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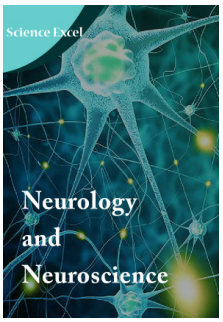

Evaluating Sudomotor Function: Aging, Diabetes, and the Sudomotor Autonomic Neuropathy Index

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Abstract

Assessing sudomotor function is essential for diagnosing and monitoring autonomic disorders, especially in cases of diabetes and small fiber neuropathies. Traditional methods are effective but often complicated and less accessible. Recent innovations, particularly the VitalScan-SudoCheck, provide a non-invasive and rapid alternative for evaluating sudomotor function through techniques such as Quantitative Sudomotor Axon Reflex Test (QSART) and Sympathetic Skin Response (SSR).

This study investigates the impact of aging on the risk of developing autonomic neuropathy within a large cohort (n=143,900) using the Sudomotor Autonomic Neuropathy Index (SANI). As individuals age from 20 to 90 years, their SANI scores increase, reflecting a higher risk of autonomic neuropathy.

Additionally, the study evaluates the effectiveness of the SANI score in detecting diabetic neuropathy compared to clinical diagnoses made by healthcare professionals for patients with type 2 diabetes mellitus (T2DM). The findings reveal that T2DM patients (n=2,560) have higher SANI scores than the elderly cohort aged 80 to 90.

The SANI, developed by SudoCheck, facilitates comprehensive monitoring of autonomic health, particularly among older adults. Despite these encouraging findings, further research is necessary to standardize sudomotor function tests and enhance their clinical utility. By addressing the barriers to the adoption of sudomotor assessments, this study highlights the importance of timely diagnosis in improving patient outcomes and managing the economic impact of diabetes-related complications.

Introduction

Diabetic autonomic neuropathy (DAN) significantly impacts various bodily systems in individuals with diabetes mellitus, particularly cardiovascular and sudomotor functions [1]. Among its manifestations, sympathetic sudomotor dysfunction (SMD) is commonly observed, resulting in reduced sweating in the feet and an increased risk of foot ulcers (Figure 1a) [2]. SMD may present as part of generalized diabetic peripheral neuropathy (DPN) or alongside distal small fiber sensory polyneuropathy (SFSN) [3]. Abnormal sweating patterns and dry skin, resulting from SMD, further elevate the risk of foot ulceration, a critical issue since 84% of non-traumatic amputations in diabetics are preceded by foot ulcers [4-6].

SMD can manifest as either increased or decreased sweating, affecting an individual's quality of life [7]. The autonomic nervous system regulates sweat gland activity in response to various factors, and sweating plays a crucial role in thermoregulation, helping to prevent heat-related illnesses [8]. SMD can result from central disorders such as strokes or neurodegenerative diseases, as well as peripheral neuropathies, commonly associated with diabetes [9,10].

DPN, characterized by chronic pain and a heightened risk of falls, ulcers, and amputations, accounts for 78% of the foot ulceration risk in diabetic patients [6,11-13]. Early detection of DPN is vital to prevent complications and limb loss. Symptoms of DPN include heat intolerance and hyperhidrosis, necessitating comprehensive assessments of patients' social habits and skin conditions to identify potential complications like skin ulcers [7,14].

The prevalence of DPN varies between type 1 (T1DM) and type 2 diabetes mellitus (T2DM), with rates reported between 6% and 51% in different populations [15-25]. Chronic hyperglycemia in both T1DM and T2DM often leads to microvascular complications, particularly DPN, which affects up to half of all diabetics [26,27]. This condition triggers oxidative stress and neuronal damage through multiple pathways (polyol, PKC, hexosamine, and AGEs), resulting in increased reactive oxygen species ((ROS) and subsequent cellular damage and inflammation [28-33]. Pro-inflammatory markers and macrophage

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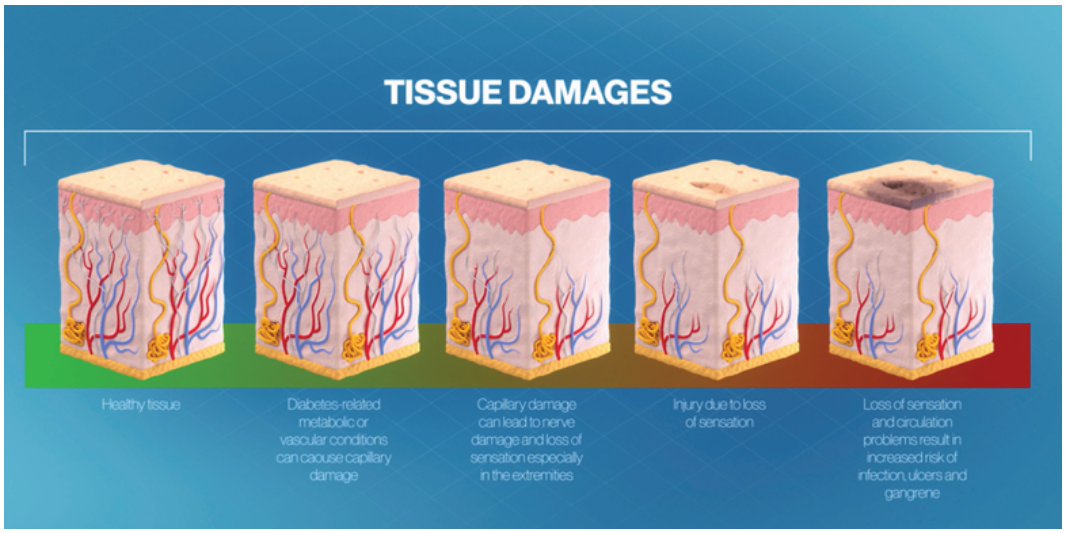

***Figure 1a**. Progressive tissue damage in diabetic neuropathy. i) Healthy tissue. ii) Diabetes-related metabolic or vascular conditions can cause capillary damage. iii) Capillary damage can lead to nerve damage and loss of sensation especially in the extremities. iv) Injury due to loss of sensation. v) Loss of sensation and circulation problems result in increased risk of infection, ulcers and gangrene.*

accumulation contribute to nerve damage [34-37]. Conversely, the AMPK signaling pathway may provide protective effects against neuropathy by enhancing mitochondrial function and reducing inflammation [38-41]. Understanding these mechanisms is vital for developing effective prevention and treatment strategies for DPN.

