Review article

Sudomotor dysfunction in diabetic peripheral neuropathy (DPN) and its testing modalities: A literature review

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A B S T R A C T

Long term consequences of diabetes mellitus (DM) may include multi-organ complications such as retinopathy, cardiovascular disease, neuronal, and kidney damage. One of the most prevalent complication is diabetic peripheral neuropathy (DPN), occurring in half of all diabetics, and is the main cause of disability globally with profound impact on a patient's quality of life. Small fiber neuropathy (SFN) can develop in the pre-diabetes stage preceding large fiber damage in DPN. Asymptomatic SFN is difficult to diagnose in early stages, with sudomotor dysfunction considered one of the earliest manifestations of autonomic neuropathy. Early detection is crucial as it can prevent potential cardiovascular events. Although punch skin biopsy is the gold-standard method for SFN diagnosis, implementation as routine screening is hindered due to its invasive, impractical, and time-consuming nature. Other sudomotor testing modalities, most of which evaluate the postganglionic cholinergic sympathetic nervous system, have been developed with varying sensitivity and specificity for SFN diagnosis. Here, we provide an overview on the general mechanism of DPN, the importance of sudomotor assessment for early detection of autonomic dysfunction in DPN, the benefits and disadvantages of current testing modalities, factors that may affect testing, and the importance of future discoveries on sudomotor testing for successful DPN diagnosis.

1. Introduction

Long term consequences of diabetes mellitus (DM) may involve multi-organ complications such as retinopathy, cardiovascular disease, neuronal, and kidney damage. One of the most prevalent complication is diabetic peripheral neuropathy (DPN), occurring in half of all diabetics, and is the leading cause of disability worldwide as it profoundly impacts the quality of life due to chronic pain. Furthermore, untreated DPN may lead to a higher risk of falls, foot ulceration, and in several cases, inevitable limb amputation [1,2]. The prevalence of DPN ranges from 21.3 to 34.5% in type 2 DM (T2DM) [3–6] and 7–34.2% in type 1 DM (T1DM) [7–10]. Prevalence becomes 45% in T2DM and 54% in T1DM when asymptomatic neuropathy is included. According to recent cross-sectional studies in US and Europe, DPN prevalence is estimated between 6% and 51% depending on the population studied [11–13].

Small fiber neuropathy (SFN) is a type of peripheral neuropathy that affects the thinly myelinated or the non-myelinated Aδ and C

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fibers, respectively [14,15]. These fibers constitute a large portion of peripheral nerve fibers, carrying information related to temperature and pain perception, in addition to regulation of the autonomic system [16]. Small fiber degeneration is considered to develop in the pre-diabetes stage and precede large fiber damage in DPN, with the process being largely asymptomatic [1,17,18]. During the early degeneration stage of small fibers, repair is highly possible, as observed in studies demonstrating repair processes of early small fiber degeneration following hyperglycaemia normalisation through lifestyle intervention or pancreatic transplantation in T1D, or following weight loss following lifestyle intervention in prediabetics [19,20].

Subclinical diabetic autonomic neuropathy (DAN) commonly occurs within a year or two of T2DM and T1DM diagnosis, respectively [21]. Clinical signs and symptoms usually occur after years of dysregulation onset, and will progress in the absence of effective therapy [16]. Diabetic autonomic neuropathy (DAN) manifests as either cardiovascular autonomic neuropathy (CAN) or sudomotor dysfunction, with the latter being the most studied. CAN is associated with life-threatening complications and other microangiopathic comorbidities [22]. Meanwhile, sudomotor dysfunction, defined as decrease of sweat gland activity, is considered one of the earliest manifestations of autonomic neuropathy [23,24], and occurs due to the inhibition of neurotransmitter release by nerve terminals in the sweat glands [25]. After a period of subclinical dysfunction, sudomotor dysregulation will lead to clinical signs and symptoms such as dry skin, lack of sweat, and cracks on the skin, which may further develop into complications such as ulcers, gangrene, and limb loss [26].

