DIABETIC NEUROPATHY: DIAGNOSTIC METHODS

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ABSTRACT

Screening and diagnostic testing for neuropathy in patients with type 1 or type 2 diabetes is needed in order to prevent complications from diabetic neuropathy. As diabetic neuropathy frequently leads to foot ulcers and amputation—major causes of morbidity and disability in people with diabetes—the American Diabetes Association recommends an annual foot exam for people with diabetes in order to identify those with high-risk foot conditions. Yet, detection and diagnosis of diabetic neuropathy can be complex. The diagnosis of neuropathy is based on both clinical and objective measures. Medical and neurological history, physical and neurological examination (evaluating sensory, motor, reflex, and autonomic function), and measurement of peripheral nerve function by clinical testing have been used and then combined into a series of clinical assessment scores that screen for and quantify the severity of diabetic neuropathy. No fewer than 12 clinical assessment scoring systems are available. This article presents the tools and methods commonly used to screen and diagnose neuropathy in patients with diabetes and discusses issues surrounding their use.

(*Adv Stud Med.* 2004;4(8A):S650-S661)

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Diabetic peripheral neuropathy (DPN) is one of the common complications of diabetes.[1] The prevalence of DPN has been estimated as 28% in 2 large UK clinic-based studies and 66% in a population-based study in Rochester, Minn.[2-4] The significant morbidity and mortality associated with DPN has provided impetus for the development of better means to screen, diagnose, and assess the condition. It is also a driving force behind clinical trials for drugs that will prevent DPN or halt its progression when it is already established.

By definition, DPN is somatic and/or autonomic neuropathy that is attributed solely to diabetes mellitus.[5] It is a heterogeneous disorder that includes mono- and polyneuropathies, plexopathies, and radiculopathies.[6] Neuropathies are classified as symmetrical or asymmetrical (focal or multifocal). The symmetrical form is primarily sensory and autonomic. The asymmetrical form can be sensory, motor, or both, as well as affecting the individual cranial or peripheral nerves.[7]

The distal symmetrical form of DPN is known by multiple names including diabetic sensorimotor peripheral neuropathy or distal symmetric diabetic peripheral neuropathy.[8,9]

DPN is often described as a stocking-glove neuropathy, affecting the longest nerves first before progressing proximally.[10] It usually presents with sensory symptoms in the toes or feet, but in some patients whose neuropathy is mainly loss of feeling, it may present with symptoms in the hands.[11] DPN may or may not be accompanied by autonomic neuropathy.[5] Significant motor symptoms usually occur late.

Detection of DPN is complicated because the disorder affects a variety of nerve fibers. For diagnosis, it is necessary to assess multiple features of neuropathy.[10] The 1988 consensus statement from the San Antonio Conference on Diabetic Neuropathy recommended, "In

general, it is advantageous to systematically assess neuropathic signs and symptoms, including sensory, motor, and reflex measures of upper and lower extremities, cranial nerves, and autonomic function."[12] To fully classify DPN, a patient needs assessment of the following: clinical symptoms, clinical signs, electrodiagnostic studies, quantitative sensory testing, and autonomic function testing.[12] Nerve biopsy is rarely needed.[12] In DPN, the role of skin biopsy for evaluation of intraepidermal nerve fibers is still under study.[5]

Risks for development and progression of DPN include poor glycemic control, undiagnosed type 2 diabetes, smoking, high alcohol intake, low socioeconomic status, and renal failure.[13] Severity of DPN correlates with markers of microvascular disease and mean glycosylated hemoglobin.[14] The only intervention currently available to stem the insidious and often irreversible progression of DPN is tight glycemic control; thus, screening and early diagnosis are of paramount importance.