DPN primarily affects small nerve fibers in the lower limbs, leading to symptoms such as foot pain, tingling, numbness, and extreme sensitivity to touch [42]. Initially mild, these symptoms can escalate to burning sensations, causing significant discomfort [43]. Small fiber neuropathy (SFN) often precedes larger fiber damage and can begin in the pre-diabetic stage [11,44,45]. Furthermore, DPN disrupts autonomic nerve function, leading to dry eyes, mouth, constipation, incontinence, and orthostatic hypotension due to loss of vascular autonomic tone [43]. The skin in affected areas may become dry and discolored, a consequence of impaired sweat production from damaged autonomic C-fibers. These unmyelinated C-fibers include sudomotor nerves responsible for stimulating sweat production from eccrine sweat glands, which number up to 4 million in the human body, primarily located in the palms and soles [46-48]. This process is regulated by efferent postganglionic autonomic signals activated by afferent signals from skin thermoreceptors. Degeneration of C-fibers can impair sweating [8].

In diabetic neuropathy, degeneration of small C-fibers from postganglionic sympathetic cholinergic neurons often begins in the subclinical pre-diabetic stage, preceding damage to larger group I and Aβ fibers [7]. Although this early degeneration is usually asymptomatic, some studies suggest that nerve repair may be achievable through lifestyle changes and weight loss, provided the degeneration is detected early [49,50].

A serious consequence of diabetic autonomic dysfunction is cardiovascular autonomic neuropathy (CAN), which affects the autonomic fibers innervating the heart [51]. Risk factors for CAN include HbA1c levels, age, obesity, hypertension, and hyperglycemia. DAN often develops early in diabetes, within one to two years after a T2DM or T1DM diagnosis, impacting cardiovascular and sweat gland functions and potentially leading to severe complications if untreated [52]. Clinical signs of CAN can include a persistently elevated heart rate, exercise intolerance, and diminished pain perception during myocardial infarction [33,51,53,54]. Early intervention is crucial for repairing small fiber damage, underscoring the importance of early detection.

SMD is typically an early sign of autonomic neuropathy and results from impaired neurotransmitter release [55]. If left untreated, it can lead to dry skin, lack of sweating, and skin cracks, increasing the risk of severe complications like ulcers, gangrene, and limb loss (Figure 1a) [37]. Early detection of diabetic neuropathy is challenging due to the absence of clear clinical signs in the initial stages. As the severity of diabetic neuropathy increases, sudomotor function declines [2]. Assessing SFN is essential, as patients may present normal neurological exam results in the early stages and SFN may be the only detectable neurologic manifestation at this point [56-60]. Symptoms like reduced skin moisture or cracked skin often emerge later [56]. SMD, often linked to SFN, can be identified through various testing methods. Early detection of SMD is crucial for evaluating and monitoring diabetic neuropathy, as it represents one of the earliest neurophysiological manifestations of SFNs [9].

Assessment of autonomic dysfunction can be achieved through sudomotor testing, which is beneficial since sudomotor function is typically the first affected in early peripheral neuropathy, providing clinicians with a valuable opportunity for early detection of diabetic neuropathy [27]. The American Diabetes Association recommends sudomotor assessments for early neuropathy detection, particularly in diabetic and pre-diabetic populations [1,61-66].

Sudomotor tests evaluate sweat glands innervated by small C-fibers involved in sympathetic activities [67,68]. The gold standard for diagnosing SFN is a skin biopsy that measures intraepidermal nerve fiber density (IENFD) [56,69-73]. While effective, this method is invasive, time-consuming, and requires specialized resources [1,74].

Non-invasive testing include the quantitative sudomotor axon reflex test (QSART), first introduced in 1983 by Phillip Low and colleagues, assesses postganglionic sudomotor function by

measuring sweat output in response to acetylcholine [47,75-77]. This test evaluates the integrity of the sudomotor system by electrically stimulating the skin and recording sweat responses from multiple sites. While some previous implementations of the QSART technology report mixed results regarding its sensitivity and reproducibility, QSART remains sensitive and effective in detecting small fiber dysfunction [78,79].

Another method for assessing autonomic function is the sympathetic skin response (SSR), which measures skin conductance changes due to sympathetic activation of sweat glands in response to stimuli like electrical stimulation, deep breathing, and stress [80]. SSR is an electromyography-based method performed in a controlled environment that assesses changes in skin electrical potential, primarily reflecting eccrine sweat gland activity. While SSR has high reproducibility and detection rates in diabetic patients can reach up to 96%, some previous implementations of the SSR technology have limitations due to variability in results and the underlying mechanisms of this somato-sympathetic reflex [80-82].

Various methods for assessing sudomotor function differ in cost, technical complexity, reproducibility, and the availability of normative data [47]. To address these challenges, the VitalScan-SudoCheck System, FDA-cleared and non-invasive, offers a comprehensive assessment of sudomotor autonomic function by combining multiple tests, including QSART, SSR, BioElectrical Conductance (BEC), Bioelectrical Impedance Analysis (BIA), and demographic data [42]. This integration derives the Sudomotor Autonomic Neuropathy Index (SANI), providing a holistic view of sudomotor function and its implications for autonomic health.

SudoCheck measurements involve applying a small electrical current through surface electrodes to assess various physiological properties of the body. The voltage drop observed as the current travels through various tissues provides indirect information about their characteristics [42]. These measurements yield valuable insights into body composition, hydration status, and nutritional health, making them useful for clinical assessments and health monitoring.

The SudoCheck technology facilitates faster and simpler assessment of sudomotor function, delivering rapid results with a specificity of 95% and sensitivity of 80% in identifying autonomic neuropathy. This correlates well with clinical neuropathy and pain scores [42].

Medeia Inc. aims to introduce the SANI as a diagnostic tool to assess the risk of autonomic neuropathy with age in a large population sample (n=143,900) and to establish a reference range for VitalScan-SudoCheck. The SANI will also evaluate the risk of sudomotor autonomic neuropathy in T2DM patients, which accounts for 90-95% of all diabetes cases [42]. Early detection of peripheral and autonomic neuropathies is critical for implementing interventions that can preserve nerve function and prevent severe complications in aging and diabetic populations in the United States (U.S.).

Materials and methods

Subject and Variable Selection

Patient data acquisition occurred between 2014 and 2023 across multiple neurology offices. Patients who qualified for the VitalScan-SudoCheck assessment were concurrently evaluated for their SANI (integrative index comprised of QSART/SSR/BEC/demographic) data. The subject selection criteria for a VitalScan-SudoCheck assessment are detailed below.

A. Inclusion/Exclusion Criteria, Demographics and Gender [83]

For subjects aged 4 to 18 years, parents completed a neurological history questionnaire for them, and psychometric evaluations were conducted. Adults (≥18 years) also completed a neurological questionnaire, and those deemed unhealthy were excluded based on questionnaire responses and/or physician comments. Physicians have access to the following questionnaires: GAD-7 (Anxiety Severity), DSM-5 Level 1 (Cross-Cutting Symptom Measures), PHQ-9 (Depression), and general neurological questionnaires. Inclusion required at least one questionnaire score below moderate and physician-verified health in that the patient was deemed healthy. Any patient records or previously known medical records with questionnaire score of 'moderate' or 'severe' were excluded from the VitalScan-SudoCheck database, regardless of other information.

