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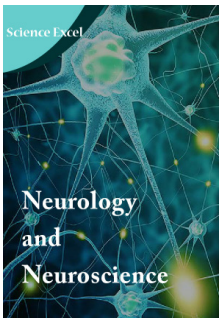
Review Article



Early Detection of Peripheral Neuropathy by Assessment of Sudomotor Function

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Abstract

Chronic hyperglycemia in both type 1 and type 2 diabetes commonly lead to diabetic peripheral neuropathy (DPN) which commonly affects small nerve fibers, including autonomic sudomotor nerves, of the lower limbs. DPN results from nerve damage leading to gradual onset of foot pain, tingling, numbness, muscle weakness, extreme sensitivity to touch, and heat intolerance. Peripheral neuropathy is associated with increased all-cause mortality and morbidities such as foot ulcers, poor wound healing, local and systemic infection, limb amputation, and painful neuropathic symptoms. DPN is also typically diagnosed during later stages when disease progression has already led to irreversible nerve damage and associated severe symptoms. As such, early detection of peripheral neuropathy is important in implementing early interventions and can help preserve nerve function and prevent serious complications of DPN.

Non-invasive methods of testing for early DPN rely on assessment of sudomotor nerve function. One method includes quantitative sudomotor axon reflex test (QSART) which measures postganglionic sympathetic function via iontophoresis which allows quantification of sweat production, and by extension, autonomic function. In general, QSART provides a non-invasive, reproducible, and precise evaluation of autonomic function in both controls and diabetics. It can be used to evaluate a large number of autonomic diseases, and the quantitative data it generates provides a measure of the extent and location of the peripheral neuropathy in each individual. Another assessment method includes the sympathetic skin response (SSR) test which measures the change in electrical potential of the skin which itself comes from activated eccrine sweat glands. The SSR test has a well-established protocol, and the results are easily-measured, and the results are quantifiable. It can be used reliably in the diagnosis of numerous autonomic disorders including DPN where a diminished or absent response correlate with sudomotor nerve damage.

SudoCheck by VitalScan is an FDA-cleared, non-invasive autonomic sdomotor assessment tool that combines QSART, SSR, BIA, and EIS to provide rapid results with a specificity of 95% and a sensitivity of 80%. It was created to enable a precise evaluation of sweat gland function, and by extension, the presence and progression of diabetic peripheral neuropathy including early sub-clinical disease.

Introduction

Diabetes is a chronic condition that affects the body's ability to utilize glucose for conversion to energy. The two most prevalent forms of diabetes are type one and type two. In type one diabetes (T1D), an individual's pancreatic β cells are targeted and destroyed by the host's immune system. The result is an absence of insulin secretion by the pancreas, impaired glucose uptake in insulin-sensitive tissues, and a resulting hyperglycemia [1]. Type two diabetes (T2D) also results in impaired glucose uptake in tissues, however, its progression is explained through genetic, as well as metabolic, and environmental risk factors [1,2]. While factors like ethnicity, age, and family history of diabetes are non-modifiable, obesity and lifestyle can be modified, and they represent the strongest risk factors for the development and progression of T2D [1]. Together type one and type two diabetes affect approximately 10% of the US population (37 million individuals) making diabetes the sixth most common chronic disease and cause of death in the united states [3, 4]. Of the total number of diabetics in the united states, approximately 90-95% of cases are type 2 [5]. The large prevalence of cases results in a total cost of approximately $327 billion, or nearly 10% of total healthcare spending in the US each year [3].