Current Screening for DPN

Screening for DPN is typically performed during a patient's routine examinations. Recommendations for screening and management are included in the international Guidelines for Diagnosis and Outpatient Management of Diabetic Peripheral Neuropathy and are summarized in Table 1.[15] The Clinical Practice Guidelines of the Canadian Diabetes Association recommend annual screening for neuropathy using the 10-g Semmes-Weinstein monofilament or 128-Hz tuning fork. Screening should begin at diagnosis in people with type 2 diabetes and after 5 years' duration of disease in individuals with type 1 diabetes who are past puberty.[16]

According to the American Diabetes Association's recommendations, people with diabetes should have an annual foot exam to identify high-risk conditions.[17] Assessment includes evaluation of protective mechanisms and foot structure and biomechanics in addition to vascular status and skin integrity. Evaluation of a low-risk foot should include a quantitative somatosensory threshold test using the Semmes-Weinstein 10-g monofilament. Additionally, individuals with one or more high-risk foot conditions should be evaluated more regularly. Individuals with neuropathy should have their feet inspected visually at every visit with a healthcare professional.

Tests for Neuropathy

Several different methods are commonly used to screen and assess DPN. These include reflex testing, superficial pain testing, light touch perception, vibration testing, sympathetic skin response, quantitative sensory testing, and nerve conduction studies.

Reflex Testing

While it is traditional in neurology to test all reflexes, in assessment of DPN it is most common to test only the ankle reflexes as these are the most sensitive to early DPN. Ankle reflex testing is performed at both ankles. While the patient is sitting or kneeling, the examiner dorsiflexes the foot and gently strikes the Achilles tendon with the reflex hammer. If no reflex occurs, the test can be repeated with reinforcement. Reflexes are typically scored as 0 (absent), 1 (present but decreased), 2 (normal), 3 (increased), or 4 (increased with clonus).[18] In a cross-sectional study conducted at 10 centers in the United States, Canada, and Switzerland, ankle reflex testing had reasonable reproducibility with moderate agreement ($\kappa = 0.59$) between examiners.[18] Ankle reflex has better reproducibility if evaluated as normal or abnormal. However, the test is a poor predictor of ulceration.[19]

Table 1. Guidelines for Diagnosis and Outpatient Management of Diabetic Peripheral Neuropathy

Annual Review Assessment	
Patient history	Age, diabetes, physical factors, lifestyle, social circumstances, symptoms, other possible etiological factors
Examination of both feet	Skin status, sweating, infections, ulceration, calluses/blistering, deformity, muscle wasting, arches, palpitation for temperature, pulses, joint mobility, examination of gait/shoes
Vascular examination	Check foot pulses
Other	Thyroid function to exclude other etiologies for neuropathy Note the presence or absence of characteristics of the "at-risk foot"

Reprinted with permission from Boulton. Guidelines for diagnosis and outpatient management of diabetic peripheral neuropathy. European Association for the Study of Diabetes, Neurodiab. *Diabetes Metab.* 1998;24(suppl 3):55-65.[15]

Superficial Pain Testing

Pain sensation can be tested with a sterile safety pin. The site of testing varies with the specific algorithm but may include the dorsum of the great toe or the plantar aspect of the distal first, third, and fifth toe of each foot. Most commonly, the stimulus is applied once per site, and patients are asked to identify the sensation as to whether they feel it at all, and whether it is sharp or dull. Results are scored accordingly. As a means of screening for neuropathy, pinprick is highly subjective and thus, poorly reproducible.[18,20]

Light Touch Perception

Light touch perception can be evaluated by using a number of methods from a finger, to cotton, to specifically calibrated devices. The best known of the calibrated devices is the Semmes-Weinstein 10-g monofilament, a nylon filament embedded in a plastic handle. Gentle pressure is applied at the handle to bow the nylon filament. The instrument is calibrated to provide a specific force measured in grams that is 10 times the log of the force in milligrams exerted at the tip of the filament (eg, the 5.07 monofilament exerts 10 g of force).[10]

Monofilaments have been manufactured in sizes ranging from 1.65 to 6.65. Studies testing various sizes of monofilaments support the utility of the 10-g monofilament—the initial study in patients with diabetes or Hansen's disease found no patient with a neuropathic ulcer could sense the 10-g monofilament.[21] Two observational studies and 5 prospective studies support use of the 10-g monofilament as the best correlate to the presence or history of an ulcer, but there are 2 other observational studies that suggest that the 4.21 (1 g) is a better discriminator.[19,22-29]