Due to its early involvement, detection of small fiber damage is important for the early diagnosis of neuropathy and for the prevention of further progression. Numerous testing methods are available to assess the small fiber with its own advantages and disadvantages. The sudomotor testing approach is highly potential, but several challenges still exist before routine implementation, such as the requirement of certain technology or skilled personnel that limits use in certain specialized centres, or the lack of standardization of more recently developed approaches [27,28]. Hence in this review, we aim to highlight the mechanism of autonomic dysregulation in DPN and provide a critical appraisal of current techniques and approaches that are available to assess sudomotor function in this population.
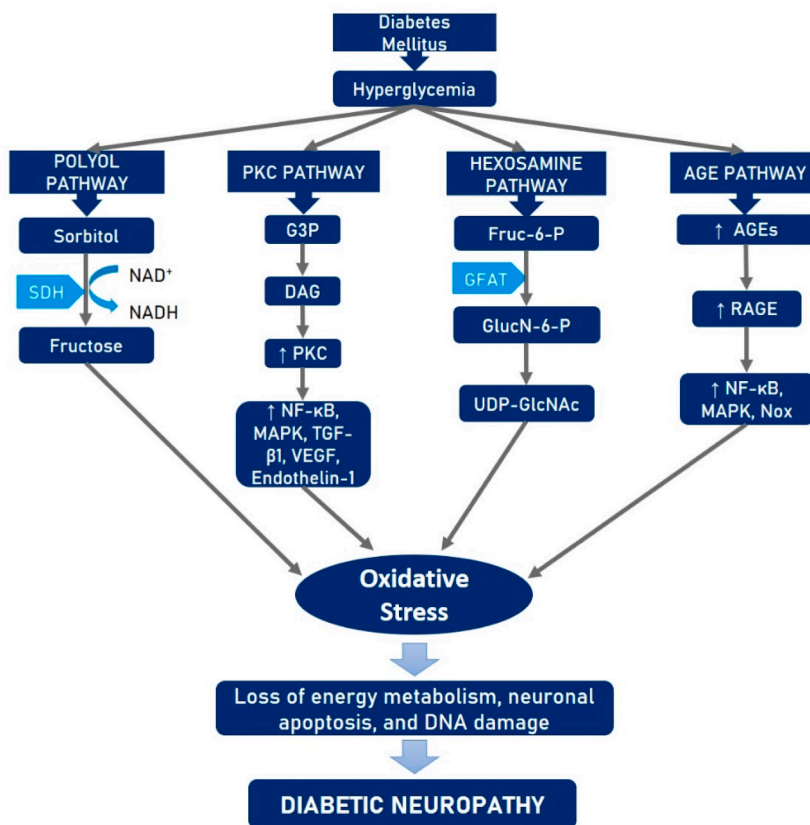

Fig. 1. Common signaling pathways that lead to oxidative stress in the mechanism of diabetic neuropathy. AGEs, advanced glycation end-products: DAF, diacylglycerol; Fruc-6-P, fructose-6-phosphate; G3P, glyceraldehyde 3-phosphate; GFAT, glutamine fructose-6-phosphate aminotransferase; GlcN-6-P, glucosamine-6-phosphate; MAPK, mitogen-activated protein kinase; NAD+, nicotinamide adenine dinucleotide; NADH, reduced from of NAD; NF-κB, nuclear factor-kappa B; Nox, NADPH oxidase; PKC, protein kinase c; ROS, reactive oxygen species; SDH, sorbitol dehydrogenase; TGF-β1, tumor growth factor β1; UDP-GlcNAc, uridine diphosphate N-acetyl-glucosamine; VEGF vascular endothelial growth factor.

