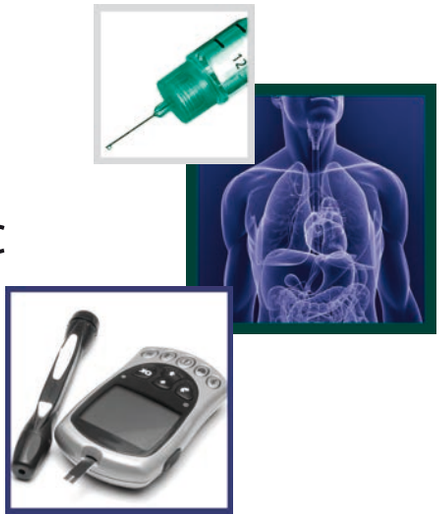
REVIEW

Technologies for detecting loss of multiple sensory modalities in diabetic foot neuropathy



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Practice Points

- Several qualitative or semiquantitative technologies exist for detecting diabetic foot neuropathy; the important ones being the Semmes–Weinstein monofilaments, the two-point touch device, biothesiometers, systems for assessing skin temperature sensitivities and nerve conduction test devices.
- These technologies and devices all suffer important drawbacks, mostly related to lack of objective assessments, interobserver differences, time-consuming examinations, testing the neuropathy at just a few specific spots (possibly missing the neuropathy at other, untested sites), and mixing patient perceptions (e.g., of temperature and pressure/touch).
- There appears to be much room for technological improvements in the field of diabetic neuropathy assessments, particularly since mapping the neuropathy status over the entire plantar surfaces of the feet would be very helpful in preventing diabetic foot ulcers.

SUMMARY Diabetic neuropathy is a peripheral nerve disorder caused by chronic, typically nonmanaged diabetes. A serious complication of diabetic neuropathy is diabetic foot ulcers, which may lead to foot or limb amputations. This paper reviews some existing technologies for diagnosing diabetic foot neuropathy that are currently being used in the clinical setting, based on principles of detecting thresholds of sensation of vibration or temperature stimuli at the plantar surface of the feet. Technological pros and cons of each method are discussed and clinical implications are addressed.

Diabetic neuropathy is a peripheral nerve disorder caused by chronic, typically nonmanaged diabetes. Neuropathy is considered to be the most common serious complication of diabetes. Pirart and coworkers studied a cohort of 4400 diabetic patients, and found that 5% of the patients already had neuropathy when first diagnosed with diabetes; after 25 years, the number of patients exhibiting neuropathy increased to 50% [1]. Though the Pirart paper is often cited in regard to the prevalence of the condition, it is very likely that the more specific protocols for the diagnosis of diabetic neuropathy that are available now would have revealed an even higher percentage of neuropathic patients [1].

Diabetic neuropathy typically evolves in multiple anatomical locations and induces damage to numerous peripheral nerves. Pathological changes to nerve tissues occur both at the bodies of axons and within myelin sheaths. First, axons are gradually thinned and enveloping myelin sheaths start to disintegrate, thereby slowing conduction velocities in the affected nerves. Subsequently, complete nerve structures are

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atrophied. While these changes occur systematically across the nervous system, they are most profound in the distal regions of the somatic nerves [2]. Sensory loss in the diabetic foot, which is caused by these pathological changes, is most commonly preceded by an exaggerated painful neuropathy. Hence, painful neuropathy can be considered to be an early predictor of sensory loss [2].

The aforementioned diabetic neuropathy condition is commonly referred to as polyneuropathy, which typically affects the arms, hands, fingers, legs and feet. Loss of sensation in the feet is the most common symptom and perhaps also the most dangerous one, given the potential for minor cuts or burns to go unnoticed and become infected, and hence develop into more complicated wounds. The loss of sensation in the feet is manifested in numbness or insensitivity to either mechanical loads or temperature, and over time, it is also being associated with progressive foot deformities such as hammertoes. Specifically, Charcot neuroarthropathy, which is associated with diabetic peripheral neuropathy, leads to collapse of the midfoot. Advanced neuropathy also leads to wasting of the small muscles of the feet, leading to clawing of the toes (which is believed to occur due to unopposed pulling of the long extensor and flexor tendons). Blisters and ulcers may appear on numb areas of the foot because sustained mechanical loading (e.g., surface pressures, shear and internal tissue stresses) and even actual injury is not detected by these patients, who have lost their 'pain alarm'. If such minor foot injuries are not treated promptly, infection may occur and spread subdermally and then into the bone, leading to osteomyelitis. Sustained mechanical loads in deep tissues (i.e., fat, fascia and muscle) may lead to deep tissue necrosis even prior to skin breakdown, which then makes timely diagnoses difficult [3,4]. Together, these processes contribute to the development of progressive ulcers, which may eventually require amputation of the foot, or amputation above the foot.

