ORIGINAL ARTICLE

Sudoscan, a Noninvasive Tool for Detecting Diabetic Small Fiber Neuropathy and Autonomic Dysfunction

Carolina M. Casellini, MD, Henri K. Parson, PhD, Margaret S. Richardson, BS,
Marie L. Nevoret, MD, and Aaron I. Vinik, MD, PhD, FCP, MACP, FACE

Abstract

Objective: Sudomotor dysfunction may be an early detectable abnormality in diabetic small fiber neuropathy. The aim of this study was to evaluate the efficacy of Sudoscan™ (Impeto Medical, Paris, France) in detecting diabetic neuropathy (DN), in comparison with other standardized tests, in patients with diabetes mellitus (DM).

Subjects and Methods: Sudoscan measures electrochemical skin conductance (ESC) of hands and feet through reverse iontophoresis. We evaluated 83 DM patients with and without DN and 210 healthy controls (HCs). Neuropathy Impairment Score—Lower Legs (NIS-LL), quantitative autonomic function testing (QAFT), and quantitative sensory testing (QST) were performed. Symptomatic pain was recorded using a visual analog scale. Receiver-operator characteristic (ROC) curves were calculated to evaluate the efficacy of Sudoscan in detecting DN compared with traditional modalities.

Results: Diabetes patients with DN had significantly worse ESCs of feet and hands than DM patients without DN and HCs (respectively, 56.3 ± 3 vs. 75.9 ± 5.5 and 84.4 ± 0.9 [$P < 0.0001$] for feet and 51.9 ± 2.4 vs. 67.5 ± 4.3 and 73.1 ± 0.8 [$P < 0.0001$] for hands). Increasing NIS-LL scores were associated with decreasing ESC values. ESCs correlated significantly with clinical (NIS-LL), somatic (QST), and autonomic (QAFT) measures of neuropathy and with pain scores. ROC curve analysis showed significant results for both hands and feet ESC (area under the curve of 0.86 and 0.88, respectively; $P < 0.0001$) with sensitivity of 78% and specificity of 92% for feet to detect DN.

Conclusions: Sudoscan is a promising, sensitive tool to detect neuropathy in patients with DM. This is a very simple, easy-to-perform test that can be done in the clinical setting in 3–5 min.

Introduction

DIABETIC PERIPHERAL NEUROPATHIES (DPNs) are among the most frequent complications of diabetes mellitus (DM), affecting up to 70% of patients over a lifetime. The typical DPN is a chronic, symmetrical, length-dependent sensorimotor polyneuropathy and is thought to be the most common variety.¹ It often involves predominantly distal small nerve fibers and often presents as painful neuropathy.² The course of a diabetic sensorimotor polyneuropathy is insidious, however, and up to 50% of patients with neuropathy may be asymptomatic³—often resulting in delayed diagnosis, reduced quality of life, and increased morbidity, mortality, and economic burden.

Changes in peripheral autonomic nervous system function are an early manifestation of distal small fiber neuropathy.¹ Sudomotor dysfunction is one of the earliest detectable neurophysiologic abnormalities in distal small fiber neuropathies. Sweat glands are innervated by small, unmyelinated sympathetic C nerve fibers that are responsible for the sweat re-

sponse. Skin biopsies have confirmed that numbers of epidermal C-nerve fibers are reduced in patients with diabetes.⁴ Furthermore, degeneration of small C-fibers innervating sweat glands has been observed in diabetes patients. Abnormalities in sudomotor function in diabetes patients were noted to correlate with the presence of autonomic neuropathy.⁵ Thus, sudomotor function represents an attractive tool to evaluate the peripheral autonomic system in people with DM.⁶ The various techniques of sudomotor function testing are variably sensitive and specific for the detection of distal small fiber neuropathy.⁷ However, most have remained underutilized in clinical practice because of lack of availability, inconsistency of results, and technical demands of the tests, with some being tedious, cumbersome, and time consuming.