To date, there is no consensus about the proper testing sites for the Semmes-Weinstein monofilament.[10] Recommendations range from sites distributed over the plantar surfaces of the toes to metatarsal heads, insole, heel, and dorsum of the foot. However, data show that the site(s) chosen may affect reproducibility. One study found that examination of the forefoot had moderate reproducibility (κ = 0.38-0.54), but examination of the arches, heel, and dorsum had only fair reproducibility (κ = 0.22-0.38).[18] Many physicians test the dorsum of the distal toe first, recording yes or no, then test more proximally if there is an abnormality.

Criteria that define an insensate foot according to testing with the Semmes-Weinstein monofilament are controversial, but all 5 of the prospective studies validating the use of the 10-g monofilament used results from more than one test site.[19,24-26,29]

Vibration Testing

Vibration testing is another measure used to evaluate nerve function. Traditionally, vibration perception has been measured with a 128-Hz tuning fork, or less commonly a 64- or 256-Hz tuning fork. There are several methods for testing vibration. Many rely on "examiner experience," which has a variable correlation with quantitative tests. An analysis of 3 large cohorts (n = 787) found that use of the tuning fork overestimated vibration sensation loss compared with quantitative sensory testing.[30] Discordance between tests was associated with age, height, and body surface area in one cohort, with age and body surface area in a second cohort, and with age in the third cohort. The authors of this analysis recommended that physicians take these factors into account when judging clinical abnormalities. Although vibration testing can be a highly subjective measure of severity of neuropathy and may be poorly reproducible, the absence of vibration sensation at the great toe is significantly associated with development of foot ulcers.[18,19]

Vibration perception threshold can also be measured semiquantitatively using a graduated tuning fork. The results from the graduated tuning fork calibrate well to other measures of vibration.[31,32] In a prospective study comparing individuals with Waldenstrom's macroglobulinemia to controls, quantitative vibration measurements correlated well to sural sensory nerve action potentials. Testing with the graduated tuning fork was rapid and showed high inter- and intrarater reliability, as well as utility in monitoring changes in sensory function over time.[33] In a prospective study of 2022 patients with diabetes, the graduated tuning fork was compared with an electronic neurothesiometer.[34] The plots of the vibration perception thresholds were comparable, indicating that the tuning fork had a high sensitivity and positive predictive value for the diagnosis of abnormal bedside tests and symptomatic neuropathy.[34]

Sympathetic Skin Response

The sympathetic skin response is a reflex that occurs in response to a change in the electrical potential of the skin.[35] It is transient in nature, and can be caused by a variety of stimuli. Measurement requires special equipment that is not typically available in most physicians' offices.

QUANTITATIVE SENSORY TESTING

Quantitative sensory testing is an extension of the sensory portion of the neurological evaluation. It is the determination of the absolute sensory threshold,[5] which is useful in assessing the integrity of the axons that form the peripheral nervous system and their distal receptors. Quantitative sensory testing aids in diagnoses by allowing differentiation of the relative deficit between small (eg, temperature) and large (eg, vibration) diameter axons and between peripheral neuropathy and mononeuropathy. It is well accepted because it is simple, noninvasive, and nonaversive.

Quantitative sensory testing systems have been developed to measure the threshold of various stimuli that pertain to distinct neuroanatomic pathways. There are typically 2 types of devices: those that generate specified vibratory or thermal stimuli, and those that deliver electrical impulses at certain frequencies.[36]

To test sensory thresholds, algorithms for testing have been developed. Generally these can be described as the method of limits and the method of levels.[36] Using the method of limits, the patient indicates when he or she first feels an increasingly strong stimulus or when he or she no longer feels a decreasing stimulus. With the method of levels, specific levels are tested, and the patient reports whether or not the stimulus is detected. The method of levels is also referred to as the "forced choice" algorithm. For various tests, normal and abnormal instrument-specific values have been determined.