B. Demographic Characteristics [83]

It is crucial that the demographic mixture of males and females, various ethnic groups, and socioeconomic statuses be reasonably representative of the expected North American clientele. This diversity was derived from a large pool of subjects obtained from eight geographically dispersed sites, reflecting the North American demographics and addressing a wide range of ethnic and socioeconomic statuses found in the de-identified patient data before review.

C. Client-Based VitalScan-SudoCheck Database [83]

Each client in the VitalScan-SudoCheck database completed a DSM-based questionnaire. Regression analysis was utilized to remove any psychopathology-related variance from the SANI data. This process ensures that the variance in the SANI data of 'healthy' subjects, which is explained by the variance in the questionnaire, is removed to create a 'psychopathology-free' SudoCheck normative database or discriminant databases for various neuropathy disorders.

Utilizing a client-based normative or discriminant database has its own set of advantages. Clients may harbor expectations distinct from those of 'healthy' subjects concerning SudoCheck recordings.

Patients were prepared for a VitalScan-SudoCheck assessment, where SANI data were collected concurrently.

VitalScan-SudoCheck Assessment

D. To Prepare the Patient for a VitalScan-SudoCheck Assessment [83]

To perform a reliable VitalScan-SudoCheck assessment, it is essential to observe the following patient preparations: patients should abstain from consuming caffeine at least 2 hours before the assessment, avoid taking any new medications or supplements unless directed by a healthcare provider, and refrain from using alcohol, marijuana, or other recreational drugs at least 6 hours prior to the assessment. Patients with pacemakers should not undergo testing during the visit and are required to complete a brief neuropsychological questionnaire about their symptoms before testing. During the testing, ensure the patient is comfortable while sudomotor measurements and activities are recorded

E. VitalScan-SudoCheck BEC

VitalScan-SudoCheck is a sophisticated device designed to assess sweat gland function using the QSART and SSR technologies. The SudoCheck system complies with 21 CFR 882.1540 as a sympathetic skin response device, offering skin

***Figure 1b**. Progressive tissue damage in diabetic neuropathy. i) Healthy tissue. ii) Diabetes-related metabolic or vascular conditions can cause capillary damage. iii) Capillary damage can lead to nerve damage and loss of sensation especially in the extremities. iv) Injury due to loss of sensation. v) Loss of sensation and circulation problems result in increased risk of infection, ulcers and gangrene.*

conductance measurements displayed on a computer screen. It utilizes low-voltage electrochemical stimulation to analyze the reaction between the electrodes and chloride ions, helping to identify potential sweat dysfunction that may not be visible under normal conditions. The device measures the electrical potential difference resulting from this reaction, applied through electrodes on areas rich in sweat glands. The test takes 3 minutes to complete.

F. Brief Guide to Operate the VitalScan-SudoCheck System for Patient Assessment (83)

The VitalScan-SudoCheck System comprises a workstation with stainless-steel electrodes (Figure 1b). The device assesses sweat gland function by having patients place their hands and feet on stainless-steel electrodes, using low voltage to stimulate sweat glands. The VitalScan-SudoCheck System enables quick and easy evaluations of peripheral neuropathies and early nerve dysfunction by measuring the electrical potential without requiring patient preparation.

To operate the VitalScan-SudoCheck System, follow these steps: Turn on your laptop, open the VitalScan-SudoCheck software, and ensure that the amplifier device's USB is properly connected. To confirm the connection, click on the settings button and press "Check Device Connection." Position the patient comfortably in a chair facing the laptop screen. In the software, select “New Measurement” and then “SudoCheck Response Test”.

Proceed to the patient information section, select "New" or "Existing Patient," and enter the patient's details, including name, date of birth, gender, weight, height, medications, symptoms, or previous diagnoses. Progress to the patient questionnaire, guiding the patient through detailed answers—an essential step. In the pre-test screen, check signal quality.

After a successful test, view the results on the overview page and disconnect the patient. The software results, starting with the neurofunctional test option, provide a general summary with scales ranging from red (abnormal) to green (healthy), helping diagnose and assess the patient's autonomic health. Light green is borderline, while yellow and orange indicate areas of concern.

G. SudoCheck Results

SudoCheck is designed to assess the sweat glands' capacity to release chloride ions in response to stimulation, similar to a galvanic skin response test. This innovative technology delivers quantitative results expressed in BEC and calculates a risk score, known as the SANI. The SANI is derived from integrating BEC values with demographic data and other assessment methods (QSART, SSR, BIA) [42]. Results, expressed as a mean ± standard deviation (SD), are available in just three minutes, enhancing the efficiency of autonomic function evaluation.

Results

Mean SANI versus Age

For both males and females, the sudomotor autonomic neuropathy indices increased with age (Figure 2a). When comparing SANI between genders across different age groups, females generally exhibited higher mean SANI values (Table 1), though the differences were not statistically significant. In every age group except for the 25-30 cohort, females had higher mean SANI values than males. The only exception was in the 20-25 age group, where males had a mean SANI value of 42.81±21.04, which was 0.13 higher than the female mean of 42.68±21.72. This difference is likely related to physiological differences between male and female patients in that age group. Overall, the SANI values for males and females were quite similar, with both curves displaying an upward trend in SANI values with age (Figure 2b).

The mean SANI values for males increased from 41.12±22.29 at age 20-25 to 63.00±21.40 at age 80-90. For females, the mean SANI values rose from 41.22±21.44 in the 20-25 age group to 64.03±20.71 in the 80-90 age group. The relative change in SANI from the young (20-25 years) to the old (80-90 years) was similar for both genders, but females experienced a slightly greater increase. Males showed an increase of 53.21% [(63.00−41.12)/41.12], while females exhibited a 55.34% increase [(64.03−41.22)/41.22]. This suggests that females may face a higher risk of sudomotor autonomic neuropathy as they age.