2. Mechanism of autonomic dysregulation in diabetic neuropathy

In DPN, both components of both the autonomic and somatic nervous systems are affected. Although the precise mechanisms of DPN are still under investigation, some hypotheses are widely accepted [29]. Potential etiologies include metabolic and autoimmune disorders, neurovascular insufficiency, and growth factor deficiencies [26]. Chronic hyperglycemia is known to increase the production of reactive oxygen species (ROS) that induce oxidative stress, leading to DNA damage, disruption of poly (ADP-ribose) polymerase (PARP), and a decrease in glyceraldehyde 3-phosphate dehydrogenase (GAPDH) [22,30,31]. Four main pathways are triggered under chronic hyperglycemic conditions, namely the polyol, protein kinase c (PKC), hexosamine, and advanced glycation end-products (AGEs) pathway. All are associated with reactive oxygen species (ROS) formation (Fig. 1), leading to the generation or aggravation of oxidative stress [32–34]. Oxidative stress results in the loss of energy metabolism, reduced functional processess, neuronal apoptosis, and is the main cause behind nervous system complications of diabetes due to the eventual damage implicated towards protein, lipids, and DNA [35,36].

Hyperglycemia increases ROS production in the mitochondria. Whilst superoxide (O_2^-), hydrogen peroxide (H_2O_2), and nitric oxide (NO) are normal free radical ROS produced in the body, overproduction can harm the mitochondria and initiate neuropathy [36,37]. Excessive superoxide (O_2) activates poly (ADP-ribose) polymerase (PARP) from NADH/ATP depletion that inhibits GAPDH. Accumulation of upstream glycolytic intermediates activates various pathways like PKC isoforms, hexosamine, and AGE formation [34,38, 39].

The chronic hyperglycemic state leads to the activation of polyol pathways, resulting in sorbitol and fructose accumulation due to glucose conversion by aldose reductase and sorbitol dehydrogenase (SDH) [29,40,41]. Over activation can lead to several metabolic and molecular consequences. Firstly, sorbitol itself is a direct contributor to increased oxidative stress by ROS formation [34]. The polyol pathway has also been associated with a reduction in nerve myoinositol, a decrease in Na+/K + -ATPase membrane activity, and axonal transport failure, all of which result in nerve damage [26,29].

Next is the PKC pathway, typically initiated by activation of diacylglycerol (DAG), although studies have also shown the role of polyol-pathway mediated Na+/K + -ATPase modulation [34]. The DAG synthesis is derived from accumulation of glyceraldehyde 3-phosphate (G3P) which is the result of isomerization of fructose 1,6-bisphosphate. Ultimately, PKC pathway activation affects the mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF-κB) signaling pathways, resulting in altered gene expression and inflammation [22,41,42]. Overactivation of PKC is associated with increased production of agents such as tumor growth factor-β1 (TGF-β1), endotelin-1, NF-κB, dan vascular endothelial growth factor (VEGF) [43], leading to vasoconstriction and decreased neuronal blood flow [44].

Activation of the AGEs pathway leads to the overproduction of AGEs, consequently resulting in cell apoptosis, damage of neuronal integrity, and interference towards cell metabolism and axonal transport. It also stimulates expression of pro-inflammatory mediators (Interleukin-1 (IL-1), Interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), transforming growth factor-β1 (TGF-β1), and vascular cell adhesion molecule-1 (VCAM-1)) by activation of specific receptor RAGEs, increasing oxidative stress [45,46]. Furthermore, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Nox), mitogen-activated protein kinase (MAPK), and various transcription factors such as NF-κB lead to vascular endothelial damage [47].

The final commonly implicated pathway is the hexosamine pathway, shown to play a role in the development of vascular complications and insulin resistance [48]. It involves changes in fructose-6-phosphate (Fruc-6-P) to glucosamine-6-phosphate (GlcN-6-P) by glutamine fructose-6-phosphate aminotransferase (GFAT). In turn, glucosamine-6-phosphate will then be converted into uridine diphosphate N-acetyl-glucosamine (UDP-GlcNAc) through the action of O-GlcNAc transferase. Furthermore, increased GFAT activity will induce neuroinflammation by TNF-α and TGF-β1 expression, a process that has also been implicated in DPN pathology [34].

