Diabetic neuropathy affects sensory, motor, and autonomic neurons of the peripheral nervous system. Sensorimotor neuropathy (distal symmetrical polyneuropathy), the most common type of diabetic neuropathy, is what most clinicians recognize as DPN. This type of neuropathy can be acute and is triggered by an episode of glycemic instability, but it is more commonly a chronic condition. Not all patients with DPN experience symptoms, but when symptoms present, they can lead to substantial economic loss. Cardiovascular autonomic neuropathy is a key cause of morbidity and mortality present in an estimated 20% of diabetes mellitus patients.
are present, they are typically described as burning, tingling (“pins and needles”), sharp, shooting and/or aching in a stocking and glove distribution. These symptoms usually begin distally at the toes and ascend proximally as the disease progresses.4,9,11-15

In addition to sensorimotor neuropathy, there has been increasing awareness of the prevalence of autonomic neuropathies such as cardiovascular autonomic neuropathy (CAN), as well as gastrointestinal (GI) and genitourinary (GU) autonomic neuropathies. More specifically, CAN is a key cause of morbidity and mortality present in an estimated 20% of diabetes mellitus patients.9

While the pathogenesis of DPN is multifactorial, it is well established that the primary risk factor is hyperglycemia. Researchers have suggested several theories concerning the hyperglycemic-induced abnormalities in metabolism and blood flow that contribute to the progression of DPN. The major theories include: metabolic flux through the polyol pathway, advanced glycation end-products contributing to segmental demyelination and axonal atrophy, activation of protein kinase C, and oxidative stress.9,11-18 All of these abnormalities contribute to nerve dysfunction and microvascular issues such as basement membrane thickening and endothelial cell hyperplasia.5,19

Past studies support that both vascular and metabolic factors are involved in all stages of the pathogenesis of DPN, but why some patients develop severe, debilitating pain while others experience no symptoms remains unresolved.11,20-21 One recent study using spectral analysis of heart rate variability (HRV) detected greater autonomic dysfunction in painful DPN patients compared to pain-free patients. The results of this study suggest that small, poorly myelinated and unmyelinated nerve fibers that mediate pain sensation and autonomic function may be vulnerable to the pathological processes that occur with diabetic neuropathy, and this may explain why some DPN patients experience pain.20

Still, further research is necessary to better understand the role of autonomic dysfunction in painful DPN, and other factors may contribute to differences in the pathophysiology of symptomatic versus asymptomatic DPN.

The loss of protective sensation caused by DPN puts the patient at an increased risk for foot ulcerations and other complications such as infections and amputations, and causes significant morbidity and mortality. Diagnosing DPN in a timely manner allows for preventive intervention. Currently, there are numerous diagnostic tools available to help in the identification of DPN, such as vibrobratory perception threshold and vibration discrimination stimuli, Semmes-Weinstein monofilament, nerve conduction studies, sudorimetry, and graded temperature stimuli. This review will take a closer look at some of the clinical tools used in the diagnosis of DPN.

**Nerve Conduction Studies (NCS) are the most sensitive and specific diagnostic tool for detecting diabetic peripheral neuropathy.**

Sudorimetry

Autonomic nerve dysfunction is a common and important aspect of DPN that is often overlooked and most likely under-diagnosed.22 One diagnostic tool for early detection of DPN in diabetic patients includes testing sudomotor function, or the function of sweat glands. Sweat glands are innervated by small unmyelinated cholinergic sympathetic fibers that could be affected early in the course of diabetes mellitus, so diagnosing sweat dysfunction could be a quick and useful screening tool for DPN.23,24 When evaluating sweating and cardiovascular function in patients with distal small fiber neuropathy, Stewart et al. found that sympathetic sudomotor fibers were more frequently affected than autonomic nerves controlling heart rate, making sudorimetry a useful diagnostic tool for peripheral neuropathy compared to tools that assess cardiovascular function such as HRV.25

The literature describes a variety of methods to test sudomotor function. The quantitative sudomotor axon reflex test (QSART) detects distal small fiber polyneuropathy with a sensitivity of around 80%.26 QSART involves infusing acetylcholine into the skin to stimulate postganglionic nerves, and then sweat production is measured. Some limitations of QSART include that it could be time-consuming and it requires expensive equipment.27