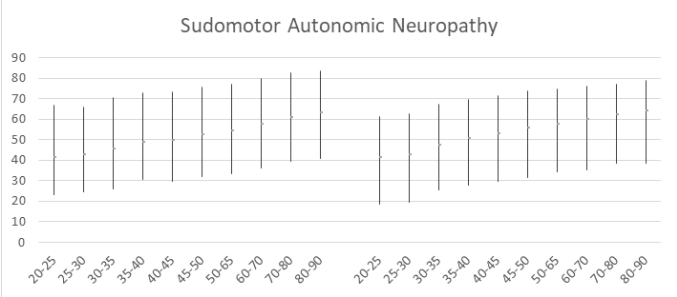

Figure 2a. *Average Sudomotor Autonomic Neuropathy Index (SANI) versus age, with error bars, shows a increase with age in both men (left) and women (right) aged 20-90 years.*

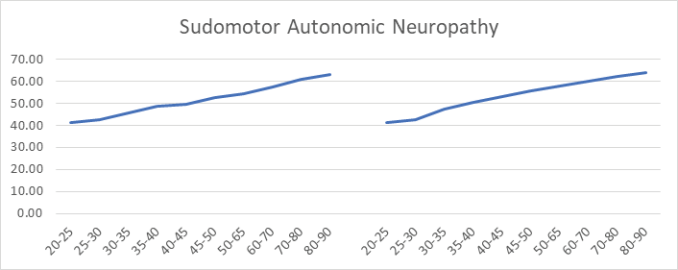

Figure 2b. *Average Sudomotor Autonomic Neuropathy Index (SANI) versus age curves increase with age in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a parallel upward trend.*

Moreover, the SD values were similar and consistent between males and females across all age groups, ranging from 21.04 to 22.67 in males and 19.78 to 21.72 in females. While the mean SANI values increased with age, the SD values remained stable, indicating the stability and reproducibility of the VitalScan-SudoCheck System. The higher SD values in males suggest greater individual variation within that population, which may also be influenced by the smaller sample size (n) of male cohorts across all age groups. Overall, the increase in mean SANI with age suggests a rising risk of sudomotor autonomic neuropathy as individuals grow older.

Impact of T2DM

In patients with T2DM (n=2,560), the mean SANI was 69.7±12.3, comparable to individuals aged 80-90 years. Notably, the SANI for T2DM patients (69.7±12.3) was higher than that of both older males (63.00±21.40) and females (64.03±20.71), indicating that T2DM patients may have a greater risk of developing autonomic neuropathy compared to their older counterparts. The population in this study aged 20 to 90 years without diabetes has SANI values between 41.12 and 64.03 (Table 1). Based on these results, individuals with values outside of this reference range may have a higher risk of autonomic neuropathy, with diabetic patients experiencing a greater risk, as shown by their mean SANI (69.7±12.3) value above the population range.

The VitalScan-SudoCheck detected the risk of sudomotor autonomic neuropathy with a sensitivity of 74.3% and specificity of 72.8%. Importantly, a sensitivity or specificity score above 70% in a large cohort is considered significant.

Discussion

Limiting Factors of Traditional Sudomotor Function Tests

Sudomotor function assessment is essential for evaluating autonomic disorders, particularly in detecting early neurophysiological changes associated with SFNs before clinical symptoms manifest. Early identification of small fiber damage is crucial for diagnosing neuropathy and preventing its progression. Various testing methods exist, each with distinct advantages and disadvantages.

While sudomotor testing shows promise, its routine use faces several challenges [58,84-87]:

1. Need for Specialized Technology and Training: Many tests require specific equipment and trained personnel, limiting their accessibility in clinical settings.
2. Lack of Standardization: Newer techniques often lack standardization, leading to variability in results and interpretation.
3. Influence of External Factors: Sudomotor function can be affected by numerous variables, including humidity, light, temperature, hydration levels, medications, age, and prior skin treatments, which may introduce artifacts. Controlling these factors is essential for obtaining reliable results.

The gold standard for invasive assessment is a punch biopsy, which, despite its sensitivity (78%-92%) and specificity (65%-90%), is time-consuming and carries surgical risks, making it impractical for routine exams [27,42].

In contrast, non-invasive methods such as QSART and SSR are more patient-friendly and crucial for diagnosing and monitoring neurologic disorders related to autonomic neuropathy. Despite their advantages, these non-invasive tests also face limitations.

Despite these challenges, sudomotor assessments remain among the most sensitive methods for detecting distal SFNs [58]. Continued improvements in testing methodologies and standardization efforts are essential for enhancing the utility of sudomotor function tests in clinical practice.

Age and Sex-Related Differences in Sudomotor Function

A study by Lee et al. quantitatively assessed age and sex-related differences in sudomotor function among healthy individuals using the QSART [88]. Conducted under controlled conditions, Lee's study found that men generally exhibited better sudomotor performance than women, suggesting a lower risk of sudomotor autonomic neuropathy in men [88]. Consistent with these findings, the current study also indicated a lower risk of sudomotor autonomic neuropathy in males compared to females that had higher SANI values virtually across all ages.

Similarly, Parashar et al. observed decreased sudomotor function with age in a study involving 62 Indian volunteers aged 25 to 80 years [89]. Their results showed that sudomotor responses were partially interrupted in elderly age group (60-80 years). Overall, their findings align with the current study, which revealed that the mean SANI increased with age, indicating a higher risk of sudomotor autonomic neuropathy as sudomotor function declines with aging.

In contrast, Mal et al. reported increased postganglionic sudomotor function with age in a study of 61 healthy Indian volunteers aged 21-50 years [90]. Additionally, they found that, although men and women had comparable sweat gland densities, men produced sweat at a higher rate.

Table 1. *Mean Sudomotor Autonomic Neuropathy Index (SANI) and standard deviation (SD) of male and female patients (n=143,900), across ages 20-90 years.*

age	sex	# of patients	Mean	SD
20-25	male	725	41.12	22.29
25-30	male	1288	42.81	21.04
30-35	male	1816	45.51	22.67
35-40	male	2494	48.58	21.42
40-45	male	3177	49.53	21.87
45-50	male	4141	52.55	21.67
50-65	male	5784	54.27	22.03
60-70	male	15427	57.60	21.87
70-80	male	19811	60.82	21.63
80-90	male	7467	63.00	21.40
20-25	female	1446	41.22	21.44
25-30	female	2457	42.68	21.72
30-35	female	3120	47.46	21.08
35-40	female	3866	50.68	20.88
40-45	female	4870	52.92	20.99
45-50	female	6186	55.85	21.29
50-65	female	8021	57.84	20.45
60-70	female	20058	60.11	20.96
70-80	female	24287	62.07	19.78
80-90	female	9484	64.03	20.71

Importance of Early Detection and Prevention of Diabetic Neuropathy

Early detection and prevention of diabetic neuropathy are crucial due to significant healthcare costs and associated risks. A study by Kiyani et al. tracking 350,000 diabetes patients over five years found that those with peripheral neuropathy were twice as likely to experience falls, three times more likely to use opioids, and sixteen times more likely to undergo limb amputation compared to those without neuropathy [42,91,92].

Additionally, patients with diabetic neuropathy incurred substantially higher healthcare costs, spending an average of three times more on medications, with median costs reaching approximately $17,000 in the first year - double that of diabetic controls [91]. Similarly, Sadosky et al. reported that healthcare costs increased with the severity of neuropathy. Patients with DPN averaged nearly $24,000 in annual costs, compared to $7,000 for those with diabetes alone, with outpatient care being the primary expense [93].