Sudoscan™ (Impeto Medical, Paris, France), a simple, noninvasive, easy-to-perform sudomotor test, was recently developed to allow the measurement of sweat gland function.^{8–10} This test is based on the electrochemical reaction between the chloride ions in sweat and stainless steel-based plate electrodes, on which the subject's hands and feet are

placed.^{11,12} A low-voltage current (<4 V) is applied through the electrodes, attracting chloride ions from the sweat glands (which are densely concentrated on the palms and soles). A measurement of conductance for the hands and feet is generated from the derivative current associated with the applied voltage.¹³ The aim of this study was to evaluate Sudoscan as a tool for assessing neuropathy in patients with DM, to examine the efficacy in detecting diabetic neuropathy (DN) in comparison with other standardized tests and to evaluate its role in discriminating painful from nonpainful neuropathy.

Subjects and Methods

The study population consisted of 83 patients with type 1 or 2 DM with and without DPN, diagnosed using the current Toronto classification of DPN.¹ Diabetes patients were compared with a database of 210 healthy controls (HCs) provided by Impeto Medical. Test-retest reliability was performed in 112 HCs. The study was approved by the Institutional Review Board of Eastern Virginia Medical School.

Sudomotor testing, quantitative sensory testing (QST), and quantitative autonomic function testing (QAFT) were performed on each participant. Complete physical and neurological examinations were done by a highly trained and skilled clinician.

Neuropathy measurements

All subjects received a complete neurological examination comprising six components: the neurological symptom score, cranial nerve function, and an evaluation of muscle weakness, muscular atrophy, bilateral reflexes, and sensory function of upper and lower extremities. Motor, Sensory, and Total Neuropathy Impairment Score—Lower Legs (NIS-LL) values, originally developed by Dyck¹⁴ and modified by us,¹⁵ were calculated for all patients.

QST was used to evaluate peripheral sensory perception. We used our previously published methods and algorithms for measuring small fiber somatosensory function, including vibration perception, pressure perception, cold and warm thermal sensation detection thresholds, and cold- and heat-induced pain detection thresholds at the big toes.^{15–17} For each of these stimuli we applied the method of limits: four trials with an interstimulus interval randomly varying from 4 to 20 s (model TSA 2001/VSA 3000; Medoc Advanced Medical, Minneapolis, MN). Thresholds were calculated as the mean stimulus intensity level over all four responses. Results are reported as δ from baseline, which is the difference between baseline and detection threshold temperature.

Symptomatic pain was recorded using a visual analog scale (11-point numerical rating scale), and pain sensitivity was determined using the Norfolk Pain Scale ratings using mechanical and cold pain perception.

QAFT was performed, as previously described.¹⁸ Power spectral analysis of heart rate variability was assessed using ANSAR (ANX 3.0 software; ANSAR Group, Inc., Philadelphia, PA). Time- and frequency-domain analyses were performed. Time-domain analysis provides a measure of the sympathetic and parasympathetic control of the heart beat (the R-R interval on an electrocardiogram) recorded with maneuvers including deep breathing, Valsalva, and standing from the sitting position, whereas frequency-domain analysis is performed under resting conditions.¹⁸ Given their com-

plementary nature both were used in this study. Specifically, total spectral power is the average low frequency plus high frequency for each phase during baseline, deep breathing, Valsalva, and postural stimulations. The sample difference of the beat-to-beat (NN) intervals measures heart rate variability and has been shown to be significantly impaired in both recently diagnosed and established diabetes patients compared with HCs in prior studies.¹⁹ The total spectral power was calculated, as well as the SD of all normal R-R intervals, a measure of both sympathetic and parasympathetic action on heart rate variability, and the root-mean square of the difference of successive R-R intervals, a measure primarily of parasympathetic activity. Baroreflex-mediated sympathoexcitation contributes to the development and progression of many cardiovascular disorders; thus, the quantitative estimation of the arterial baroreceptor-heart rate reflex is now regarded as a synthetic index of neural regulation at the sinus atrial node.²⁰ Low-frequency power, measured during power spectral analysis, was used to quantify baroreflex function.^{21,22}