Thermoregulatory sweat tests evaluate the pattern of sweating by increasing the skin temperature and then using an indicator dye. While these tests are not quantitative, they can be used to either screen the whole body, or just focal areas of sweat loss.27 The silastic imprint method stimulates sweat via acetylcholine, and then silastic material is placed over the skin. Sweat beads indent the silastic material and can be quantified.28 This test is easy to conduct, but the silastic material is prone to dry out.28

**Cold temperature sensation is mediated by small myelinated A-delta fibers.**
to artifacts such as dirt and hair.27

Another device that evaluates sweat gland function is based on an electrochemical reaction between electrodes and chloride of the sweat glands after stimulation by low-level voltage. Quantitative results are expressed as Electrochemical Sweat Conductance (ESC) for the hands and feet. One study tested 265 diabetic patients for clinical signs and symptoms of DPN and found lower ESC at the feet to be significantly associated with increasing VPT and CAN. The authors concluded that lower ESE was suggestive of sudomotor dysfunction and this may be a simple clinical test to alert physicians to early DPN.28

Sudomotor denervation is a significant presentation of diabetic neuropathy, and thus the use of sudomimetry during screening of diabetes patients may allow for a more comprehensive assessment of potential neuropathy. Because sudomotor dysfunction may result in dryness of the foot and skin and has been associated with foot ulceration, detecting sweat gland dysfunction early can enable the clinician to provide appropriate care to prevent ulceration due to anhidrosis.29,30

Graded Temperature Stimuli
Another method of detecting small fiber dysfunction in DPN is temperature discrimination. Temperature can be one of the first sensations that is affected in diabetes patients.31 Lack of temperature sensation may predispose patients to burns and other thermal injuries, and so techniques to clinically diagnose temperature sensation dysfunction are of clinical relevance. Because warm temperature sensation is mediated by small unmyelinated C fibers and cold temperature sensation is mediated by small myelinated A-delta fibers, both warm and cold stimuli should be utilized when testing for temperature sensation.32

Most techniques for temperature discrimination utilize the Peltier principle, which involves a thermo-electric device creating a temperature change by passing current through two different types of metal. Devices can either be heated or cooled depending on the direction of the electric current.33,34 While the use of such thermal techniques has largely been for research purposes, the availability of these quantitative tools may enable clinicians to integrate temperature stimuli into routine assessments.35

One hand-held device screens for DPN by testing the combination of temperature stimuli and vibration discrimination stimuli. This combination allows for the testing of small fiber disease via the patient’s ability to discriminate a two-degree Celsius temperature change from a range of between 15 degrees to 40 degrees Celsius as well as large fiber disease by testing five amplitudes of the standard 128 Hz vibration frequency.

Vibratory Perception Threshold (VPT) and Vibration Discrimination Stimuli
VPT is the most widely used quantitative sensory diagnostic method, and is defined as the lowest voltage at which vibration can be detected up to 50% of the time.31,36 Experts describe VPT as a quick, accurate risk and low risk for long-term neuropathic complications vary by the type of instrument that is used.28 Common devices for measuring VPT include a graduated 128-Hz tuning fork and semi-quantitative electromechanical instruments such as the biothesiometer and neurothesiometer.

A standard, non-graduated 128-Hz tuning fork, while still widely used by many clinicians, has limited ability as it can only determine the presence or absence of vibration perception and is therefore psychophysical in nature. The standard, non-graduated 128-Hz tuning fork also lacks quantification of clinical findings and standardization of user technique. The graduated 128-Hz tuning fork uses vibration extinction threshold on a scale of 0 to 8, and still has the advantages of portability and ease of operation that the standard tuning fork has.36 A cut-off score of less than 4 out of 8 would indicate that a patient is at high risk for long-term neuropathic complications with the graduated tuning fork.37

A novel 128-Hz electronic tuning fork (ETF) was recently developed to perform accurate timed vibration tests and help overcome limitations of traditional tuning fork exams. The ETF reproduces the same vibration output and decay rate as the traditional tuning fork and contains an integrated timer that facilitates performance of accurate and reproduc-

The quantitative sudomotor axon reflex test (QSART) involves Infusing acetylcholine into the skin to stimulate post-ganglionic nerves.