DPN is a significant complication of diabetes, linked to high mortality rates and severe issues such as foot ulcers, poor wound healing, limb amputation, and infections [94]. A 2003 analysis estimated the cost of DPN in the U.S. at $4.6 to $13.7 billion, which translates to approximately $7.68 to $22.89 billion in 2023 when adjusted for inflation [95]. These findings highlight the substantial economic and health impacts of early detection and management of diabetic neuropathy [95]. Early detection of peripheral neuropathy is critical for implementing interventions that can preserve nerve function and prevent severe complications.

Importance of Early Screening for SMD

Calikoglu's research emphasized the high prevalence of SMD in individuals with diabetes and its correlation with diabetic complications, particularly retinopathy [96]. In a large cohort of 690 individuals, Calikoglu et al. found that SMD prevalence was 18.8% in the T1DM group, 44.3% in T2DM, 59.1% in pre-diabetes, and 15% in healthy controls [96]. Among T2DM participants with retinopathy, 66.7% exhibited SMD, with 56.3% of these having clinical diabetic polyneuropathy [96]. Factors such as retinopathy, female gender, and estimated glomerular filtration rate were significantly associated with SMD. Moreover, SMD could manifest even before clinical signs of polyneuropathy appear, highlighting a need for early detection and intervention. However, Calikoglu et al. noted the necessity for larger, prospective studies to establish universally accepted threshold values for routine screening, ensuring effective measures can be implemented to prevent further complications in diabetic patients [96].

The SSR has been validated as a reliable measure of sweat gland innervation in diabetic neuropathy [81]. Levy et al. demonstrated that SSR can be effectively measured in 96% of randomly selected diabetic patients, surpassing the detection rate of traditional sensory electrophysiological tests [81]. By quantifying SSR responses rather than simply recording their presence or absence, the technique provides significant advantages in assessing nerve function, with established reference ranges. Key findings included longer latency and smaller amplitude in SSR responses for diabetic subjects compared to healthy individuals [81]. The study also noted that while age positively correlated with total sweat volume,

it inversely correlated with latency periods. Notably, SSR amplitude decreased with age in diabetic patients.

Methodological improvements contributed to the success of Levy's study, such as using a lower cutoff frequency for filters, employing deep inspiration instead of electrical stimulation, and utilizing proprietary electrodes for more consistent responses [81]. Temperature control was crucial, as increased local foot temperature led to higher SSR amplitudes, though changes in latency were less consistent [81]. Nonetheless, the findings suggest that SSR may reflect advanced neuropathy rather than mild forms, warranting further investigation into its clinical utility.

Each method for detecting SFN has unique advantages and disadvantages, impacting their reliability and practicality for routine clinical use. Overall, while several promising approaches exist, challenges remain in standardization and accessibility for widespread clinical implementation.

VitalScan-SudoCheck has addressed these technical challenges in the current large population study to establish SANI reference ranges for the aging population.

VitalScan-SudoCheck Integrative Analysis

Quantitative assessment of sudomotor function is essential for evaluating autonomic dysfunction. It aids in confirming diagnoses, track disease progression, and assess treatment effectiveness. The core method of SudoCheck, the BEC test, offers a promising alternative to traditional sudomotor function assessments, which can be complex and less accessible. VitalScan-SudoCheck represents a significant advancement in non-invasive testing for autonomic dysfunction, allowing for quicker and simpler assessments while providing critical data on risks of developing sudomotor autonomic neuropathy.

Results from this study indicate that T2DM patients are at a higher risk of developing sudomotor autonomic neuropathy compared to aging individuals, as evidenced by higher SANI scores outside of the population range. Notably, no significant differences in SANI-associated risk were found between males and females across all ages, as the mean SANI values were similar in the age cohorts.

Thus, VitalScan-SudoCheck serves as a vital monitoring tool for disease detection and progression, particularly in diabetic patients. The economic burden of diabetes is substantial, with related costs estimated at $327 billion annually, accounting for nearly 10% of total U.S. healthcare spending [42,97].

One of the key advantages of SudoCheck is its integration of multiple methods ─ QSART, SSR, and BEC ─ to provide rapid, comprehensive results in the form of SANI as a risk index for sudomotor autonomic neuropathy in both aging and diabetic individuals. This technology enables Medeia Inc. to develop reference ranges that monitor individual risk as they age.

Furthermore, the introduction of SANI facilitates ongoing disease surveillance, allowing for tracking and assessment of progression throughout the life of individuals at risk, especially those with diabetes. The study highlighted several advantages of VitalScan-SudoCheck: it is non-invasive, quick, objective, and quantitative. Its reproducibility makes it suitable for large-scale screening, with results available within three minutes. This convenience makes it an excellent tool for general practitioners, cardiologists, and neurologists to screen for autonomic neuropathy and neuropathic pain in diabetic patients.

Overall, the effectiveness of VitalScan-SudoCheck for early detection of SFNs positions it as an attractive option for broader clinical use.

Conclusion

While sudomotor assessment is increasingly recognized for its potential in diagnosing neurological conditions, further research and standardization are essential to enhance its clinical applicability and precision. Technologies like the VitalScan-SudoCheck hold promise for improving diagnostics for autonomic disorders, particularly given the early indicators of sudomotor involvement in conditions such as diabetes. Future studies should focus on identifying and addressing the various factors that influence the clinical application of these assessments, thereby facilitating their broader adoption in routine clinical practice.

References

1. Tesfaye S, Boulton AJM, Dyck PJ, et al. Diabetic neuropathies: Update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010;33(10):2285-2293. doi:10.2337/dc10-1303
2. Ishibashi F, Kojima R, Kawasaki A, et al. Correlation between sudomotor function, sweat gland duct size, and corneal nerve fiber pathology in patients with type 2 diabetes mellitus. J Diabetes Investig. 2014;5(5):588-596. doi:10.1111/jdi.12171
3. England JD, Gronseth GS, Franklin G. Practice parameter: Evaluation of distal symmetric polyneuropathy: Role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review): Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology. 2009;72(2):177-184.
4. Tentolouris N, Marinou K, Kokotis P, et al. Sudomotor dysfunction is associated with foot ulceration in diabetes. Diabet Med. 2009;26(3):302-305.
5. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990–2010. N Engl J Med. 2014;370(16):1514-1523.
6. Barshes NR, Sigireddi M, Wrobel JS, et al. The system of care for the diabetic foot: Objectives, outcomes, and opportunities. Diabetes Foot Ankle. 2013;4:21847. doi:10.3402/dfa.v4i0.21847
7. Ziemssen T, Siepmann T. The investigation of the cardiovascular and sudomotor autonomic nervous system—A review. Front Neurol. 2019;10:53. doi:10.3389/fneur.2019.00053
8. Gagnon D, Crandall CG. Sweating as a heat loss thermoeffector. In: Thermoregulation: From Basic Neuroscience to Clinical Neurology Part I. Vol 156. Handbook of Clinical Neurology; 2018:211-232.
9. Freeman R. Autonomic peripheral neuropathy. Lancet. 2005;365(9470):1259-1270.
10. Siepmann T, Illigens BMW, Reichmann H, Ziemssen T. Axon-reflex based nerve fiber function assessment in the detection of autonomic neuropathy. Nervenarzt. 2014;85(11):1309-1314.
11. Burgess J, Frank B, Marshall A, et al. Early detection of diabetic peripheral neuropathy: A focus on small nerve fibres. Diagnostics. 2021;11(2):165. doi:10.3390/diagnostics11020165
12. Yovera-Aldana M, Velásquez-Rimachi V, Huerta-Rosario A, et al. Prevalence and incidence of diabetic peripheral neuropathy in Latin America and the Caribbean: A systematic review and meta-analysis. PLoS ONE. 2021;16(6) doi:10.1371/journal.pone.0251642
13. Boulton AJ. What you can't feel can hurt you. J Vasc Surg. 2010;52(3):28S-30S.
14. Buchmann SJ, Penzlin AI, Illigens BMW. Assessment of sudomotor function. Clin Auton Res. 2018;19(2):79.
15. Hicks CW, Selvin E. Epidemiology of peripheral neuropathy and