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Diabetic Peripheral Neuropathy

Chronic hyperglycemia in both T1D and T2D commonly lead to microvascular diseases of the eyes, kidneys, and peripheral nerves [6]. Diabetic peripheral neuropathy (DPN) commonly affects small nerve fibers of the lower limbs first and can result in nerve damage leading to gradual onset of foot pain, tingling, numbness, muscle weakness, extreme sensitivity to touch, and heat intolerance among other symptoms [7]. Initially, these symptoms can be mild and vague with patients reporting a wooden or numb sensation in one or both feet. Progression of DPN most-often leads to a characteristic burning sensation with a "stocking and glove" distribution which becomes progressively more painful throughout the day [8]. A number of patients with DPN report such tender skin around the lower limbs that they are unable to sleep with sheets covering their feet, while others report no pain at all [8]. In addition to sensory nerve fiber disruption, DPN also affects the autonomic nervous system. Accordingly, patients may also develop symptoms associated with autonomic function such as dry eyes and mouth, constipation, incontinence, and orthostatic hypotension due to loss of vascular autonomic tone. Additionally, the skin overlying the affected area often appears dry and discolored due to sudomotor dysregulation [8]. This is due to the fact that small autonomic C fibers are the first peripheral nerves affected by DPN and their destruction compromises the skin's ability to release sweat.

An often-overlooked manifestation of diabetic autonomic nerve disfunction is cardiovascular autonomic neuropathy (CAN) which arises due to damage to autonomic fibers innervating the heart [9]. HbA1c, age, obesity, hypertension, and hyperglycemia are all risk factors associated with the development of this complication. Epidemiological reports vary widely about the prevalence of CAN due to differences in study methodologies and end points which reports the frequency of CAN to be between 1 and 90% in those diagnosed with diabetes [9]. Its clinical manifestations can include a fixed, elevated heart rate at rest due to vagus nerve impairment, exercise intolerance, intraoperative cardiovascular instability, orthostatic hypotension, and reduced awareness of myocardial infarction pain which can delay prompt recognition and treatment of this deadly emergency [9].

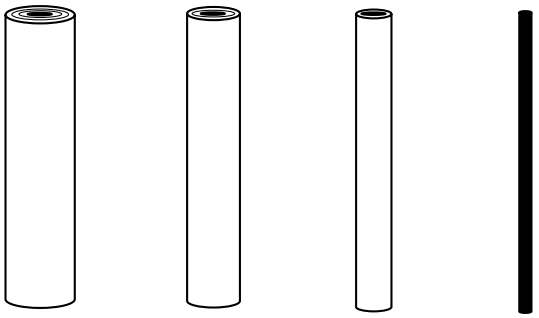
While intense research has been conducted in recent years into the development and progression of DPN, there is no consensus about its pathophysiology. Some studies have shown that increased systemic iron levels are associated with increased risk of developing diabetes [10,11]. This led the authors to conclude that high iron levels might be associated with the progression and severity of diabetes symptoms. Yet, Baum et al. demonstrated the opposite in an animal model; low iron levels were associated with increased inflammation and nerve fiber degeneration. Additionally, they found that obesity and dyslipidemia were associated with increased peripheral nerve inflammation [12]. In their model, chronic hyperglycemia leads to an increase in reactive oxygen species (ROS) in tissues including peripheral nerves. Increased ROS presence upregulates transcription factors like NFκB which ultimately produces a cocktail of pro-inflammatory cytokines: IL-1β, IL-2, IL-8, IL-6, TNF-α, CCL2, and CXCL1 [12]. Chronic inflammation of peripheral nerves leads to their destruction and ultimately the emergence of symptoms associated with DPN.

Under physiologic conditions, Schwann cells (SCs) play a central role in the survival and repair of peripheral neurons. They secrete various neuroprotective factors that provide neural support against reactive oxygen species (ROS), and inflammation in pathological as well as physiologic states [13,14]. Both peripheral neurons (PN) and Schwann cells are sensitive to excessive ROS levels like those seen in T2D. Therefore, T2D could lead to a state of enhanced PN death both directly from ROS, and indirectly from SC death [15].

Somatic innervation

Peripheral neuropathy is a serious complication of diabetes and is associated with increased all-cause mortality and morbidities such as foot ulcers, poor wound healing, local and systemic infection, limb amputation, and painful neuropathic symptoms [16]. DPN is also typically diagnosed during later stages when disease progression has already led to irreversible nerve damage and associated severe symptoms. As such, early detection of peripheral neuropathy is important in implementing early interventions and can help preserve nerve function and prevent serious complications of DPN.