Aside from oxidative stress, inflammation is another important mechanism involved in DPN since it causes the reduction of neurotrophic growth factors and fatty acids, leading to decreased blood flow, hypoxia, and neuronal damage [26]. DPN has been associated with increased proinflammatory markers like c-reactive protein (CRP), TNF-α, TGF-β, NF-κB, IL-1, IL-6, and IL-12. As an example, studies have observed that relative to normal subjects, those with DPN had higher concentrations of plasma TNF-α, a marker produced by activated macrophages and monocytes, which can cause demyelination of schwann cells or oligodendrocytes [49–51]. Additionally, NF-κB stimulates inducible nitric oxide synthase (iNOS) formation, resulting in the release of inflammatory mediators like NO [34,52], while upregulation of NF-κB activates cyclooxygenase-2 (Cox-2) that results in accumulation of prostaglandin E2 and ROS [53,54]. NF-κB also stimulates cytokines responsible for macrophage invasion of affected nerves and induction of cell apoptosis. Several DPN mechanisms such as cytokine release (IL-1, IL-6, IL-12, and TNF-α), ROS, and proteases are induced by macrophage accumulation in the nerve, which lead to cellular death and myelin disruption, as well as reduced neuronal repair ability [52,55].

Aside from an understanding of pathways leading to neuropathy, it is also crucial to consider mechanisms that may alleviate the alteration and have protective impact in diabetic neuropathy. A prominent example is the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway [56]. The main function of AMPK is to regulate adenosine triphosphate (ATP), and induction of AMPK signaling enhances glucose uptake into cells through increasing glucose transporter 4 (GLUT4) activity and inhibiting intracellular glucose production. Upregulation of AMPK has been shown to exert a protective effect by inhibiting cell death, inflammation, and oxidative stress. Several studies also found improved mitochondrial function, decreased inflammatory agents, and declining glucose levels upon activation of the AMPK pathway [57,58]. On the other hand, AMPK downregulation, often induced by chronic hyperglycemia, has been shown to result in mitochondrial damage, a prominent finding in diabetic neuropathy. Demyelination and axonal dystrophy occurs as an end result following mitochondrial damage of schwann cells mediated by AMPK downregulation [56, 59].

Table 1
Diagnostic modalities of Sudomotor dysfunction.

