–2 cm increments while asking the subject to respond when they first feel “any sharpness,” and again more proximally when the pin feels “as sharp as they would expect.” Repeat to firmly establish these levels. On each side, two points are scored for each region in which the patient fails to feel any sharpness. One additional point is scored for each additional region in which the pin feels less sharp than expected. Only distal sensory loss is scored. So, for

instance, a person who reported absent pin sensation to the mid foot dorsum (four points) and reduced sensation to the low ankle (1 point) bilaterally would score a total of ten points for this portion of the UENS. Vibration is tested by first acquainting the subject with vibration (as opposed to pressure) sensation, then holding the maximally vibrated tuning fork to the dorsum of the great toe at the distal interphalangeal joint. Extinction of vibration in less than 10 s is considered “diminished,” while “absent” requires that the patient cannot detect the maximally vibrating tuning fork at the toe. The motor examination is limited to great toe dorsiflexion. Other aspects are as typically performed in neurological examination. Figure courtesy of A. Gordon Smith, co-creator of the Utah Early Neuropathy Scale. The Scale is further detailed in [78]

11.1 Scale Face Validity

The scale does not include symptoms, and therefore in the context of diabetic DSP would be amenable for use as a screening tool to identify Stage 1b disease. Furthermore, the relative weight of sensory signs is high, including small fiber function, such that variation of scores likely represent earlier-stage neuropathy when interventions and therapies are most likely to be of benefit.

11.2 Test Quality, Reliability, and Accuracy

Reproducibility has not been evaluated cross-sectionally within and between examiners, but the 1-year change in score showed very high consistency and has been reported as an indication of excellent reproducibility [78]. Additionally, it correlated with other scoring systems. For Stage 2 polyneuropathy confirmed by nerve conduction studies, in a study sample with a very high proportion of polyneuropathy participants it showed very good overall concurrent validity by area under the receiver operating characteristics curve [78]. This level of accuracy appeared to be similar to other scales [78], and it has been examined in other causes of polyneuropathy [79, 80]. However, it is our view that this scale may show advantage in study samples that reflect general diabetes practice, with lower prevalence of advanced polyneuropathy and higher prevalence of early disease [81].

11.3 Effect on Treatment Decisions, Impact on Patient Outcomes, Economic Analysis

Similar to the previous composite scores, the Utah Early Neuropathy Scale has not been studied for effect on the treatment decisions made by clinicians or screening and diagnosis outcomes as it primarily represents a research tool. However, it has been extensively applied as a neuropathy outcome in cohort studies and clinical trials that by design focus on earlier stages of diabetic DSP [82–84].

12 Neuropathy Symptom Score (NSS)

First described in 1993 in a descriptive study of the prevalence of the hospital-based clinic diabetes population in the United Kingdom [85], the Neuropathy Symptom Score was an interviewer-based questionnaire meant to evaluate the presence and severity of specific polyneuropathy manifestations, with a particular emphasis on painful diabetic DSP. In the interview, patients are asked about their experience of pain or discomfort in the legs. Characteristics are evaluated such that burning, numbness or tingling in the legs provides two points, and fatigue, cramping or aching 1 point. Location provides 2, 1, and 0 points for feet, calves, and elsewhere, respectively. Nocturnal symptoms provide 2 further points, 1 if also daytime, 0 if only daytime. An additional point was assigned if patients are awoken at night from symptoms. Finally, alleviating factors are scored: 2, 1, and 0 if alleviated by walking, standing, or laying down. With a maximum of 9, it is implied that symptoms are present if a minimum score of 3 is achieved. Severity was graded as mild (score of 3–4), moderate (score of 5–6), or severe (score of 7–9).

12.1 Face Validity

The score, at face value, weighs heavily on painful diabetic DSP and its consequences, including night-time symptoms and awakening, and the alleviating symptoms in the context of such awakening. Consequently, its primary role is in the classification of the presence and severity of painful diabetic DSP.

12.2 Test Quality and Reliability

While not tested formally for reproducibility, the NSS has served as a historical benchmark for the development of updated symptom scores that correlate highly with it, and that themselves have excellent reproducibility in small studies [86].

12.3 Diagnostic Accuracy: Concurrent

During the development of the NSS, studies of its intrinsic validity were not conducted. However, it has been evaluated by independent groups primarily in combination with a physical examination scale termed the Neuropathy Disability Scale that is discussed below [87, 88].