Somatic sensation can be grouped into four main categories: discriminative touch, proprioception, nociception, and temperature sense (Figure 1). Peripheral nerve fibers supplying these sensations are classified by myelination status (group I-IV), with group I fibers possessing the most myelination, and group IV fibers lacking myelin altogether. Group I (Aα) fibers conduct electrical signals the fastest and are involved in muscle proprioception, and group II (Aβ) fibers are less myelinated and communicate mechanoreceptor signals in the skin. Group III (Aδ) fibers conduct more slowly and transmit sharp pain and cold temperatures, whereas group IV (C) fibers transmit the slowest, are non-myelinated and are responsible for transmitting itch, dull pain, and warm temperature information to the primary sensory cortex (S1). Most Aδ and C fibers bifurcate at the spinal cord, and the ascending branch travels uncrossed for a period through the dorsolateral (Lissauer's) tract before finally entering the dorsal horn where they cross as projection neurons in the spinal cord and ascend to S1 via the spinothalamic tract.



Group I (Aα) Group II (Aβ) Group III (Aδ) Group IV (C)

Figure 1. Afferent nerve fiber groups classified by myelination and function. Group I fibers are highly-myelinated and send information to the central nervous system (CNS) regarding muscle proprioception. Group II fibers transmit information from skin mechanoreceptors, and group III fibers conduct cold temperature and nociception information from the periphery to the CNS. Group IV fibers, also known as C fibers are non-myelinated and send afferent signals to the CNS regarding hot temperatures, dull aches, and itching sensation. Post-ganglionic efferent C fibers send signals to sweat glands in the skin via acetylcholine and trigger sweat release.

Lesions of second order (projection) neurons will present with the loss of pain and temperature sense several levels below the lesion on the contralateral side.

Sudomotor function & dysfunction

C fibers are composed of many subgroups of nerve fibers based on the sensory information they carry. Although they contain no myelin, they are surrounded by Schwann cells forming bundled groups that vary in size and distribution [17]. Sudomotor nerves are a type of C fiber that is responsible for sweat production from eccrine sweat glands (Figure 2) [18]. This process is controlled by efferent post-ganglionic autonomic signals which are triggered by afferent signals from thermoreceptors in the skin, and degeneration of these fibers can lead to impaired ability to sweat [18].

In diabetic neuropathy (DN), small C fibers begin to degenerate in the sub-clinical, pre-diabetic stage and precede larger group I and Aβ fiber destruction. This process is mostly asymptomatic, however, some studies have shown nerve repair is possible in the early stage through lifestyle modifications and weight loss [19, 20]. This is only possible, however, if small fiber degeneration is detected early.

Early detection of DN, however, is challenging since clear clinical findings tend to be lacking in the early stages. Autonomic dysfunction, however, can be observed and quantified through sudomotor testing [21]. This is convenient since sudomotor function tends to be the first affected in the early stages of peripheral neuropathy giving clinicians the earliest possible chance at detecting DN in affected patients [21].

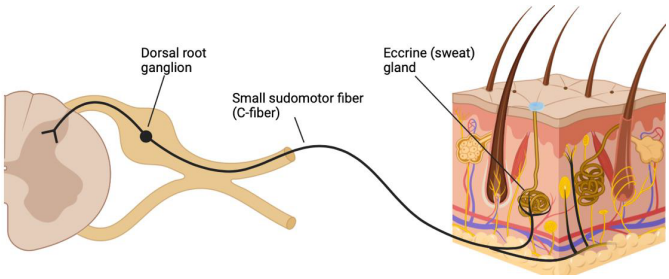


Figure 2. Small, afferent sudomotor fibers arise from dorsal root ganglia and supply autonomic control of eccrine (sweat) glands in the skin throughout the body. .