Unfortunately, diabetic foot ulcers are relatively common, and are estimated to occur in 15% of the diabetic population [5]. The diabetic population is growing rapidly, with the latest numbers of world-wide diabetes prevalence being approximately 366 million patients [101]. The National Institute of Diabetes and Digestive and Kidney Diseases of the US NIH reports that half of the amputations caused by diabetic neuropathy are preventable if minor problems are caught and treated in a timely manner, particularly if patients are aware of their neuropathy condition [102].

Other than the risk for foot ulcers, the continuous numbness and tingling of the hands and feet substantially compromise the quality of life of patients with diabetic neuropathy. Despite the progress made in basic and clinical research in diabetes, presently, once nerve damage occurs, it is irreversible. Symptoms are often minor at first, and because most of the damage to neural tissues occurs over several years, mild cases may not be correctly diagnosed for long periods, but can suddenly deteriorate into severe neuropathy. Hence, it is a consensus that prevention is the key issue in appropriate management of diabetes and in managing diabetic neuropathy in particular. Using strategies that typically combine medications, diet and moderate physical exercise programs, practitioners are attempting to control the glucose levels in diabetic patients to avoid cases of hyperglycemia, which may then lead to organ damage and to neural tissue damage, which causes the neuropathy.

With regard to preventing diabetic foot ulcers, the clinical practice is to protect the feet by prescribing high-quality, well-fitted footwear, including custom-made footwear. In order for this approach to work appropriately, patients at risk first need to be identified. Then, their footwear needs to be carefully designed to the specific condition of the individual, in order to protect the most vulnerable regions on the feet by redistributing mechanical loads onto other, less susceptible foot areas. This is commonly carried out by first measuring static and dynamic plantar pressures and then designing custom-made orthoses or footwear to off-load the sites that are susceptible to injury. However, it is the localization of the neuropathy in the feet, as opposed to the levels of pressure, that is the most important predictor of possible foot ulcerations [6].

Screening for the presence of neuropathy using standard and simple clinical tools, such as the neuropathy disability score, neuropathy symptom score, pressure perception using Semmes–Weinstein monofilaments and vibration sensation with neurothesiometer devices has been shown to be important in identifying individuals at risk for foot ulceration. However, these tools assess mainly large fiber function [7]. It has been suggested that small unmyelinated C-fibers, which are responsible for sensing heat

(i.e., are responsive to skin temperatures from 30 to over 45°C) may be selectively damaged in the early stages of diabetes [7].

It is important for the development of any new technology in this arena to point to the pros and cons of each existing approach for detecting diabetic neuropathy, and in particular, to recognize existing technological limitations. These are the topics covered by this paper. The following search terms were used for searching the (English) literature in preparation for writing this review on technology for detecting diabetic neuropathy: sensory threshold testing, vibration sensation, vibration threshold, thermal threshold, temperature threshold (all in combination with diabetic neuropathy or diabetes and neuropathy).