Preliminary studies from the 1970s suggested that testing for thermal thresholds might detect preclinical DPN.[36] Abnormalities of thermal sensory thresholds have been reported in 70% patients with long-term type 1 diabetes, and in more than 27% of patients who were newly diagnosed.[37,38]

In testing thermal and vibration sensation abnormalities using the noncomputerized Marstock device (Somedic AB, Stockholm, Sweden), thermal sensation was abnormal in all 22 patients with neuropathy, foot ulcers, or Charcot joints, in 10 of 15 patients with neuropathic pain, and 9 of 10 patients with autonomic neuropathy. In comparison with thermal sensitivity, vibration sensation was affected less often.[39]

Another instrument that quantifies vibration perception is the Bio-Thesiometer (Bio-Medical Instrument Company, Newbury, Ohio). Shaped like a probe, this instrument vibrates at 100 Hz with an amplitude varying from 0 to 50 volts. Studies show that a drop of more than 25 volts in the vibratory threshold is a strong predictor of future ulceration.[24,40-42]

Vibration perception threshold can also be measured via Horwell Neurothesiometer (Scientific Laboratory Supplies, Nottingham, UK) and Vibratron II (Physitemp Instruments, Clifton, NJ). In a comparative head-to-head trial, Bril and coworkers found repeated neurothesiometer measurements were less variable than repeated measurements of the Vibratron (8% vs 6% for the right and left toes for the neurothesiometer, compared with 31% vs 34% for the right and left toes for the Vibratron).[43]

Bril and coworkers evaluated 337 subjects with diabetes mellitus comparing sympathetic skin responses, nerve conductions, CASE IV (WR Medical Electronics Co, Stillwater, Minn.) measuring cooling detection threshold with the 4-2-1- stepping algorithm, and the neurothesiometer detecting vibration perception threshold using the method of limits algorithm.[35] These researchers found that sympathetic skin response correlated better with vibration perception threshold and sural nerve amplitude than with the cooling detection threshold or clinical symptoms. They also found no correlation between the sympathetic skin response and the symptoms of pain or autonomic dysfunction.

It is important to note that the devices commercially available to measure thermal thresholds assess different physical properties and probably different subpopulations of small nerve fibers. Thus, although quantitative methods exist to measure both large and small nerve fiber sensory function, measures of the vibratory threshold by different devices is more consistent, providing greater reliability in measuring the function of large sensory nerve fibers.[44]

Based on the status of existing evidence in 2003, the Subcommittee on Therapeutics and Technology Assessment of the American Academy of Neurology stated that quantitative sensory testing is an effective tool in documenting sensory abnormalities in patients with DPN and in documenting changes in a longitudinal evaluation, but that there is no credible prospective evidence that these abnormalities ultimately develop into clinical neuropathy. Thus, the utility of quantitative sensory testing as a screening tool is unproven.[36]

NERVE CONDUCTION STUDIES

Nerve conduction studies are frequently used to assess the presence and severity of peripheral nerve involvement in patients with diabetes. They are sensi-

tive, specific, reproducible, and easily standardized. Studies typically are performed on upper and lower limbs on motor and sensory nerves. Most clinicians reserve the use of nerve conduction studies including electromyography to those with symptomatic, confusing, unusual, or severe neuropathy.

Although nerve conduction studies can be performed with surface or needle electrodes, surface techniques are more widely used, technically easier to perform, more comfortable, and produce results that are easier to measure.[5] Results of nerve conduction studies show amplitudes, distal latency of compound muscle action and sensory potentials, conduction velocity of fastest conducting fibers, and minimal F-wave latencies. Nerve conduction studies are also well suited to longitudinal or population evaluations.

Nerve conduction studies do not always correlate well with symptoms and signs.[5] There are several reasons for this. First, some electrodiagnostic abnormalities reflect metabolic changes that are not associated with symptoms; second, some symptoms and signs are not clearly associated with electrodiagnostic changes.