13 The Revised Neuropathy Disability Score (NDS)

Developed as a simplification of the NIS-LL and also first described in 1993 along with the Neuropathy Symptom Score in a descriptive study of neuropathy prevalence, the score incorporates small fiber sensory attribute, and large fiber sensory and motor attributes. It involves examination of the ankle reflex, vibration, pinprick and temperature (cold tuning fork) sensation at the great toe. The sensory modalities are scored as either present = 0 or reduced/absent = 1 for each side, and reflexes as normal = 0, present with reinforcement = 1 or absent = 2 per side. With a maximum abnormal score of 10, classification of severity is graded as mild (score of 3–5), moderate (score of 6–8), and severe (score of 9 or 10). Generally, a score of 6 or more has been used to define presence of signs for identification of DSP [89, 90].

13.1 Face Validity

This score includes small fiber sensory attributes that could identify pre-symptomatic or symptomatic early-stage DSP, as well as later large-fiber stages owing to sampling of vibration sensation and reflexes.

13.2 Test Quality and Reliability

There are no published studies examining intra- and inter-rater reproducibility of the revised NDS.

13.3 Diagnostic Accuracy: Concurrent

During the development of the revised NDS, studies of its intrinsic validity were not conducted. However, it has been partially evaluated by independent groups [87, 88]. While there are no cross-sectional studies evaluating the optimal threshold for the identification of diabetic DSP, a score of 6 or more has traditionally been used in studies in which it is the reference standard [89, 90].

13.4 Diagnostic Accuracy: Predictive

While many longitudinal designs have been conducted, we were unable to find in the literature analyses that explored whether a certain test score in those without DSP could predict future onset of diabetic DSP. However, among those followed in a diabetic foot clinic (and likely had presence of diabetic DSP), the revised NDS was generally associated with short-term risk of incident ulceration, though in this study population the best prediction was associated with abnormality in foot pressure sensation measurement [91]. In combination with the NSS, the revised NDS has been used by several research groups for the identification of higher risk patients for diabetic DSP, and as the clinical sign and symptom measures to define presence of diabetic DSP [92, 93].

14 Perspectives on the Comparison of Scales

Each of the scales chosen for review in this chapter has been designed with specific research purposes in mind. At face value they reflect different aspects of diabetic DSP (from early sensory signs in the Utah Early Neuropathy Scale, to those that include advanced foot deformity and ulceration like the Michigan Neuropathy Screening Instrument Examination). As summarized in the above sections and in Table 4, they have different levels of

Table 4 Composite symptom scales, sign scales, and combined scales: general attributes and comparisons

Scale name	Acronym	Considerations for face validity			Considerations for technical performance			Other considerations
		Granularity (range of scores)	Symptom or signs components	Weighted toward earlier (sensory) or later (motor) stages	Reproducibility	Diagnostic Accuracy (concurrent validity) For NCS-based reference standard		
Michigan neuropathy screening instrument	MNSI questionnaire [52]	0–15	Symptoms only	Later	Not formally assessed	Low	Can be used as a self-administered questionnaire for screening in virtual care	
Michigan neuropathy screening instrument	MNSI examination [52]	0–10	Signs	Later	Not formally assessed ^a	Good [51]	Operationalized in cardiovascular disease intervention trials [21, 53–56]	
Toronto clinical neuropathy score	TCNS [59]	0–19	Both	Later	Very good to excellent [60]	Very good for T1D, good for T2D	Its validation has been extensive, including agreement with NCS, disease severity, and sural nerve biopsy nerve fiber density [59, 60] Evaluated in multicenter study [60]	
Modified Toronto clinical neuropathy score	mTCNS [60]	0–33	Both	Earlier	Very good to excellent [60]	Correlated with NCS, not formally assessed	In a study comparing multiple scales in the setting of pre-diabetic neuropathy, this scale had the highest numerical sensitivity and specificity compared to others [73, 94]	
Neuropathy impairment score of lower limbs	NIS-LL [71]	0–88	Signs	Later	Not formally assessed	Very good ^b [75]	This represents the signs component of the NIS-LL+7, a scale that includes seven objective small and large fiber tests [72] Diagnostic accuracy evaluated in pre-diabetic neuropathy [73]	