Early detection of peripheral neuropathy

The potential benefits of early detection and prevention of diabetic neuropathy (DN) cannot be overstated. For example, Kiyani et al. utilized a healthcare database to track approximately 350,000 patients with diabetes and diabetes with peripheral neuropathy over a five-year period. Healthcare resource use by these patients was quantified, and he found that individuals with peripheral neuropathy were two times as likely to be involved in a fall, three times as likely to use opioids, and sixteen times as likely to undergo limb amputation compared to those with diabetes alone [22]. Additionally, he found that those suffering from diabetic neuropathy spent an average of three times as much for prescriptions to manage complications, and the total median healthcare costs were two times higher in the first year at approximately $17,000 when compared to diabetic controls [22]. Furthermore, these comparisons persisted throughout the five year time period and widened with time.

Sadosky et al. conducted a similar study in which medical expenses of four cohorts of patients: diabetes alone, and diabetes with: peripheral neuropathy (DPN), painful diabetic neuropathy (pDPN), and severe diabetic neuropathy (severe pDPN) were tracked for twelve months after initial diagnosis and then quantified [23]. Their results showed that healthcare resource utilization was positively correlated with DPN severity with the average annual cost for individuals with DPN was near $24,000 compared to $7,000 for those with diabetes alone. Sadosky et al. also demonstrated that outpatient care was the primary driver of costs [23].

A 2003 analysis of the cost of DPN in the US (Gordois et al.) was estimated to be between 4.6 and 13.7 billion dollars [24]. Adjusting for inflation, that estimate would be between 7.68 to 22.89 billion dollars annuals in 2023. The total social and physical costs, and the annual healthcare expenditures of DPN provide a clear indication of the enormous impact that early detection and management of DPN can have.

Sudomotor function testing

Several methods of testing sudomotor function exist including invasive and non-invasive modalities. Invasive methods include the gold standard punch biopsy which has a sensitivity between 78%-92% and a specificity of 65%-90%. However, it is time-consuming and requires special training. And, as a surgical procedure, comes with the risk of surgical complications and is impractical to be performed as part of a routine physical exam [21].

Quantitative Sudomotor Axon Reflex Test (QSART)

One non-invasive method includes quantitative sudomotor axon reflex test (QSART) which measures postganglionic sympathetic function via iontophoresis which allows quantification of sweat production, and by extension, autonomic function [25]. It is used to evaluate the integrity of the postganglionic sudomotor system along the axon reflex to define the distribution of sweat loss. This is accomplished by the release of bio-impedance electrical stimulation the skin which activates receptors on the eccrine sweat gland. The sweat response is recorded from four sites (forearm and 3 lower extremity sites) and assessed for deficits. The test is a sensitive, reproducible, and quantitative method to test sudomotor function to assess autonomic nervous system disorders, peripheral neuropathies and some types of pain disorders [26].

The basis of the test is that the axon terminal of the sweat gland under the plate electrode is activated by bio-electrical stimulation; the impulse travel centripetally to a branch point and then distally to the axon terminal and a sweating response results [26]. Use of the term "axon reflex" should be discouraged, because only the postganglionic sympathetic sudomotor axon is considered to be involved in this setup. With a latency of 1 to 2 min after the induction of the stimulus, sweat output increases rapidly while stimulation continues; then the stimulator is turned off, and sweat output returns to its pre-stimulus baseline within 3 min. The area under the curve in (Figure 3) below represents the total amount of sweat output expressed in microliter per square centimeter, and the normal value varies depending on the site of testing, gender, and age of the subject. Distal limbs, male, and younger subjects tend to sweat more. Reduced or absent response indicates postganglionic disorder. Normal response does not rule out preganglionic involvement. Excessive and persistent sweating is also considered abnormal. Comparison is made between the two limbs, and an asymmetry of more than 25% is considered to be abnormal [26].