The most sensitive electrophysiologic indicator of active axonal degradation may be evidence from needle electromyography showing changes in fibrillation potentials and positive sharp waves. The evidence from examination of the proximal and distal muscles in the upper and lower limbs, with bilateral studies (if needed) provide information for localizing and grading the severity of axonal lesions. The amplitude and area of compound muscle action potentials and sural nerve action potentials is indicative of the number of active nerve fibers as indicated from the summated fiber action potentials. Sural nerve action potentials are particularly useful in identifying the more distal nerve involvement, given that lesions proximal to the dorsal root ganglia have no effect on the distal sensory nerve. Abnormalities of compound muscle action potentials and sural nerve action potentials are characteristic of clinical sensory and motor deficits. Conduction velocity abnormalities may reflect specific metabolic abnormalities or segmental demyelination and remyelination, but they are a poor indicator of axonal degeneration.

From these measures of upper and lower limb motor and sensory nerve function, it is possible to determine the presence, distribution, and severity of peripheral nerve disease.[45] Nerve conduction study findings also correlate to clinical endpoints: nerve action potential amplitudes reflect nerve fiber loss.[46] However, they are limited because they do not provide information about small fiber function.[47]

Studies suggest nerve conduction abnormalities are present at diagnosis in 29% to 70% of patients with type 1 diabetes and 45% to 60% of patients with type 2 diabetes.[48-50] These numbers are higher than comparable numbers using either symptoms or signs to detect neuropathy, demonstrating that nerve conduction testing is extremely sensitive in detecting neuropathy in those with diabetes. Nerve conduction studies show how diabetic sensorimotor peripheral neuropathy progresses. First, sensory and motor amplitudes of distal nerves are lost; then, changes occur in the more proximal nerves and in the upper limbs.[51]

Although nerve conduction studies can be used to determine the extent and severity of DPN, recent data suggest measures of sural nerve action potential are useful in identifying patients with early DPN. A study by Bril and coworkers compared sural nerve action potential, vibratory detection threshold, and other nerve conduction parameters, peroneal, tibial motor, and ulnar sensory nerve conduction velocity, amplitude, and onset latency in 205 patients with diabetes.[52] They found that sural nerve conduction correlated well to early, mild DPN, potentially allowing patients to be identified and treated at an earlier stage of the disease.

Whether individual attributes of nerve conduction scores or composite scores are more useful in diagnosis has not yet been determined. In an analysis based on the data from the Rochester, Minn. cohort study, Dyck and colleagues found that composite scores tended to be more reproducible than individual attributes and generally correlated better to neurologic impairment.[53] They predicted that with the availability of microprocessors and normative databases, composite scores would become more widespread.

Testing of the Autonomic System

Testing of the autonomic nervous system is complex. In individuals with diabetes, autonomic failure occurs in 2 ways: as autonomic neuropathy with a structural lesion of the peripheral autonomic neuron, and functional failure where no known structural lesion occurs.[54] Because the autonomic nervous system innervates all tissues and organs, the autonomic failure can affect any or multiple systems or tissues in the body. Major areas typically affected include cardiovas-

cular, eye, gastrointestinal, genitourinary, sudomotor, and endocrine. Consequently, testing must be organ- and system-specific.

A number of tests are sufficiently standardized to allow longitudinal assessment of patients with diabetes.[55] Testing for cardiovascular abnormalities