Patients are categorized as high risk if the vibratory perception threshold (VPT) in at least one foot is > 25V.
The test is simple and inexpensive as it provides sensory testing for light touch perception using a 5.07 monofilament that produces a characteristic 10 g perpendicular force to specific contact points on the dorsal and plantar aspects of the foot.\textsuperscript{13,14}

In general, patients are instructed to lie supine with their eyes closed during testing, and if a patient is unable to sense the SWM on any part of the foot, the patient should be provided with preventative care.\textsuperscript{17,44}

There is, however, a lack of standardization and conflicting recommendations when it comes to proper testing methodologies.\textsuperscript{12,14,41}

Methodology from past studies testing the sensitivity and specificity of SWM have described using anywhere from one to ten testing sites.\textsuperscript{46} A systematic review by Dros, et al., evaluating SWM as a diagnostic test for DPN, found wide ranges in both sensitivity and specificity in past studies likely due to differences in monofilament site placement, the number and combination of sites tested, and the interpretation of the test.\textsuperscript{47}

Because the SWM test is widely used, especially for diabetes patients, methodology should be standardized to make SWM an adequate clinical assessment for sensory loss. Ten common testing sites may include: the first, third and fifth metatarsal heads and toes, the medial and lateral plantar midfoot, the heel, and the space between the first and second toes on the dorsal surface of the foot.\textsuperscript{46,48}

One study conducted SWM tests on the ten sites described above, and evaluated the impact of each site and combinations of the sites. Based on the results of the study, sensitivity and specificity of the test at the ten sites were 93.1\% and 100\%, respectively. Sensitivity and specificity at two sites, the plantar aspects of the third and fifth meta-

Warm temperature sensation is mediated by small unmyelinated C fibers.

Vibratory Perception Threshold (VPT) is defined as The lowest voltage at which vibration can be detected up to 50\% of the time.
Patients with small fiber neuropathies may still have normal nerve conduction velocities.

direct correlation has been shown to exist between inadequate screening and under-utilization of preventative interventions that may decrease the rates of ulceration and amputation by up to 60% and 85%, respectively.46

No single standard for determining clinical neuropathic dysfunction currently exists, but early detection of DPN is critical for identifying at-risk patients and immediately implementing a preventative management plan.52 Currently, the recommendation is to combine multiple diagnos-

A cut-off score of less than 4 out of 8 using a graduated tuning fork would indicate that a patient is at high risk for long-term neuropathic complications.

Summary

Peripheral neuropathy occurs commonly in the population with diabetes and its management continues to rely on early recognition. A
53 Rith-Najarian, SJ, T. Stolusky, DM Gohdes. Identifying diabetic patients at high risk for lower-extremity amputation in a primary health care setting: a prospective evaluation of simple screen-
1) Which of the following is a true statement regarding diabetic peripheral neuropathy (DPN)?
   A) Only symptomatic patients have DPN.
   B) Symptoms usually begin proximally and descend distally towards the toes as the disease progresses.
   C) Cardiovascular autonomic neuropathy is a key cause of morbidity and mortality present in an estimated 20% of diabetes mellitus patients.
   D) The incidence of DPN decreases in patients with long duration of diabetes.

2) What are nerve conduction studies (NCS)?
   A) Electrodiagnostic tests that evaluate the ability of both motor and sensory nerves to conduct electrical impulses
   B) Electrodiagnostic tests that evaluate the ability of only motor nerves to conduct electrical impulses
   C) Electrodiagnostic tests that evaluate the ability of only sensory nerves to conduct electrical impulses
   D) None of the above

3) Which of the following is described as the most sensitive and specific diagnostic tool for detecting diabetic peripheral neuropathy?
   A) Visual Analog Scale (VAS)
   B) Vibratory Perception Threshold (VPT)
   C) Electromyography (EMG)
   D) Nerve Conduction Studies (NCS)