Utah early neuropathy score	UENS [78]	0–42	Signs	Earlier	Not formally assessed ^e	Very good ^b [75]	The score incorporates multiple levels of sensory deficit in the lower limbs (see Fig. 2)
Neuropathy symptom score	NSS [85]	0–9	Symptoms only	Both (pain)	Not formally assessed on its own	Not formally assessed on its own [87, 88]	Interview-based questionnaire Focused on painful neuropathy and its consequences
Revised neuropathy disability score revised	NDS [85]	0–10	Signs	Earlier	Not formally assessed on its own	Not formally assessed on its own [87, 88]	Associated with short-term risk of ulceration [91]

Note that for all scales different diagnostic thresholds have been proposed depending on specific outcomes and specific settings. For example, for screening a more sensitive threshold is preferred, for diagnosis a more specific threshold is preferred. Many of these scales have been incorporated into reference standard definitions for diabetic DSP that use confirmatory nerve conduction studies. In those settings, generally a score of only 1 or more is required to support the presence of a symptom or a sign [9]

NCS nerve conduction studies, *T1D* type 1 diabetes, *T2D* type 2 diabetes

^aModified versions have been studied [57, 58]

^bStudy sample had very high proportion with diabetic DSP

^cOne-year change was evaluated and reproducibility was high, but generally change over time is a different attribute of ability to detect change in nerve function rather than reproducibility

research published on the hierarchy of investigative test research principles, studies of validity include different study samples, study sizes, prevalence of neuropathy, spectrum of disease, variable reference standard definitions. Even with harmonization of such procedures, systematic review and meta-analysis of diagnostic tests are complex as they require Bayesian techniques like clinical trial network meta-analysis methods [95]. Though we present their attributes and critical appraisal in detail, for these methodological reasons we intentionally do not present a quantitative side-by-side comparison of their diagnostic operating characteristics. One research group has undertaken a direct comparison of many of these scales in the setting of pre-diabetic neuropathy and, while they imply that some are more valid than others (the modified TCNS), uniformly in that study most scales had unexpectedly high levels of concurrent diagnostic accuracy [73]. We challenge clinicians to consider operationalizing these scales in clinical setting to suit specific needs: For example, the self-administered Michigan Neuropathy Screening Instrument questionnaire, the Neuropathy Symptom Scale, or the symptom subscales of other composite scores like the modified Toronto Clinical Neuropathy Score, can be applied for virtual diabetes care as has been required during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, while others could be selected for physical examination screening and evaluation in the clinical setting.

15 Differential Diagnosis: A Diagnosis of Diabetic DSP Requires Consideration of Other Causes of Polyneuropathy

A clinical evaluation consistent with the features of diabetic DSP requires consideration of other etiologies for distal and symmetric polyneuropathies. First, the presence of atypical features listed in Table 2 should be identified, as they may further indicate other causes of peripheral nerve damage other than polyneuropathy, such as focal, multifocal, or nonlength dependent forms of neu-

ropathies. These include focal nerve entrapments and other non-distal and non-symmetric forms (chapters “The Epidemiology of Diabetic Neuropathy” and “Treatment Induced Neuropathy of Diabetes (TIND)”), rare conditions such as hereditary neuropathy with propensity to pressure palsies (HNPP), and polyneuropathies without sensory predominance such as common forms of chronic inflammatory demyelinating polyneuropathy (CIDP) and its variants. Furthermore, consideration should be made for factors associated with potentially similar polyneuropathy to diabetic DSP such as alcohol, hypothyroidism, toxins, and drugs. With this in mind, a simple laboratory panel should be undertaken: comprehensive metabolic panel to determine current metabolic risk factors such as glycemic exposure, presence of hypertriglyceridemia, renal dysfunction; thyroid hormone to indicate hypothyroidism; complete blood cell count may indicate macrocytosis associated with alcohol or nutritional deficiencies and infectious causes; the B12 level itself; erythrocyte sedimentation rate potentially associated with inflammatory causes; and serum protein immune-electrophoresis to suggest malignancy, monoclonal gammopathy, or gammopathy associated with rare syndromes like Polyneuropathy, Organomegaly, Endocrinopathies, Monoclonal protein, and Skin lesions (including hemangioma, hyperpigmentation, hypertrichosis or Raynaud’s phenomenon as part of the “POEMS” Syndrome). Testing for infectious causes of polyneuropathy should be guided by history, as would consideration of familial forms of DSP. It is important for the clinician to recognize that the patient with a consistent chronic, insidious, sensory-predominant distal and symmetric clinical history and physical examination for diabetic DSP typically only requires this focused laboratory work-up, and that the most common causes of DSP other than diabetes are B12 deficiency, alcohol, and hypothyroidism, and diabetic DSP exacerbated by renal failure. Referral to specialist neurology should be strongly considered in the uncommon case of atypical features (Table 2), or if rare causes are suspected (Table 5) that require confirmatory work-up that specialized