Table 2. Tests for Neuropathy

Test	Advantages/Disadvantages	Ease of Use	Level of Skill Required	Cost
SWMF	Rapid; differentiates nondiabetic controls, diabetic patients with, without neuropathy	Easy to use	Requires minimal training; medical or nonmedical staff can perform	Inexpensive
SPS	Rapid; less effective than NCS in distinguishing neuropathy in patients with diabetes	Easy to use	Requires minimal training; medical or nonmedical staff can perform	Inexpensive
VO/O	Rapid; not universally standardized; many false positives and false negatives	Easy to interpret	Requires minimal training; medical or nonmedical staff can perform	Inexpensive
Vibration by Times Method	Takes longer than SWMF, SPS, or VO/O	More complicated than SWMF, SPS, or VO/O	Requires minimal training; medical or nonmedical staff can perform	Inexpensive
Vibration Perception Threshold Using Biothesiometry	Cumulative incidence of foot ulceration with VPT <15 = 2.9% Cumulative incidence of foot ulceration with VPT >25 = 19.8% (OR = 7.99%; CI = 3.65-17.5; *P* < .01)	Takes 5-10 minutes to use	Requires minimal training; medical or nonmedical staff can perform	Instrument costs several hundred dollars Less expensive, time consuming, and simpler than measuring plantar pressures
Tip-Therm Temperature Discriminator	98.3% of patients with no monofilament sensation had no sensation with tip-therm; 97.3% of patients with biothesiometry-diagnosed neuropathy had no sensation with tip-therm	Simple	Requires minimal training; medical or nonmedical staff can perform	Inexpensive
Quantitative Sensory Testing	Different modalities have measurement errors of >30%. Even when variance is reduced using standardized methods, does not attain the precision of motor or sensory conduction velocity measures of NCS	Varied approaches	Requires extensive training	Expensive equipment
Electrophysiologic Studies/ NCS	Highly sensitive; poor sensitivity for ulceration, amputation, and overall neuropathic impairment; may or may not correlate with symptoms; limited availability; procedure discomfort; insensitive in identifying small fiber neuropathy (sensory or autonomic)	Complicated	Requires extensive training	Expensive equipment

SWMF = Semmes-Weinstein 10-g monofilament; DPN = diabetic polyneuropathy; SPS = superficial pain sensation; NCS = nerve conduction studies; VO/O = vibration by on/off; VPT = vibration perception threshold; OR = odds ratio; CI = confidence interval.
Data from Mayfield et al[10]; Pham et al[24]; Young et al[40]; Perkins et al[44,46]; Olaleye et al[54]; Viswanathan et al[55]; Jamal et al[56]; Dyck.[57]

involves a series of measurements: the resting heart rate, the beat-to-beat heart rate variation, the Valsalva maneuver, the difference in blood pressure between lying and standing, and the QTc interval. Testing of the eye involves dark-adapted pupil size after total parasympathetic blockade. Testing of the sudomotor system involves use of the quantitative sudomotor axon reflex test to evaluate postganglionic function.

Testing of motor disturbances of the gastrointestinal tract is more symptom-specific. For example, the evaluation for gastroparesis will usually first assess the level of glycemic control and medication history.[56] Gastroduodenoscopy can be performed to exclude pyloric or other mechanical obstruction. When

Table 3. Sensitivity and Specificity for Positive and Negative Likelihood Ratios for 4 Simple Screening Tests

Test	Abnormal Test Likelihood Ratio >1 of 8 Attempts Insensate	Specificity	Normal Test Likelihood Ratio <1 of 8 Attempts Insensate	Sensitivity
Vibration (VO/O)	26.6	99	0.51	53
Monofilament	10.2	96	0.34	77
Superficial Pain	9.2	97	0.50	59
Vibration (Timed)	18.5	98	0.33	80

Sensitivity is derived from the threshold of normality; specificity is derived from the threshold of abnormality.
VO/O = vibration by on-off.
Reprinted with permission from Perkins et al. Simple screening tests for peripheral neuropathy in the diabetes clinic. *Diabetes Care*. 2001;24(2):250-256.[46]