Existing technologies for detecting neuropathy & their limitations

■ Semmes–Weinstein monofilaments

The most commonly used method for diagnosing peripheral neuropathy today is clearly the Semmes–Weinstein monofilament method. The monofilament method was developed in the late 1800s by von Frey, who used horse hairs with different diameters and lengths to test the skin's pressure sensation. Semmes, Weinstein and colleagues improved this technique in the late 1950s for studying peripheral neuropathy in brain-injured veterans, using a nylon filament embedded in a plastic handle [8], which is still the clinically accepted design today. The Semmes–Weinstein monofilament test essentially assesses the threshold of sensation for light touch or light pressure in a semi-quantitative manner [9]. There is controversy about which receptors and axons carry 'deep pressure' information to the CNS so here we consider 'light touch' and 'light pressure' as similar stimuli. The principle of the Semmes–Weinstein test is based on exploiting the unique physical properties of buckling columns. Buckling columns theoretically yield reproducible quantifiable forces regardless of the force applied to the handle [10]. However, there is a rather large gap between theory and clinical practice in the sense that theoretical values assume that the column (filament) is perfectly perpendicular to the surface (skin), that there are no effects of slip of the tip, such as those due to perspiration or moisture, that the filament material is perfectly elastic and so on. Filaments are calibrated to provide a specified force measured in grams and are identified by a number that is ten-times the log of the force in milligrams that is exerted at the tip of the filament (e.g., the 5.07 monofilament exerts 10 g of force). Monofilaments are commercially available in sizes ranging from 1.65 to 6.65. The pressure delivered to the skin surface during the test can be estimated as the force divided by the cross-sectional area of the filament. However, this approximated pressure again varies in real-world conditions depending on the angle of the filament with the skin, as well as the existence of any tip slip artifacts. Moreover, friction between the filament and skin is not being considered in the measurements, but may vary considerably across individuals and as a function of the environmental conditions during the testing (e.g., the ambient vs skin temperature and humidity), thereby introducing inherent errors into these monofilament measurements. Lastly, the Semmes–Weinstein monofilaments are susceptible to material property changes with repetitive use. The stiffness and bending properties are altered with fatigue of the filament structure, so monofilaments should be changed after a certain period of clinical use, as recommended by the relevant manufacturers.

Many clinicians consider the Semmes–Weinstein monofilament test a good predictor of foot ulcerations, hence its widespread clinical use in addition to being inexpensive and easy to run [11,12]. Importantly, however, most clinicians will also agree that the Semmes–Weinstein monofilament test detects neuropathy rather late, when the disease is well established, and that it is able to estimate only a rough range of skin sensitivities. Also, the Semmes–Weinstein test clearly does not make measurements on a continuous scale. Moreover, sensitivity is only being assessed at specific discrete locations where the monofilaments actually touch the skin, which makes mapping sensitivities over the foot a laborious task. Indeed, there are serious doubts among medical experts regarding the efficacy of the Semmes–Weinstein method. In a large cohort study by Johnson and colleagues, 63% of the patients were identified as showing symptoms of diabetic neuropathy, but only 16% of those could be diagnosed as neuropathic by means of the Semmes–Weinstein method [13]. The authors of the study concluded that "simply using a 10-g monofilament is not sufficient to screen subjects for neuropathy. Without other methods, there is likelihood that a large portion of patients with sensory deficits will be missed" [13].

Additionally, the Semmes–Weinstein examinations are onerous; based on conversations of the author with practitioners, performing a complete Semmes–Weinstein examination for one foot takes at least 6 min, during which the expert (i.e., the podiatrist ot neurologist) is completely occupied with the examination. Indeed, the issue of this examination being a time-consuming one has been raised in the medical literature, and some shortcuts were proposed [14], but these might lower the sensitivity of this examination, which is already being reported as low [13].

■ Two-point touch (two-point discrimination testing)

An alternative technique to detect neuropathy, which is based on a similar concept, is to use a two-point static touch. The two-point technique measures how far apart two distinct touch points need to be before they are perceived by the tested patient as being two separate points of contact (rather than just one). The tip of the test device (which is sometimes called an esthesiometer) is typically composed of two pin-pricks that are held parallel to each other (i.e., the device is fork-shaped). The distance between the two pins can be adjusted by either using different 'forks' or by changing the distance between the pins in the same 'fork' by means of a mechanical dial. A disk-shaped device also exists in the market, in which two rotating plastic disks are joined together to allow the examiner to roll it over the skin, thereby detecting the threshold for discrimination between two moving points. For this purpose, rounded tips along the peripheries of the disks are spaced at standard testing intervals, typically being between 1 and 25 mm apart. Other than in suspected neuropathy, the test is usually conducted for evaluating nerve repairs, grafts and innervated tissue transfers for desensitization or to determine a level of neural impairment. This two-point test has technological drawbacks that are very similar to those of the Semmes–Weinstein test described previously. Namely, the outcomes of the two-point test might be affected by the orientation of the device when holding it against the skin, by the frictional properties between the device and the skin of the individual, and the existence of a perspiration or moisture layer, which affects the forces transferred from the device to the skin. Also, sensation thresholds could and will probably depend on the magnitude of the pressure applied by the examiner over the tested skin regions.

■ Biothesiometers™

A method that is considered to be less subject to inter-observer variability compared with the two aforementioned ones, is the use of a vibration perception threshold meter, called a biothesiometer™ (Bio-Medical Instrument, Newbury, OH, USA) [103]. The technology of biothesiometers probably evolved from the classic tuning fork test (which applies 120–128 Hz vibrations to the surface of the foot). Tuning forks are still being used today to assess vibration sense, as they are a simple, quick and cheap test.