Sources (Author, Year)	Methodology Described			Conclusions		
	Diagnostic Examination	Measured Parameters	Measurement Methods	Advantages	Disadvantages	Diagnostic Performance
Burgess et al., 2021, Sharma et al., 2022, Carmichael et al., 2021, Quan D 2022, Terkelsen et al., 2017	**Punch skin biopsy** [1,16, 27,29,69]	*Intraepidermal nerve fiber density* (INFD)	A standard 3-mm skin punch skin biopsy sample is obtained from the site of interest, measured, and interpreted in terms of density and number of intraepidermal nerve fibers/millimeter	Current gold standard for the diagnosis of SFN	• Invasive and impractical • Time-consuming • Requires special skills and training to perform sampling and interpretation • Risk of complications such as infection, post operative pain, and bleeding • Cannot be done routinely	Sensitivity (78%–92%) and specificity (65%–90%) for the diagnosis of SFN [74]
Thaisetthawatkul et al., 2013, Buchmann et al., 2018, Raasing et al., 2021, Ziemssen and Siepmann 2019, Illigens and Gibbons 2009, Chesire et al., 2021	**QSART** [60,73, 75,76]	Postganglionic sympathetic cholinergic function	Iontophoresis (inducing sweat using acetylcholine)	• Non-invasive test • High accuracy for the diagnosis of SFN	• Requires special skills and training • Uncomfortable procedure • Time-consuming	Sensitivity 52–80% and specificity ≥80% [76,77]
Ponirakis et al., 2014, Carmichael et al., 2021, Papanas et al., 2012, Quattrini et al., 2008, Tentolouris et al., 2008, Liatis et al., 2007	**Neuropad** [27, 78,79,80]	Quantify small amounts of sweat	Cobalt-salt based chemical reaction (blue to pink color change)	Rapid (10 min) and non-invasive test	• Inconsistency of color grading in several examinations and studies • Varying means of interpretations • No established standard measurement protocol	Sensitivity 70–97.8% and specificity 50–67% [78, 80–82]
Carmichael et al., 2021, Vinik et al., 2015, Carbajal-Ramirez et al., 2019, Casselini et al., 2013, Krieger et al., 2018, Selvarajah et al., 2015, Yajnik et al., 2012, Smith et al., 2014	**Sudoscan** [27, 28,61,70,83]	*Electrochemical skin conductance* (ESC) from sweat on hands and feet	*Reverse iontophoresis* followed by ESC measurement	Rapid and non-invasive test	• Inconsistent cut-off value (52–77 μS) across studies • Expensive price	Sensitivity 70–87.5% (ESC on feet) dan specificity 53–92% [70, 83–86]
Illigens et al., 2009, Ziemssen and Siepmann 2019, Cheshire et al., 2021, Raasing et al., 2021	**Thermoregulatory sweat test** [60, 73,75,76]	Evaluation of the topographic distribution of sweat	Using topographical changes in color indicators in response to sweat (*iodine and starch, quinizarin, alizatin-red*)	Able to determine the topographical distribution of sweat patterns	• Impractical test (requires environmental control with a certain humidity) • Results depend on technique • Long processing time • Requires special skills to perform and interpret the procedure • Not applicable to certain patients (unable to lie down for a certain period of time)	N/A
Gibbons et al., 2008, Siepmann et al., 2017	**QDIRT** [87,88]	Postganglionic sympathetic	Iontophoresis method is applied and results are photographed every 15 s	• Fast and Non-invasive test	• Impractical test (requires controlled	N/A

Table 1 (*continued*)

Sources (Author, Year)	Methodology Described			Conclusions		
	Diagnostic Examination	Measured Parameters	Measurement Methods	Advantages	Disadvantages	Diagnostic Performance
		cholinergic function	for 7 min to assess the characteristics of sweat droplets	• Does not require special techniques	environment with specific temperature and humidity) • Requires further validation	
Raasing et al., 2021, Emad et al., 2013, Al-Moallem et al., 2008, Vetrugno et al., 2003	**Sympathetic Skin Response** [60,89–91]	Sympathetic cholinergic sudomotor function	Assess the amplitude and latency recorded by Electromyography after being given stimuli	• Fast and Non-invasive test • Easy to use	• High variability • Less sensitive • Uncomfortable	Sensitivity 87.5% and Specificity 88.2% in research in Saudi Arabia [89]

QSART: *Quantitative Sudomotor Axon Reflex Test*, QDIRT: *Quantitative Direct and Indirect Axon Reflex Test*; SFN: Small Fiber Neuropathy; N/A: Not Availablenesses

3. The clinical value of sudomotor assessment in diabetic neuropathy

One of the challenges in SFN assessment is the lack of obvious clinical findings, with patients often presenting with normal physical and neurological examination results. In these populations, diagnosis is often difficult as neurological manifestations are not present, and results of coordination, motor, reflex, and sensory examinations are within normal limits [15,60]. It is only in the advanced stages that patients may show a decrease of said signs. Other less prominent local signs that may be observable include reduction in skin moisture, as indicated by the presence of cracked or shiny skin [15].

An early pathology of distal SFN is peripheral autonomic dysfunction, with sudomotor dysfunction being the earliest detectable abnormality. The American Diabetes Association (ADA) has previously recommended sudomotor assessment as strategy for the early neuropathy detection in diabetics [61–63], and many researchers are currently using this for diabetes and even in pre-diabetes [64–67]. Sudomotor testing assesses the sweat glands responsible for sudomotor response, which are innervated by small, unmyelinated C fibers in the dermis that is primarily involved in sympathetic functions [68,69]. Early detection of autonomic dysfunction can help prevent cardiovascular events [28,70]. Furthermore, sudomotor function tests can also be used to detect cardiovascular complications of diabetes, as one of the parameters for the measurement of sympathetic cholinergic function in CAN workup [63].