lower extremity disease in diabetes. Curr Diab Rep. 2019;19(10):86.
16. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. Nat Rev Dis Primers. 2019;5:41. doi:10.1038/s41572-019-0092-1
17. Walter-Höliner I, Barbarini DS, Lütschg J, et al. High prevalence and incidence of diabetic peripheral neuropathy in children and adolescents with type 1 diabetes mellitus: Results from a five-year prospective cohort study. Pediatr Neurol. 2018;80:51-60.
18. Callaghan BC, Price RS, Feldman EL. Distal symmetric polyneuropathy: A review. JAMA. 2015;314(21):2172-2181.
19. Kisozi T, Mutebi E, Kisekka M, et al. Prevalence, severity and factors associated with peripheral neuropathy among newly diagnosed diabetic patients attending Mulago hospital: A cross-sectional study. Afr Health Sci. 2017;17(2):463-473. doi:10.4314/ahs.v17i2.21
20. Li L, Chen J, Wang J, Cai D. Prevalence and risk factors of diabetic peripheral neuropathy in Type 2 diabetes mellitus patients with overweight/obesity in Guangdong province, China. Prim Care Diabetes. 2015;9(3):191-195.
21. Pai YW, Lin CH, Lee IT, Chang MH. Prevalence and biochemical risk factors of diabetic peripheral neuropathy with or without neuropathic pain in Taiwanese adults with type 2 diabetes mellitus. Diabetes Metab Syndr. 2018;12:111-116.
22. Ponirakis G, Elhadd T, Chinnaiyan S, et al. Prevalence and risk factors for painful diabetic neuropathy in secondary healthcare in Qatar. J Diabetes Investig. 2019;10:1558-1564. doi:10.1111/jdi.13037
23. Jaiswal M, Divers J, Dabelea D, et al. Prevalence of and risk factors for diabetic peripheral neuropathy in youth with type 1 and type 2 diabetes: SEARCH for diabetes in youth study. Diabetes Care. 2017;40:1226-1232. doi:10.2337/dc17-0179
24. Mizokami-Stout KR, Li Z, Foster NC, et al. The contemporary prevalence of diabetic neuropathy in type 1 diabetes: Findings from the T1D Exchange. Diabetes Care. 2020;43:806-812. doi:10.2337/dc19-1583
25. Pan Q, Li Q, Deng W, et al. Prevalence of and risk factors for peripheral neuropathy in Chinese patients with diabetes: A multicenter cross-sectional study. Front Endocrinol. 2018;9:617. doi:10.3389/fendo.2018.00617
26. Goyal RSM, Jialal I. Type 2 diabetes. StatPearls. Updated June 23, 2023. Accessed October 29, 2023. https://www.ncbi.nlm.nih.gov/books/NBK513253/
27. Akbar M, Wandy A, Soraya GV, et al. Sudomotor dysfunction in diabetic peripheral neuropathy (DPN) and its testing modalities: A literature review. Heliyon. 2023;9(7). doi:10.1016/j.heliyon.2023.e18184
28. Pang L, Lian X, Liu H, et al. Understanding diabetic neuropathy: Focus on oxidative stress. Oxid Med Cell Longev. 2020;2020:9524635. doi:10.1155/2020/9524635
29. Sujithra M. Study on polyol pathway and oxidative stress in markers and diabetes mellitus. J Adv Sch Res Allied Educ. 2019;16:366-373.
30. Sandireddy R, Yerra VG, Areti A, Komirishetty P, Kumar A. Neuroinflammation and oxidative stress in diabetic neuropathy: Futuristic strategies based on these targets. Internet J Endocrinol. 2014;2014:674987. doi:10.1155/2014/674987
31. Figueroa-Romero C, Sadidi M, Feldman EL. Mechanisms of disease: The oxidative stress theory of diabetic neuropathy. Rev Endocr Metab Disord. 2008;9:301-314.
32. Sharma S, Kumar A, Kaundal R. Protective effects of 4-amino-1,8-napthalimide, a poly (ADP-ribose) polymerase inhibitor in experimental diabetic neuropathy. Life Sci. 2008;82:570-576.
33. Verrotti A, Prezioso G, Scattoni R, Chiarelli F. Autonomic neuropathy in diabetes mellitus. Front Endocrinol. 2014;5:205. doi:10.3389/fendo.2014.00205
34. Quan D. Diabetic neuropathy: Practice essentials, background, anatomy. Medscape. Updated July 26, 2024. Accessed October 29, 2023. https://emedicine.medscape.com/article/1170337-overview
35. Hosseini A, Abdollahi M. Diabetic neuropathy and oxidative stress: Therapeutic perspectives. Oxid Med Cell Longev. 2013;2013:168039. doi:10.1155/2013/168039
36. Balogh M, Janjic JM, Shepherd AJ. Targeting neuroimmune interactions in diabetic neuropathy with nanomedicine. Antioxidants Redox Signal. 2022;36:122–143. doi:10.1089/ars.2021.0123
37. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care. 2003;26(5):1553–1579. doi:10.2337/diacare.26.5.1553
38. Entezari M, Hashemi D, Taheriazam A, et al. AMPK signaling in diabetes mellitus, insulin resistance, and diabetic complications: A pre-clinical and clinical investigation. Biomed Pharmacother. 2022;146:112563. doi:10.1016/j.biopha.2021.112563
39. Hasanvand A, Amini-Khoei H, Hadian MR, et al. Anti-inflammatory effect of AMPK signaling pathway in a rat model of diabetic neuropathy. Inflammopharmacology. 2016;24:207–219. doi:10.1007/s10787-016-0275-2
40. Xu X, Wang W, Wang Z, et al. DW14006 as a direct AMPKα activator ameliorates diabetic peripheral neuropathy in mice. Diabetes. 2020;69:1974–1988. doi:10.2337/db19-1084
41. Zhang Q, Song W, Zhao B, et al. Quercetin attenuates diabetic peripheral neuropathy by correcting mitochondrial abnormality via activation of AMPK/PGC-1α pathway in vivo and in vitro. Front Neurosci. 2021;15:636172. doi:10.3389/fnins.2021.636172
42. Whaley D, Danev S, Alexander M, Lakey JR. Early detection of peripheral neuropathy by assessment of sudomotor function. Neurol Neurosci. 2024;4(1):002.
43. Tavee J, Zhou L. Small fiber neuropathy: A burning problem. Cleve Clin J Med. 2009;76(5):297–305.
44. Breiner A, Lovblom LE, Perkins BA, Bril V. Does the prevailing hypothesis that small-fiber dysfunction precedes large-fiber dysfunction apply to type 1 diabetic patients? Diabetes Care. 2014;37(5):1418–1424. doi:10.2337/dc13-2005
45. Umapathi T, Tan WL, Loke SC, et al. Intraepidermal nerve fiber density as a marker of early diabetic neuropathy. Muscle Nerve. 2007;35(5):591–598. doi:10.1002/mus.20732
46. Baker LB. Physiology of sweat gland function: The roles of sweating and sweat composition in human health. Temperature. 2019;6(3):211–259. doi:10.1080/23328940.2019.1632145
47. Buchmann SJ, Penzlin AI, Kubasch ML, Illigens BMW, Siepmann T. Assessment of sudomotor function. Clin Auton Res. 2019;29(1):41–53. doi:10.1007/s10286-018-0530-2
48. Machado-Moreira CA, Smith FM, van den Heuvel AMJ, Mekjavic IB, Taylor NAS. Sweat secretion from the torso during passively induced and exercise-related hyperthermia. Eur J Appl Physiol. 2008;104(2):265–270. doi:10.1007/s00421-007-0646-x
49. Azmi S, Jeziorska M, Ferdousi M, et al. Early nerve fibre regeneration in individuals with type 1 diabetes after simultaneous pancreas and kidney transplantation. Diabetologia. 2019;62(8):1478–1487. doi:10.1007/s00125-019-4897-y
50. Tavakoli M, Mitu-Pretorian M, Petropoulos IN, et al. Corneal confocal microscopy detects early nerve regeneration in diabetic neuropathy after simultaneous pancreas and kidney transplantation. Diabetes. 2013;62(1):254–260. doi:10.2337/db12-0574
51. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation. 2007;115(3):387-397.
52. Pfeifer MA, Weinberg CR, Cook DL, et al. Autonomic neural dysfunction in recently diagnosed diabetic subjects. Diabetes Care. 1984;7(5):447-453. doi:10.2337/diacare.7.5.447.
53. Gandhi PG, Gundu HR. Detection of neuropathy using a sudomotor test in type 2 diabetes. Degener Neurol Neuromuscul Dis. 2015;5:1-7. doi:10.2147/DNND.S75857.
54. Low PA. Evaluation of sudomotor function. Clin Neurophysiol. 2004;115(7):1506-1513. doi:10.1016/j.clinph.2004.01.023.
55. Hu Y, Converse C, Lyons MC, Hsu W. Neural control of sweat