Impact of QSART

In general, QSART provides a non-invasive, reproducible, and precise evaluation of autonomic function in both controls and diabetics. Additionally, this test can be repeated up to three or four times in the same area with a high coefficient of regression [27]. The sweat response elicited by QSART is virtually symmetrical on the left and right side of the body which allows the operator to compare autonomic function on either side of the body with a high degree of reliability. Furthermore, it can be used to evaluate a large number of autonomic diseases, and the quantitative data it generates provides a measure of the extent and location of the peripheral neuropathy in each individual [28]. Abnormal QSART responses have also been shown to be highly-predictive of underlying cardiac arrhythmia where 78% of individuals with an abnormal response had an underlying arrhythmia. This makes it a potentially useful test when assessing for cardiac autonomic neuropathy and direct measurement of heart rate variation is not possible [29].

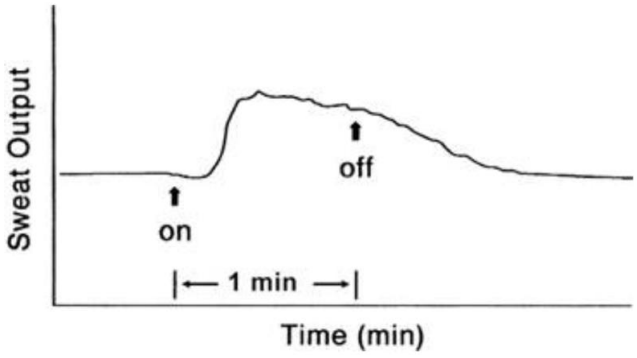


Figure 3. *Sweat output as a function of electrical stimulus duration to test sudomotor nerve function in distal limbs. .*

Sympathetic skin response test (SSR)

The sympathetic skin response (SSR) test which captures amplitude and latency information gathered by electromyography. It measures the change of the electrical potential of the skin. The recorded skin potential comes from the activated eccrine sweat gland. The amplitude and configuration are adjusted by sweat gland epithelium and the overlying epidermis [21, 30].

A standard method of obtaining SSR is to place a recording electrode on the palmar and plantar surfaces, because these recording sites yield higher amplitudes. A stimulator is placed on either the median or the tibial nerve of the opposite limb, and the stimulus is given randomly at a rate of less than one per minute, and with a stimulus intensity that is sufficient to cause mild pain. A 2 to 10 responses should be recorded, and SSR responses are obtainable 60% to 100% of the time in normal subjects [30]. Waveforms are usually triphasic, with an initial small negativity followed by a large positive wave, and a subsequent prolonged negative wave (Figure 4) [31]. Waveforms can also be monophasic or diphasic with an initial negative or positive peak. Maximal peak-to-peak amplitudes and mean latencies are measured. Amplitude and latency variability can be minimized by reducing stimulus frequency, increasing stimulus intensity, and/or changing stimulus site or mode. Low skin temperature, low level of attention, medication (especially anticholinergics), age, and habituation will also attenuate the response [31]. Normal amplitude is more than 1 mV for the hand, and more than 0.2 mV for the foot. Mean palmar latency is 1.4 +- 0.1 second and plantar latency is 1.9 +- 0.1 second. The SSR measures change of epidermal resistance due to sweat gland activity. The somatic afferent limb depends on the stimulus type (electrical shock, loud noise, visual threat, deep breathing); with the electrical stimulation, the afferent limb occurs via large myelinated fibers. The efferent limb is a sympathetic pathway, originating in the posterior hypothalamus, descending through the spinal cord to the intermediolateral cell column, and paravertebral ganglia and then to the sweat gland via small unmyelinated fibers [30].

Impact of SSR

The SSR test has a well-established protocol, and the results are easily-measured. The results can also be quantified and compared to an established reference range rather than a binary "present" or "absent" response [32]. It has been shown to have a detection rate of up to (96%) in diabetic patients which is higher than alternative electrophysiological measurements [33]. Additionally, SSR has a reproducible response after repeated stimulation, its responses are symmetrical bilaterally, and are well-correlated with autonomic and sudomotor nerve function [32].