4. Sudomotor testing modalities in DPN

Sweat glands receive sympathetic nervous system innervation, and are divided into two components; the preganglionic and postganglionic neurons [71]. The preganglionic neuron, which arise from the intermediolateral column of the thoracal and lumbar spinal cord, will synapse with the postganglionic neuron through an acetylcholine-activated nicotinic receptor. The postganglionic neuron stimulates sweat glands by releasing acetylcholine binding on muscarinic receptors in skin [72,73].

Several sudomotor testing modalities are available with varying sensitivity and specificity for SFN detection. Punch skin biopsy remains the gold-standard method for diagnosis SFN with high specificity (65%–90%) and sensitivity (78%–92%) [15,16]. In recent years there has been a steady development of non-invasive sudomotor testing modalities including the quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test (TST), sympathetic skin response (SSR), neuropad, sudoscan, and quantitative direct and indirect axon reflex test (QDIRT). However, lack of availability, inconsistent results, impractical use, time consuming nature, and technical demands of the tests are an obstacle in clinical use [23,70]. The advantages and disadvantages of the sudomotor testing methods are presented in Table 1.

4.1. Punch skin biopsy

The technique is usually performed as 3-mm punch biopsies on the skin of lower extremities, although it can be taken on other locations. Intraepidermal nerve fiber density (IENFD) is quantified through standardized procedure and the results are documented in the number of intraepidermal nerve fibers per millimeter (no/mm^2) [74]. Lack of IENFD in diabetic patient with normal NCS and no clinical manifestation can indicate diagnosis of SFN. In early or mild SFN cases, where reduced nerve fiber density has not occurred, morphologic abnormalities of the fibers can be used for diagnosis [92,93]. Although it has been used as the gold-standard for SFN diagnosis, this technique is invasive and time-consuming. Implementation into routine screening is also difficult as it requires specialized resources such as electron-microscopy, and highly-skilled personals to interpret, rendering it unsuitable for routine screening [62]. And while the occurrence rare, the biopsy procedure also poses risks of infection, pain, and bleeding in certain cases (September 1, 1000) [94].

4.2. Quantitative sudomotor axon reflex test (QSART)

The quantitative sudomotor axon reflex test (QSART) is an alternative examination for the assessment of postganglionic sympathetic cholinergic function [75,95]. In this technique, local sweat production is induced through the iontophoresis of acetylcholine into the skin, which stimulates an axon reflex that ultimately excites neighboring sweat glands. To detect the axon reflex–mediated sweat output, dry gas is passed over the non-stimulated region, and the change in gas humidity is then quantified [15,73]. A software is then utilized to measure parameters such as latency, magnitude, temporal resolution, and duration of the sudomotor response [27]. Several studies reported QSART was abnormal in patients with SFN [15]. Even though QSART is non-invasive procedure and highly sensitive test, it has several disadvantages such as highly technical demands and causing discomfort [75,96].

4.3. Neuropad

Neuropad is a non-invasive screening test based on a chemical reaction, for detection of diabetic neuropathy in 10 min. It works thorugh observation of a color change on the foot of a patient with suspected neuropathy, which indicate the sudomotor function. A cobalt-salt containing adhesive pad is attached for 10 min on the soles of the subject's foots. Normally, a blue-to-pink color change is observable on the patch, but in subjects with impaired sweat function the pad will remain blue or turn patchy in color [78,97]. This abnormal response on the neuropad is typically found in subjects with autonomic neuropathy. The neuropad has several advantages including speed, easy and painless use, with potential for self-administration [16,60]. However, studies have been inconsistent regarding the placement location of the neuropad on the foot, and the neuropathy disability score (NDS) cut-off value selected to suggest clinical DPN. Additionally, there have been varied interpretation of the results, with studies using parameters such as percentage change [78], score out of 1 [79], and normal or abnormal [98]. To address these challenges, a smartphone based software with integrated image processing system (Digital therapeutics; DTx app) has been developed to increase the neuropad diagnostic performance [27].