Table 4. Selected Studies Comparing Different Screening Entities

Study	Setting	Methods Compared	Investigator Conclusions
Pham et al[24]	Diabetic foot centers	1. Neuropathy symptoms score 2. Neuropathy disability score 3. VPT 4. Peak planter foot pressures 5. Vascular status	1. Clinical examination, 5.07 SWMF: most sensitive tests for identifying foot ulcer at-risk patients; best used together 2. VPT: useful alternative 3. Foot pressure measurements: higher specificity
Perkins et al[46]	Diabetes clinic	1. SWMF 2. SPS 3. VO/O 4. Vibration testing (timed)	1. Tests comparable in sensitivity, specificity 2. SWMF, SPS, VO/O: rapid (around 60 sec) 3. Vibration (timed): more complicated interpretation 4. Accuracy not enhanced by 2-test combination
Olaleye et al[54]	Diabetes clinic	1. SWMF 2. SPS 3. VO/O	1. Positive correlation with NCS 2. Stronger correlation with increasing disease severity 3. SWMF, VO/O: significantly differentiate nondiabetic controls, diabetic patients with or without neuropathy
Viswanathan et al[55]	Hospital; follow-up diabetic patients	1. Tip-therm 2. SWMF 3. Biothesiometry	1. 98.3% of patients with no monofilament sensation had no sensation with tip-therm 2. 97.3% of patients with biothesiometry-diagnosed neuropathy had no sensation with tip-therm
Rahman et al[77]	Population based; diabetes (n = 544) no diabetes (n = 544)	1. Vibration threshold (light touch) 2. Vibration threshold (thermal sense) 3. Modified Michigan Neuropathy Screening Instrument Questionnaires	1. Biothesiometer is most valid measure 2. Monofilament appropriate for identifying patients at risk for neuropathy, foot ulcers

VPT = vibration perception threshold; SWMF = Semmes-Weinstein 10-g monofilament; SPS = superficial pain sensation; VO/O = vibration by on-off; NCS = nerve conduction studies.

glycemic control has been optimized, isotope scintigraphy may be indicated to measure solid-phase gastric emptying times.

MORPHOLOGICAL TESTING

Measures such as sural nerve biopsies provide an opportunity to study the biochemical and morphometric parameters of myelinated and unmyelinated fiber populations, vasculature, perineurium, and their basement membranes, but this information seldom benefits the patient and may be associated with complications.[5] Thus, such studies should only be performed to address well-defined clinical or research questions.

There are several protocols to address morphological assessment of myelinated nerve fiber abnormalities using the light microscope. Analysis includes examination of the myelinated nerve fiber size and distributions, myelinated nerve fiber density, index of circularity, and a measure of focal fiber loss.[57]

COMPARING TESTS FOR DPN

Tests commonly used for DPN have advantages and disadvantages; they differ in ease of use, required skill levels, and costs (Table 2). They also differ according to their sensitivity and specificity (Table 3). Limited information is available comparing the relative benefits of different screening entities (Table 4).

Table 5. Neuropathy Composite Scores

Test	Composite Measures	References
Neuropathy Symptom Score	Sensory, motor, and autonomic symptoms	Dyck[58]; Dyck et al[78,79]
Neuropathy Symptom Profile	Sensory, motor, and autonomic symptoms	Dyck[79]
Neuropathy Disability Score	Sensory and motor signs; reflexes	Dyck[58]; Dyck et al[53,78-80]
NIS-LL	Sensory and motor signs and reflexes in the lower limbs	Dyck et al[60]
NIS-LL + 4	Sensory and motor signs and reflexes in the lower limbs + motor NCS	
NIS-LL + 5	Sensory and motor signs and reflexes in the lower limbs + motor NCS + QST (vibration)	
NIS-LL + 7	Sensory and motor signs and reflexes in the lower limbs + motor and sensory NCS + QST (vibration) + AFT	
Neuropathy Symptom Change Score	Changes in symptoms over time	Dyck[58]
Clinical Neuropathy Examination	Sensory signs, reflexes	Valk et al[61,62]; van de Poll-Franse et al[63]
Michigan Diabetic Neuropathy Score	Sensory and motor signs; reflexes; sensory and motor NCS	Feldman et al[69]
Total Neuropathy Score	Sensory, motor, and autonomic symptoms; sensory and motor signs; reflexes; QST (vibration); sensory and motor NCS	Cornblath et al[70]
Michigan Neuropathy Screening Instrument	Sensory and motor symptoms; peripheral vascular examination	EDIC Research Group[71]
Diabetic Neuropathy Examination Score	Sensory symptoms	Meijer et al[73,81]
Toronto Clinical Scoring System	Sensory symptoms and signs; reflexes	Bril et al[74]
Total Symptom Score	Sensory symptoms	Ziegler et al[75]
Neuropathy Total Symptom Score-6	Sensory symptoms	Bastyr et al[76]

AFT = autonomic function test; NIS = Neuropathy Impairment Score; NIS-LL = Neuropathy Impairment Score-Lower Limbs; NCS = nerve conduction studies; QST = quantitative sensory testing; EDIC = Epidemiology of Diabetes Interventions and Complications.