It can be used reliably in the diagnosis of numerous autonomic disorders like: diabetic neuropathy, multiple sclerosis, brain infarct, and spinal and peripheral nerve lesions, to name a few [29]. The absence of SSR response has been shown to be highly predictive of underlying cardiac arrhythmia where 94% of individuals with absent SSR response had an underlying arrhythmia [29]. The high correlation between abnormal SSR (94%) and QSART (78%) and the presence of cardiac arrhythmias suggests that a combination of the two tests could be useful in the early detection of peripheral neuropathies and otherwise undetected cardiac autonomic dysfunction.

Bioelectric Impedance Analysis (BIA)

IBioelectric impedance measurements (BIM) is the term representative for a variety of traditional and new noninvasive procedures and technologies that use electric current. With the help of one or more surface electrodes, a tiny amount of electrical current is activated and is detected at surface electrodes placed elsewhere on the body, once the resultant electricity pulse has passed through. As it quickly proceeds through the various physiological sections of the body, and passes through, a drop in voltage occurs [34]. The current encounters impedance or resistance inherent in the fluids and tissues it passes through the

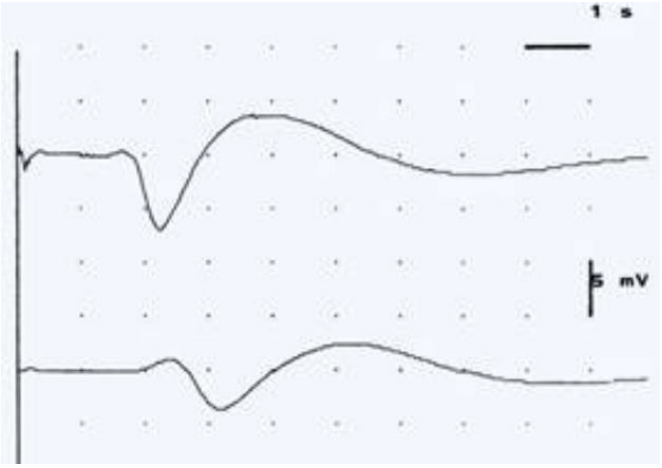


Figure 4. *Triphasic sympathetic skin response test waves recorded from different extremities..*

various areas, among them the intracellular space, the lymphatic system, the bloodstream and others. The drop in voltage delivers indirect information about the physical properties of the sections, where current has passed through.

Calculated BIM parameters include total body water (TBW) which measures electrolyte water contained in tissue. Orally ingested water, which has not yet been absorbed by the body, is not measured; the same goes for ascites, because it is not part of the lean body mass. Administered solutions, however, are detected immediately. Lean body mass (LBM) is for the most part made up of inner organs, muscles, the skeletal system and the central nervous system, and refers to the tissue mass of the body that contains no fat [34]. These organ systems, although morphologically very different, contain matching functional structures. Body cell mass (BCM) which is the sum of all cells that are actively involved in the metabolic processes. While it is rather a functionally defined section and not so much an anatomically one above all, it consists of all the cells of the inner organs and muscles, with the muscles and the highest percentage to constitute the largest part of the BCM. Connective tissue with low fibrocyte content however only makes up a small percentage of the entire BCM, and adipocytes, due to their low energy metabolism are not at all considered to be part of the BCM. Consequently, the sum of adipocyte cells therefore forms its own compartment in the body [34].

Bioelectric impedance analysis can also calculate extra-cellular mass (ECM) which is the term for the lean body mass that exists outside the cells of the BCM. Skin, elastin, collagen, tendons, bone and fasciae are the established connective tissue structures of the ECM, with the fluid parts consisting of plasma, interstitial and trans-cellular water. Trans-cellular water is the description of fluids that are present in the body cavities, for example the contents of the gastro-intestinal lumen and the spinal fluid, while non-physiological trans-cellular fluids appear as ascites, or as pericardial or pleural effusions [34]. An ECM/BCM index is also calculated as it is An important parameter for the assessment of nutritional condition is the ECM/BCM. As the body cell mass BCM in healthy persons is always considerably larger than the extra-cellular mass ECM, resulting in an index that is smaller than 1. An increase in the ECM/BC index is an early sign of a nutritional status that has been affected and is declining. A decrease of BCM points to early stages of malnutrition. It is accompanied by an increase of extra-cellular mass, while weight and lean body mass remain constant [34].