4.4. Sudoscan

Sudoscan is a tool used to measure electrochemical skin conductance (ESC) of sweat in the hands and feet, following sweat induction using the reverse iontophoresis technique [28,83]. A low-voltage current across the electrodes will draw chloride ions out of the sweat glands and result in changes of skin conductance. In other words, the technique measures a reaction between the chloride ions and stainless steel-based plate electrodes placed on hands and feet. An abnormal response present as reduced ESC, which indicate sweat gland dysfunction [70]. Due to higher result variability on the hands, ESC measurements on the feet are preferred for the detection of diabetic neuropathy. This tool exhibits some advantages because it is non-invasive, easy to perform, minimal clinician error, and good combination with IENFD and QSART [28,61,83]. Several studies showed high sensitivity of foot-ESC results for DPN detection (70–87.5%). However, due to the use of varying ESC cut-off points of sudomotor dysfunction that range between 52 uS [84] and 77 uS [85], a broad range of specificity also exists in the literature, ranging from 53 to 92% [84–86]. Additionally, more evidence is required to validate the tool before use as a routine DPN screening method, as some studies have shown no significant ESC differences between DPN patients and controls [73,99].

4.5. The sympathetic skin response (SSR)

Another simple and non-invasive approach is the sympathetic skin response (SSR), which assesses the transient change in electrical potential generated by multisynaptic reflex of the sweat glands in response to a various stimulus (electric, magnetic [26,100,101], or emotional state [102]). In this technique, surface electrodes are placed on the skin and then connected to a standard electromyogram instrument [26,103]. The SSR is determined by measuring changes in skin conductance, which are recorded following sudomotor stimulation in areas with the most eccrine glands such as palms or soles [103]. However due to the varying amplitude and latency of SSR waveforms [104] and its tendency to habituate with closely repeated stimuli [105], the SSR can't be used to quantitatively assess sudomotor function. Other disadvantages include the fact that the SSR evaluation is based on the appearance of a response rather than a comparison with a reference range. Older people may also show no SSR waveform [106], while a normal result in cases of dysautonomia shouldn't be ignored if the clinical features were found. Due to these reasons, the SSR is still rendered not sufficiently reliable for diagnostic purposes [101].

4.6. Thermoregulatory sweat test (TST)

The thermoregulatory sweat test (TST) is a semiquantitative technique that assess sudomotor function at both pre- and post-ganglionic levels. The TST is performed by increasing the core temperature using heat stimuli. Required environmental settings are a standard temperature of 45–50 °C and humidity control (35–40%) while the subject is in a supine position for 45–65 min [28,73,107]. Prior to the induction, the skin surface is covered with agents such as iodine and starch, quinizarin, or alizarin-red. And as sweat is released and interact with said agents, color changes according to sweat distribution can be observed [108], whilst a lack of color change indicates autonomic dysfunction such as hypohidrosis or anhidrosis [109]. The advantage of this technique is the ability to identify sweat topography and remains an indispensable tool in the diagnosis of neurological disorders such as neuropathies, ganglionopathies, or generalized autonomic failure. However, the technique is technically demanding and impractical, and is unable to

distinguish pre- and postganglionic sudomotor lesion [73,75].

4.7. Quantitative direct and indirect test of sudomotor function (QDIRT)

The QDIRT is a postganglionic sudomotor assessment measuring axon-reflex-induced sweating with iontophoresis of acetylcholine in skin. The indicator dye (povidone-iodine and cornstarch) is first placed on the volar side of the forearm, and images are repeatedly taken every 15 s until 7 min with higher resolution of digital camera upon iontophoresis. Several evaluated parameters of sweat droplets in the axon reflex region include its size and number, as well as its axon-reflex spread. Axon reflex region is the result of total area of sweating with excluding area in contact with acetylcholine. Although it is a rapid, non-invasive test with low technical demands, this technique is not validated and requires controlling specific temperature humidity [73,87].