Composite Scores of Neuropathy

To screen for and quantify the severity of neuropathy, various clinical composite scores have been developed, and some have been validated (Table 5). Each composite system has advantages and disadvantages, proponents and opponents; depending on the use, a particular system may be preferred. For example, in clinical trials high levels of reproducibility and precision may be needed, while in field studies cost and ease of performance may be more important.

The Mayo Clinic group was one of the first to develop composite measures. Each, however, was specific to a component of the neurologic exam. The Neuropathy Symptom Profile and Neuropathy Symptom Score measured subject sensory symptoms, and the Neuropathy Disability Score (NDS) quantitated the neurologic exam.[58] Later, the Neuropathy Impairment Score (NIS) replaced the NDS by eliminating some tests from the NDS that were not expected to be abnormal in DPN.[59]

Because DPN is primarily a distal peripheral axonopathy, the subset of scores for the lower limbs has been used as a more specific assessment: the NIS-Lower Limb (NIS-LL).[60] Subsequently, recognizing that additional measures of nerve function may enhance the value of the directed exam, Dyck and coworkers created a series of additional composite measures: NIS-(LL) + 4 = NIS-(LL)+Peroneal Conduction Velocity, Amplitude, and Onset Latency and Tibial Onset Latency; NIS-(LL) + 5 = NIS-(LL) + 4 + Vibration Detection Threshold; NIS-(LL) + 7 = NIS-(LL) + 5 + Sural Amplitude + Heart Rate During Deep Breathing.

The Clinical Neuropathy Examination (CNE) scores reflexes and sensory testing in the lower limb and includes a distal to proximal gradient for light touch.[61-63] The CNE correlates well with electrophysiology results. It has good inter- and intrarater variability and has acceptable specificity and sensitivity using vibration perception threshold as the basis for diagnosing DPN. In some reports the scale has been modified from the original published version.[64-68]

The Michigan Diabetic Neuropathy Score (MDNS)[69] and the Total Neuropathy Score (TNS)[70] combined results of the neurological examination with electrophysiologic studies and, in the case of the TNS, quantitative sensory testing results into a single score. Later, the Michigan Neuropathy Screening Instrument was developed to serve as an initial simple screening tool to be followed by the MDNS for definitive diagnosis of DPN.[71] The Diabetic Neuropathy Examination score has been validated as a diagnostic tool.[72,73]

The Toronto Clinical Scoring System (TCSS) provides a single score based on reflex and sensory test scores, but also includes an assessment of symptoms.[74] The TCSS has been validated against electrophysiologic and morphologic severity of DPN, although the symptom and reflex subscores did not correlate with either electrophysiology or morphology.

The Neuropathy Total Symptom Score-6 questionnaire was developed from the 4-symptom (pain, burning, numbness, and prickling) Total Symptom Score[75] and measures the frequency and intensity of 6 symptoms of diabetic peripheral neuropathy: numbness, prickling, aching pain, burning pain, lancinating pain, or allodynia. Validation studies have been performed.[76]

In choosing one of these composite measures, it is important to note that there is a lack of data demonstrating specificity in differentiating treatment effects.[44]

Conclusion

Several distinct subtypes of neuropathy exist, but DPN is the most common complication associated with both type 1 and type 2 diabetes. A finding of DPN is of great significance for many patients with diabetes because it can lead to substantial discomfort and pain, and in more advanced cases, nonhealing foot ulcerations, amputations, and loss of ambulation. The current concept of DPN is that nerve damage begins early in the course of diabetes, worsening gradually over time without clinical symptoms until the condition is fairly advanced. Because DPN is associated with significant morbidity and mortality, and the only intervention proven to alter its pathogenesis is glycemic control, it is important for clinicians to diagnose DPN early in order to limit its progression.

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