The biothesiometer is an electrically-powered device that allows the examiner to raise the volume of vibration of a vibrating tip that oscillates at a constant frequency (typically 120 Hz) and is placed against the skin of a patient, until the patient feels and reports the vibration. A dial is used to adjust the voltage that controls the amplitude of the vibration, which is proportional to the square of the applied voltage. The vibration perception threshold is the voltage (measured in V) at which the patient was able to identify the stimulation. If vibratory sensations are perceived at a level that exceeds 25 V the patient has approximately sevenfold greater risk for foot ulceration [15], which made the biothesiometer technology clinically accepted, with many clinicians believing that the test results can predict foot ulcerations [16,17] or even mortality [18]. It is also generally accepted, however, that this is a psycho–physical test that requires patient concentration and compliance. Variant versions of the biothesiometer are the Vibrameter® (Somedic AB, Sweden) [104], the Vibratron II™ (Physitemp Instruments, Clifton, NJ, USA) [105] and the Maxivibrometer™ [19]. These devices can measure the level of vibration in micrometers (the Vibrameter, for instance, employs an accelerometer for this purpose), which is a more direct physical measure of the delivered stimulus with respect to voltage. The major limitation of all these vibration stimulation-based devices, however, is that they produce a mechanical vibration wave, which progresses and spreads through superficial and deep tissues around and away from the point of contact between the vibrating tip and skin, as opposed to a local stimulus, which also stays localized. By spreading across a relatively large volume of tissue, the vibratory waves make it rather difficult to identify the specific locations of the most severe neuropathy, where the foot skin should be protected or off-loaded.

■ Devices for assessing the temperature sensitivity of the skin

A rather simple but elegant device that measures the sensitivity of plantar skin to temperature and is available commercially is the 'tip therm®' (AXON GmbH, Dusseldorf, Germany [106]), which is a pen-shaped device made of a combination of a polymer part and a metal alloy part. The polymer side typically feels warmer and the metal alloy side cooler, owing to the different thermal conductivity properties of these materials. The examiner places the two sides of the tip therm on the patient's foot surface at irregular intervals and asks whether it feels cold or not so cold at the particular spot. Being a completely passive thermal element (which could be considered an advantage as no source of power is required), the tip therm does not provide quantitative sensitivity readings, and therefore it does not allow systematic comparisons with normative sensitivity threshold databases. An additional limitation resulting from the passive principle of operation is that the efficacy of the tip therm should depend on the ambient conditions. The manufacturer recommends that the tip therm be used in rooms kept under 23°C, which means that in certain climates, it is necessary to use this technology only in air-conditioned facilities. Another drawback is that the device is pressed against the patients' skin during the examination, and therefore, the local perception of temperatures might be masked by the perception of contact pressures in the individual.

More sophisticated, but also substantially more costly systems are, for example, the Computer-Aided Sensory Evaluator–IV (CASE IV; WR Medical Electronics, Stillwater, MN, USA [107]) and the TSA-II NeuroSensory Analyzer (Medoc Advanced Medical Systems, Ramat Yishay, Israel [108]). Such systems are designed mostly for neurology departments in hospitals, and accordingly, they provide a wide spectrum of possible sensory stimulation types, including vibrations, cooling and warming, and they also typically allow control of the wave shape of each stimulus. The thermal stimulators of the CASE IV and TSA-II systems are both equipped with one thermoelectric unit that is placed, in this instance, against the foot. The range of temperature stimulations is up to 50°C. For example, in the CASE IV system, temperatures that can be attained are 9°C delivered for 10s for testing cold perception or 45°C delivered for 10 s for warm perception. The thermal sensitivity threshold in these and similar systems (e.g., the Marstock thermostimulator; Somedic AB, Sweden [104]) or the PATH-tester MPI 100 [20], is defined as the minimal temperature change from the baseline skin temperature that the tested individual can correctly detect.