secretion: A review. Br J Dermatol. 2017;178. doi: 10.1111/bjd.15808. doi:10.1111/bjd.15808.

56. Hovaguimian A, Gibbons CH. Diagnosis and treatment of pain in small fiber neuropathy. Curr Pain Headache Rep. 2011;15(3):193-200. doi:10.1007/s11916-011-0181-7.
57. Raasing LRM, Vogels OJM, Veltkamp M, van Swol CFP, Grutters JC. Current view of diagnosing small fiber neuropathy. J Neuromuscul Dis. 2021;8:185-207. doi:10.3233/JND-200490.
58. Low VA, Sandroni P, Fealey RD, Low PA. Detection of small-fiber neuropathy by sudomotor testing. Muscle Nerve. 2006;34(1):57-61. doi:10.1002/mus.20551.
59. Themistocleous AC, Ramirez JD, Serra J, Bennett DLH. The clinical approach to small fibre neuropathy and painful channelopathy. Pract Neurol. 2014;14(6):368-379. doi:10.1136/practneurol-2013-000758.
60. Boger MS, Hulgan T, Haas DW, et al. Measures of small-fiber neuropathy in HIV infection. Auton Neurosci. 2012;169(1):56-61. doi:10.1016/j.autneu.2012.04.001.
61. Ziegler D, Papanas N, Rathmann W, et al. Evaluation of the Neuropad sudomotor function test as a screening tool for polyneuropathy in the elderly population with diabetes and pre-diabetes: The KORA F4 survey. Diabetes Metab Res Rev. 2012;28:692-697. doi:10.1002/dmrr.2340.
62. Carbajal-Ramírez A, Hernández-Domínguez JA, Molina-Ayala MA, Rojas-Uribe MM, Chávez-Negrete A. Early identification of peripheral neuropathy based on sudomotor dysfunction in Mexican patients with type 2 diabetes. BMC Neurol. 2019;19:109. doi:10.1186/s12883-019-1332-4.
63. Yajnik CS, Kantikar V, Pande A, et al. Screening of cardiovascular autonomic neuropathy in patients with diabetes using non-invasive quick and simple assessment of sudomotor function. Diabetes Metab. 2013;39:126-131. doi:10.1016/j.diabet.2012.09.004.
64. Khalfallah K, Ayoub H, Calvet JH, et al. Noninvasive galvanic skin sensor for early diagnosis of sudomotor dysfunction: Application to diabetes. IEEE Sensors J. 2012;12(2):456-463. doi:10.1109/JSEN.2010.2103308.
65. Müller G, Parfentyeva E, Olschewsky J, Bornstein SR, Schwarz PEH. Assessment of small fiber neuropathy to predict future risk of type 2 diabetes. Prim Care Diabetes. 2013;7(4):269-273. doi:10.1016/j.pcd.2013.08.001.
66. Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care. 2006;29(6):1294-1299. doi:10.2337/dc06-0224.
67. Park KH, Park KJ. Neurological aspects of anhidrosis: Differential diagnoses and diagnostic tools. Ann Clin Neurophysiol. 2019;21:1. doi:10.14253/acn.2019.21.1.1.
68. Terkelsen AJ, Karlsson P, Lauria G, et al. The diagnostic challenge of small fiber neuropathy. Curr Diab Rep. 2013;13(6):838-844. doi:10.1007/s11892-013-0428-4.
69. Sharma S, Vas P, Rayman G. Small fiber neuropathy in diabetes polyneuropathy: Is it time to change? J Diabetes Sci Technol. 2022;16(2):321–331. doi:10.1177/1932296821996434.
70. Lauria G, Cornblath DR, Johansson O, McArthur JC, Mellgren SI, Nolano M, Rosenberg N, Sommer C. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. Eur J Neurol. 2005;12(9):747–758. doi:10.1111/j.1468-1331.2005.01260.x.
71. Ragé M, Acker N, Knaapen MW, Timmers M, Streffer J, Hermans MP, Sindic C, Meert T, Plaghki L. Asymptomatic small fiber neuropathy in diabetes mellitus: Investigations with intraepidermal nerve fiber density, quantitative sensory testing and laser-evoked potentials. J Neurol. 2011;258(10):1852–1864. doi:10.1007/s00415-011-6031-z.
72. Hoeijmakers JG, Faber CG, Lauria G, Merkies IS, Waxman SG. Small-fibre neuropathies—advances in diagnosis, pathophysiology and management. Nat Rev Neurol. 2012;8(7):369–379. doi:10.1038/nrneurol.2012.97.
73. Løseth S, Stålberg E, Jorde R, Mellgren SI. Early diabetic neuropathy: Thermal thresholds and intraepidermal nerve fibre density in patients with normal nerve conduction studies. J Neurol. 2008;255(8):1197–1202. doi:10.1007/s00415-008-0872-0.
74. Petropoulos IN, Ponirakis G, Khan A, Almuhannadi H, Gad H, Malik RA. Diagnosing diabetic neuropathy: Something old, something new. Diabetes Metab J. 2018;42(4):255. doi:10.4093/dmj.2018.0056.
75. Illigens BMW, Gibbons CH. Sweat testing to evaluate autonomic function. Clin Auton Res. 2009;19(2):79–87. doi:10.1007/s10286-008-0506-8.
76. Freeman R, Chapleau MW. Testing the autonomic nervous system. In: Said G, Krarup C, eds. Handbook of Clinical Neurology. Vol 115. Elsevier; 2013:115–136.