5. Factors affecting sweat excretion

Another important point to consider aside from the variety of available techniques, is the multitude of factors that may impact sweat excretion therefore affecting the results of sudomotor assessment. The increase in sweat excretion depends on the activated sweat gland density (ASGD), the sweat output rate per gland (SGO), or a combination of both [110]. There are several factors (internal and external) that influences this [111]. The internal factors include age [112], gender [113], race [114], body mass [115], circadian rhythm [116], and menstrual cycle [117,118]. To illustrate, the elderly tend to display reduced sweat function relative to younger age groups [119,120], the mechanism of which is likely related to the decline in aerobic fitness levels. Another potential age-related mechanism is reduced sensitivity with age, hence leading to heat acclimation [121–123]. In women, the density of sweat glands was found to be greater than men [124,125]. However, men have higher sweating rates and metabolic heat production than women because of the higher cholinergic responsiveness and maximal sweating rate in men [124,126–128]. However, a cross-sectional study showed that body mass and heat-producing metabolism matter more than gender [129,130]. Certain race and ethnicities demonstrate no significant differences in either regional or whole-body sweating rates [114]. But people who live in tropical or hot climates were found to have lower ASGD and SGO due to heat adaptation [131,132].

Thermal stimuli and physical exercise are the main factors that stimulate eccrine sweat glands [133–135]. The mechanism of sweat gland activation differs slightly depending on the type of stimuli. An increase in environmental heat stress (due to either increased room temperature and solar radiation or a decline in air velocity) affects the whole-body and regional sweating rate by elevating the core body temperature [136]. As core body temperature increases, induction of both central and regional thermoreceptors occur, which then convey the stimulation to the anterior hypothalamus (preoptic area) [137–139].

Meanwhile, sweating due to exercise stimuli is associated with increased skin temperature, central command, mechanoreceptors, metaboreceptors, and baroreflexes [110,140,141]. Emotional stimuli such as pain, fear, or anxiety activates eccrine and apocrine sweat glands, resulting in higher sweat output especially in the palms, soles, face, and axilla [135,142]. Dehydration states can also affect sweat output by decreasing the sensitivity and increasing the threshold temperature affecting sweating [143–145]. Hypovolemic states can also reduce sweat sensitivity [146], although results have been inconsistent [147]. The use of clothing and covering of the whole body will increase the regional sweating rate and the whole-body sweating rate [148].

Certain substances have also been shown to affect sweating rate or output. Studies have shown that caffeine consumption increases ASGD and sweating sensitivity through stimulation of the autonomic nervous system [149,150]. Certain medications can also result in either hyperhidrosis (excessive sweating) or hypohidrosis (deficient sweating). Drugs that stimulate excessive sweating are acetylcholinesterase inhibitors [151], selective serotonin reuptake inhibitors [152], opioids [153] and tricyclic antidepressants [154–156]. Meanwhile, drugs that cause decreased sweating are antimuscarinic anticholinergic agents [157], carbonic anhydrase inhibitors [158], botulinum toxins [159], and antipsychotic agents [160].

6. Conclusion

Diabetic peripheral neuropathy is a highly common and debilitating complication of diabetes. Since SFN constitutes the earliest changes, detection of autonomic change in the form of sudomotor dysfunction is a strategic option for early diagnosis and monitoring, in order to prevent further complications. Because punch biopsy, the current gold-standard method, is impractical and cumbersome for routine screening, many alternative sudomotor assessment strategies have been developed over the past few years, each with its own advantages and disadvantages. Future protocols need to consider the multitude of factors that may affect the results of sudomotor assessment, and future work should focus on innovative approaches for more practical and precise detection of sudomotor dysfunction in an effort to prevent the debilitating consequences of DPN.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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