4) Which of the following statements regarding the Semmes-Weinstein Monofilament (SWM) are true?
   A) The 5.07, 10g SWM is one of the most widely used screening instruments for DPN.
   B) The 5.07 monofilament produces a characteristic 10 g perpendicular force to specific contact points on the dorsal and plantar aspects of the foot.
   C) There is a lack of standardization and conflicting recommendations when it comes to proper testing sites.
   D) All of the above

5) Cold temperature sensation is mediated by:
   A) Small myelinated A-delta fibers
   B) Large myelinated A-alpha fibers
   C) Small myelinated B fibers
   D) Small unmyelinated C fibers

6) Which of the following diagnostic tools is the least effective in detecting small fiber dysfunction in diabetic peripheral neuropathy?
   A) Temperature discrimination
   B) Quantitative sudomotor axon reflex test (QSART)
   C) Nerve Conduction Studies (NCS)
   D) The silastic imprint method

7) The quantitative sudomotor axon reflex test (QSART) involves ____.  
   A) Evaluating patterns of sweating by increasing skin temperature
   B) Stimulating sweat glands with a low-level voltage
   C) Quantifying sweat beads
   D) Infusing acetylcholine into the skin to stimulate post-ganglionic nerves

8) The primary risk factor for DPN is ____.
   A) Hypertension
   B) Hyperglycemia
   C) Hypercholesteremia
   D) Obesity

9) Which of the following sudomimetic screening tools evaluates the pattern of sweating by increasing skin temperature and using an indicator dye?
   A) quantitative sudomotor axon reflex test (QSART)
   B) Silastic imprint method
   C) Thermoregulatory sweat test
   D) Electrochemical sweat conductance

10) The current recommendation for neuropathic screening is to ____.
    A) Utilize VPT and graded temperature stimuli to ensure an early diagnosis
    B) Combine multiple diagnostic tools to ensure that screening is comprehensive
    C) Always use NCS in addition to SWM since there is a lack of standardization
    D) Never use graded temperature stimuli because they should only be used for research purposes

11) Which of the following are specific NCS techniques?
    A) Motor nerve conduction studies
    B) Sensory nerve conduction studies
    C) F waves
    D) All of the above

12) Patients are categorized as high risk if the vibratory perception threshold (VPT) in at least one foot is ____.
    A) > 15V
    B) > 25V
    C) > 50V
    D) > 75V

13) Which of the following are common devices used to measure vibratory perception threshold (VPT)?
    A) Graduated 128-Hz tuning fork
    B) Biothesiometer
    C) Neurothesiometer
    D) All of the above

14) Vibratory Perception Threshold (VPT) is defined as ____.
    A) The lowest voltage at which vibration can be detected up to

Continued on page 110
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50% of the time
B) The lowest voltage at which vibration can be detected all of the time
C) The highest voltage at which vibration can be detected all of the time
D) This highest voltage at which vibration can be detected up to 50% of the time

15) Warm temperature sensation is mediated by
A) Small myelinated A-delta fibers
B) Large myelinated A-alpha fibers
C) Small myelinated B fibers
D) Small unmyelinated C fibers

16) Which of the following type of test typically utilizes the Peltier Principle?
A) Temperature discrimination
B) Vibration discrimination
C) Light touch perception
D) Nerve conduction tests

17) Sudorimetry specifically tests which of the following?
A) Sweat gland function
B) Autonomic nervous system
C) Somatic nervous system
D) Macrovascular function

18) Which NCS technique is useful in testing proximal segments of nerves?
A) Motor nerve conduction studies
B) Sensory nerve conduction studies
C) Autonomic nerve conduction studies
D) F waves

19) Which of the following is a true statement regarding nerve conduction studies (NCS)?
A) Most NCS use surface electrodes that only measure slow conducting fibers.
B) Patients with small fiber neuropathies may still have normal nerve conduction velocities.
C) When a motor nerve conduction test is performed, the impulse only goes proximally to the anterior horn cell.
D) F waves represent early motor responses.

20) What is the cut-off score when using a graduated tuning fork that would indicate that a patient is at high risk for long-term neuropathic complications?
A) Greater than 4 out of 8
B) 0 out of 8
C) less than 2 out of 8
D) less than 4 out of 8

SEE ANSWER SHEET ON PAGE 111.
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