77. Low PA, Caskey PE, Tuck RR, Fealey RD, Dyck PJ. Quantitative sudomotor axon reflex test in normal and neuropathic subjects. Ann Neurol. 1983;14(5):573–580. doi:10.1002/ana.410140513.
78. Peltier A, Smith AG, Russell JW, Sheikh K, Bixby B, Howard J, Goldstein J, Song Y, Wang L, Feldman EL, Singleton JR. Reliability of quantitative sudomotor axon reflex testing and quantitative sensory testing in neuropathy of impaired glucose regulation. Muscle Nerve. 2009;39(4):529–535. doi:10.1002/mus.21210.
79. Krieger SM, Reimann M, Haase R, Henkel E, Hanefeld M, Ziemssen T. Sudomotor testing of diabetes polyneuropathy. Front Neurol. 2018;9:803. doi:10.3389/fneur.2018.00803.
80. Vetrugno R, Liguori R, Cortelli P, Montagna P. Sympathetic skin response: Basic mechanisms and clinical applications. Clin Auton Res. 2003;13(4):256–270. doi:10.1007/s10286-003-0107-5.
81. Levy DM, Reid G, Rowley DA, Abraham RR. Quantitative measures of sympathetic skin response in diabetes: Relation to sudomotor and neurological function. J Neurol Neurosurg Psychiatry. 1992;55(10):902–908.
82. Novak P. Electrochemical skin conductance: A systematic review. Clin Auton Res. 2017;15(3):193–201. doi:10.1007/s10286-017-0467-x.
83. Young ATL, Danev S, Lakey JRT. HRV analysis of autonomic function in aging and disease: Insights from large population samples. Am J Biomed Sci Res. 2024;23(3).MS.ID.003079. doi:10.34297/AJBSR.2024.23.003079.
84. Carmichael J, Fadavi H, Ishibashi F, Shore AC, Tavakoli M. Advances in screening, early diagnosis and accurate staging of diabetic neuropathy. Front Endocrinol. 2021;12:671257. doi:10.3389/fendo.2021.671257.
85. Vinik AI, Nevoret M-L, Casellini C. The new age of sudomotor function testing: A sensitive and specific biomarker for diagnosis, estimation of severity, monitoring progression, and regression in response to intervention. Front Endocrinol. 2015;6:94. doi:10.3389/fendo.2015.00094.
86. Low PA. Testing the autonomic nervous system. Semin Neurol. 2003;23:407–421.
87. Low PA. Clinical autonomic disorders: Evaluation and management. Boston: Little, Brown and Company; 1993:355–365.
88. Lee JB, Lee IH, Shin YO, Min YK, Yang HM. Age- and sex-related differences in sudomotor function evaluated by the quantitative sudomotor axon reflex test (QSART) in healthy humans. Clin Exp Pharmacol Physiol. 2014;41(6):392–399. doi:10.1111/1440-1681.12234.
89. Parashar R, Amir M, Pakhare A, Rathi P, Chaudhary L. Age related changes in autonomic functions. J Clin Diagn Res. 2016;10(3) . doi:10.7860/JCDR/2016/16889.7497.
90. Mal K, Abhishekh HA, Chawla MP, Raju TR, Sathyaprabha TN. Influence of age and gender on the function of postganglionic sympathetic sudomotor axons. Natl Med J India. 2017;30:136-138.
91. Smith AG, Živković S. The hidden costs of painful diabetic neuropathy revealed. Neurol Clin Pract. 2020;10(1):3–4.
92. Kiyani M, Yang Z, Charalambous LT, Adil SM, Lee H-J, Yang S, Pagadala P, Parente B, Spratt SE. Painful diabetic peripheral neuropathy: Health care costs and complications from 2010

to 2015. Neurol Clin Pract. 2020;10(1):47–57. doi:10.1212/CPJ.0000000000000671.

93. Sadosky A, Mardekian J, Parsons B, Hopps M, Bienen EJ, Markman J. Healthcare utilization and costs in diabetes relative to the clinical spectrum of painful diabetic peripheral neuropathy. J Diabetes Complications. 2015;29(2):212-217. doi:10.1016/j.jdiacomp.2014.10.013.
94. Sloan G, Selvarajah D, Tesfaye S. Pathogenesis, diagnosis and clinical management of diabetic sensorimotor peripheral neuropathy. Nat Rev Endocrinol. 2021;17(7):400–420.
95. Gordois A, Scuffham P, Shearer A, Oglesby A, Tobian JA. The health care costs of diabetic peripheral neuropathy in the US. Diabetes Care. 2003;26(6):1790–1795.
96. Calikoglu BF, Celik S, Idiz C, Bagdemir E, Issever H, Calvet J-H, Satman I. Electrochemical skin conductance values and clinical factors affecting sudomotor dysfunction in patients with prediabetes, type 1 diabetes, and type 2 diabetes: A single center experience. Prim Care Diabetes. 2023;17(5):499-505. doi:10.1016/j.pcd.2023.06.002.
97. American Diabetes Association. Statistics about diabetes. Accessed July 28, 2022. https://diabetes.org/about-us/statistics/about-diabetes.