Despite the fact that the thermal stimulation elements are active in these systems, the issues of mixture between temperature and pressure perceptions (the stimulators are again pressed onto the patients' skin), and the localization of the examination to just one spot on the skin, are major limitations. The CASE IV and TSA-II devices have been specifically criticized for being expensive, for requiring substantial experience to operate and for being cumbersome [15]. Most importantly, however, these devices can only detect insensitivity where the stimulators are attached, and so information on other insensitive spots (which were not tested) could be missed (if the examiner did not test them). It has been stated that estimation of thermal thresholds using the Marstock thermostimulator device may take 15 min at each examination site, and therefore measurements at more than two sites become too laborious and time-consuming [21]. Essentially (and similarly to the critique mentioned above concerning vibrating devices), these tests are also psycho–physical in nature, which requires patient concentration and compliance, making these tests less objective. Finally, again, using these devices it is difficult to fully map the state of neuropathy in the feet of individuals in a resolution that is sufficient for preparing an effective intervention plan (e.g., design custom-made orthoses to off-load certain sites in the plantar feet).

■ Nerve conduction studies

Nerve conduction studies assess nerve function, which, in the context of diabetic neuropathy, refers to electrical conduction in sensory nerves. The test is essentially carried out by electrically stimulating a peripheral nerve using a stimulating electrode and then recording the signal from a purely-sensory portion of that nerve using a second, recording electrode. An important physiological parameter that is determined during the test is the sensory nerve conduction velocity, which is calculated from the latency and the distance between the two electrodes Some clinicians consider these tests more objective with respect to the other technologies reviewed herein [22], since nerve conduction studies assess the physiological function of nerve tissues and hence may better correlate with clinical end points [23]. The

diagnostic sensitivity of nerve conduction tests can be improved by the incorporation of several parameters into the test, such as anthropometric factors or F-wave testing (the recording of action potentials from muscles activated by the stimulated nerves) [24,25]. However, nerve conduction tests also involve some important limitations. First, these tests can only assess the function of large nerve fibers, which is not always relevant to loss of sensation in the diabetic foot. In other words, diabetic neuropathy, importantly, is also caused by damage to small nerve fibers and nerve ends, which cannot be detected by current nerve conduction test devices. Second, the devices are costly and therefore have limited availability for routine clinical testing. Third, the results of the test may be impacted by external factors, such as the temperature of the limbs. Fourth, nerve conduction in neuropathy patients is typically recorded around the ankle or calf, not at the sole of the foot, which is the susceptible location for ulcerations. Lastly, these tests may induce some patient discomfort.

Conclusion & future perspective

Available technologies for detecting neuropathy use either pressure or temperature stimuli in attempt to identify the condition. To improve over existing technologies, there is a need to develop sensory stimulators that avoid inducing a mixture of pressure and temperature perceptions, as these two factors could potentially mask each other. There is also a need to avoid inter-observer variations. The Semmes–Weinstein monofilament, which is the most popular technique for detecting neuropathy today, the two-point touch, the biothesiometer and similar devices, and the existing devices for assessing sensitivity to skin temperatures are all handheld (excluding some hospital systems where stimulators are nonphysiologically attached to the skin with straps). Accordingly, the mechanical or thermal stimuli, their angle of application and the exact pattern by which they are delivered and are spread in superficial and deep tissues appear to be potentially highly variable across different examiners.

It should be emphasized that biothesiometers or similar vibrating instruments, as well as temperature stimulators, all suffer from the same fundamental limitation: the tip of the device that delivers the stimuli to the foot's skin surface is applied with light touch/pressure to the skin. Therefore, these methods are practically testing 'multiple' sensory modalities concurrently (e.g., temperature and pressure), so it is indistinguishable as to which specific sensory modality is lost, given that the patient or examiner cannot isolate them. This may not be critical in severe/advanced diabetic foot diseases where serious structural damage to the peripheral nervous system has already occurred (causing multiple sensory impairments). However, in early stages of neuropathy, crucial information that could be helpful in identifying the status of the neuropathy and its trend of progression (i.e., loss of function of certain nerve types) is likely to be lost.

Moreover, all existing devices appear to provide localized readings of the level of neuropathy, just at the (manually) tested sites. In order to produce detailed mapping of the severity of the neuropathy over the entire sole of the foot in individuals, lengthy examinations are required, in which the stimulators should be placed over and over again to cover all of the clinically important spots. Hence, there is much room for technological innovations in this important field, since successful mapping of the neuropathy over the plantar foot area is a key factor for prevention of diabetic foot ulcers.

Financial & competing interests disclosure

The author is conducting active research work on the subject matter and hence previously had relevant awarded research grants and currently has pending grant applications as well as patent applications that concern prevention of diabetic foot ulcers and detection of diabetic neuropathy. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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