Body fat and cellular fraction (%) are calculated from BIA data as well. Body fat performs as an insulator to alternating current. With a density of 0.9 g/cm3, and with scarcely any of the typical properties of the cells of the body cell mass (BCM), it barely has any capacitive resistance (reactance) [34]. The difference between body weight and lean body mass is calculated as the fat mass. The lean body mass is the term that defines in its entirety ECM and BCM, which are both, functionally, quantitatively, and morphologically, closely related. The BCM cell percentage of the lean body mass is a unit of measurement that evaluates a body's physical and nutritional condition. Called cell percentage, it is a good qualifier of the lean body mass in an individual.

VitalScan Sudocheck

SudoCheck by VitalScan is an FDA-cleared, non-invasive autonomic assessment tool that combines QSART, SSR, BIA, and EIS to provide rapid results with a specificity of 95% and a sensitivity of 80%. This device was created to enable a precise evaluation of sweat gland function. Based on a measuring method, patients place their hands and feet on stainless-steel electrodes. The method uses low voltage to stimulate the sweat glands and measure the electrochemical reaction between electrodes and chloride ions. This active, new method provides information and evidence of a sweat dysfunction that might otherwise not be detectable in physiological conditions. Bioelectrical Conductances (BEC, in micro siemens, µS) for the hands and feet express the quantitative results, while a risk score derives from demographic data and the BEC values.

VitalScan SudoCheck is, similar to a galvanic skin response stress test, a functional test that measures the sweat glands' capacity to release chloride ions following an electrochemical stimulation. It works by measuring the electrical potential difference caused by the electrochemical reaction of electrodes, which are applied to the skin and stimulated by a low voltage of variable amplitude. VitalScan SudoCheck comes with 4x2 independent electrodes for placement on feet or palms and other areas with a high number of sweat glands. VitalScan SudoCheck also provides information that determines the cardiometabolic risk in patients.

Discussion

Chronic hyperglycemia in both type 1 and type 2 diabetes commonly leads to microvascular diseases of the eyes, kidneys, and peripheral nerves [6]. Diabetic peripheral neuropathy (DN) commonly affects the lower limbs first and can result in nerve damage leading to gradual onset of foot pain, tingling, numbness, muscle weakness, and extreme sensitivity to touch [7]. Diabetic peripheral neuropathy (DN) leads to structural and functional changes in peripheral nerves including autonomic sudomotor nerves. This occurs most-commonly in the lower extremities and results in increased morbidity and mortality [16]. The study of sudomotor function presents a valuable tool to assess autonomic disorders since it is known to reflect sympathetic activity and provide insight into postganglionic autonomic innervation. Additionally, sudomotor dysfunction has been established as one of the earliest detectable neurophysiologic abnormalities in distal small fiber neuropathies, even when diabetes symptoms are subclinical.

The VitalScan SudoCheck system helps clinicians assess peripheral neuropathies and early nerve dysfunction. The assessment focuses on small unmyelinated C-fibers that are responsible for the function of sweat glands within the autonomic nervous system. With Sudocheck, this assessment can be carried out quickly and easily through the measurement of chloride ion and electric potential of the skin between electrodes. Sudocheck is convenient in that it does not require any patient preparation, such as blood drawing or fasting, is non-invasive and delivers immediate results, with findings within 3 minutes. It was developed for general practitioners, cardiologists, and neurologists to assist in the effective screening of cardiometabolic risk in patients, and to assess autonomic neuropathy and neuropathic pain in individuals with diabetes. It is a highly-effective tool that that can evaluate patients with diabetes mellitus to assess autonomic neuropathy and neuropathic pain with a sensitivity of 80% and specificity of 95%, and the data correlate significantly with clinical neuropathy scores, pain scores and measures of autonomic dysfunction. VitalScan SucoCheck can also be used to diagnose complex pain and enzyme disorders, dysautonomia, and reflex sympathetic dystrophy (RSD).

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