Table 5 An non-exhaustive list of diagnoses on the differential of diabetic distal symmetric polyneuropathy^a

Metabolic and nutritional disorders
B12 vitamin deficiency (more common)
Other vitamin deficiencies: pyridoxine, folate, thiamine, vitamin E
Malabsorption: Bariatric and gastric surgeries, inflammatory bowel disease
Renal disease (more common)
Thyroid disease (more common)
Acromegaly
Inflammatory
Chronic inflammatory demyelinating polyneuropathy (CIDP) and its variants (may be more common)
Systemic disorders
Peripheral arterial disease
Monoclonal gammopathy/paraproteinemia (more common)
Amyloidosis
POEMS ^b
Sarcoidosis
Vasculitis ^a
Critical illness polyneuropathy
Infectious ^a
HIV
Hepatitis B
Lyme
Syphilis
Leprosy
Drugs
Neurologic and mood: phenytoin, amitriptyline, lithium
Antimicrobials: nitrofurantoin, metronidazole, chloramphenicol, tuberculosis therapies, chloroquine, hydroxychloroquine
Cardiovascular: amiodarone, flecainide, hydralazine, nitrous oxide
Rheumatic: colchicine, gold, leflunomide, methotrexate
Immunologic: tacrolimus, interferon- α , ipilimumab, nivolumab, pembrolizumab, bortezomib
Antineoplastic: chemotherapeutic agents, paclitaxel and other taxanes, vinca alkaloids, platinum analogues, doxorubicin, etoposide, ifosfamide, misonidazole, antinucleosides
Toxins
Alcoholism (more common, frequently painful neuropathy)
Heavy metal: lead, arsenic, inorganic mercury, zinc, thallium, gold
Herbicides: dichlorophenoxyacetic acid, agent orange
Organophosphate pesticides: parathion, dioxin
Industrial: acrylamide, polychlorinated biphenyl, vinyl chloride
Solvents: hexacarbons (glue sniffing), dry cleaning solvents, carbon disulfide, perchloroethylene, trichloroethylene, triorthocresyl phosphate, ethylene oxide, styrene, toluene, methyl n-butyl ketone, mixed solvents, and others
Hereditary
Hereditary neuropathy with propensity to pressure palsies (HNPP) ^a
Multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy
Other hereditary motor, sensory and autonomic neuropathies

^aSome causes listed here are unlikely to present symmetrically. Differential diagnosis lists in the literature frequently include causes of non-distal and non-symmetrical neuropathies, such as focal entrapment syndromes and other etiologies discussed in chapters “The Epidemiology of Diabetic Neuropathy” and “Diagnostic Techniques for Diabetic Peripheral Neuropathy”. We have made an attempt to minimize these conditions on this list, but those indicated with an asterisk are potential exceptions

^bPolyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin abnormalities

testing might clarify (chapter “Diagnostic Techniques for Diabetic Peripheral Neuropathy”).

16 Concluding Overview

The clinical diagnosis of diabetic DSP, initiated either by a screening test or a symptomatic complaint, requires careful consideration of the historical features, symptoms, and signs, where each finding revises for the clinician an estimate of disease probability. Composite scores, reviewed in detail in the chapter, help to remind the clinician of key supportive symptoms and signs for diagnosis and are commonly used in cohort studies and clinical trials. Even if the clinical evaluation is consistent with typical features of diabetic DSP, simple laboratory tests are likely to identify the presence of other causes. It is essential that the clinician identify atypical features (listed in Table 2) or the suspicion of other causes (listed in Table 5) to seek confirmatory tests and expert opinion through neurology specialist referral.

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