Sudomotor function assessment

Sudoscan is a new patented device designed to perform precise evaluation of sweat gland function based on sweat chloride concentrations through reverse iontophoresis and chronoamperometry.^{8–10} The apparatus consists of two sets of large-area stainless steel electrodes for the hands and feet that are connected to a computer for recording and data-management purposes; the electrodes are alternately used as an anode or cathode, and a direct current incremental voltage of ≤ 4 V is applied to the anode. Through reverse iontophoresis, the device generates voltage to the cathode and a current (intensity of around 0.2 mA) between the anode and cathode proportional to chloride concentration. At low voltages (<10 V), the stratum corneum is electrically insulating, and only sweat-gland ducts are conductive (Supplementary Fig. S1; Supplementary Data are available online at www.liebertpub.com/dia). The electrochemical skin conductance (ESC), expressed in microSiemens (μS), is the ratio between the current generated and the constant DC stimulus (≤ 4 V) applied to the electrodes. Sudomotor dysfunction is evaluated according to the ESC measured on the feet: $>60 \mu S$ =no dysfunction; $60\text{--}40 \mu S$ =moderate dysfunction; and $<40 \mu S$ =severe dysfunction. These threshold values have been defined on the basis of previous studies,^{8,10} and we have used a normative database on 210 subjects. During the test, patients were required to place their hands and feet on the electrodes and to stand still for 2–3 min. The device produces ESC results for individual right and left hands and feet. It then calculates an average score between right and left hands and feet. All the ESC results presented in this study correspond to the average ESC between right and left sides for both hands and feet. Neither special subject preparation nor specially trained medical personnel are required. The reproducibility of this sweat function measurement had been successfully validated in previous studies, and interdevice reproducibility has been confirmed through measurements with two different devices.^{10,23}

Statistical analysis

Continuous data are presented as mean $\pm$ SEM values. Analysis of variance was used to compare mean differences

between the groups. If significance was observed, post hoc analysis was performed (Tukey–Kramer test). Correlation was determined using Spearman's rho rank tests. Association between ESC and biological determinants (age, gender, body mass index, presence of DM, presence of neuropathy, etc.) was tested using multiple linear regression analysis. We constructed receiver-operator characteristic (ROC) curves to evaluate the sensitivity and specificity of Sudoscan in detecting DN compared with traditional modalities. We used the NIS-LL total score as the gold standard measure of the degree of neuropathy based on the cutoff values extracted from a large group of healthy subjects. JMP Pro 10.0 software (SAS Institute, Inc., Cary, NC) was used for all statistical analyses. Significance was accepted at the $P < 0.05$ level.

Results

Eighty-three patients with DM were included in the study and compared with a database of 210 HCs provided by Impeto Medical. Demographic characteristics of both groups are presented in Supplementary Table S1. Twenty patients had type 1 DM, and 63 patients had type 2 DM. Sixty patients had neuropathy with a total neuropathy score of >2 . HCs were not age and gender matched with DM patients because this database was provided by the sponsor. However, ESC values of feet and hands were not influenced by either age or gender on a multiple linear regression model (see below).

Sudoscan was accepted by the subjects without complaints; none of the subjects experienced discomfort during the test, and no safety events were reported.

ESC values of both feet and hands were significantly better in HC and DM patients without DN compared with DM patients with DN (Fig. 1 and Supplementary Table S2).

FIG. 1. Feet and hands electrochemical skin conductance (ESC) in healthy control (HC) subjects and diabetes mellitus (DM) patients with and without diabetic neuropathy. Data are mean $\pm$ SEM values. $*P < 0.0001$ versus HC and DM without neuropathy (by analysis of variance with post hoc analysis).

DM patients with painful DN had significantly worse ESC of their feet than patients with nonpainful DN (52.8 ± 3.6 vs. 68 ± 6.6 , $P < 0.05$) (Supplementary Fig. S2).

Type 1 DM patients with neuropathy had feet and hands ESC values similar to those of type 2 DM patients with neuropathy (48.75 ± 6.47 vs. 59.58 ± 3.70 [$P = \text{not significant}$] for feet and 49.86 ± 4.79 vs. 52.84 ± 2.91 [$P = \text{not significant}$] for hands).

An association was detected between NIS-LL scores and ESC in the feet. Increasing NIS-LL scores were associated with decreasing ESC (Supplementary Fig. S3). An ESC of $<60 \mu\text{S}$ was considered abnormal. Patients with abnormal feet ESC readings had significantly worse motor, sensory and total NIS-LL scores (Fig. 2).

ESCs correlated significantly with clinical (NIS-LL), somatic (QST), and autonomic (QAFT) measures of neuropathy and with pain scores (Table 1).

On multiple linear regression analysis, lower feet ESC was independently associated with higher NIS-LL total scores ($P < 0.001$) and with the presence of neuropathy ($P < 0.05$) but not with age, gender, or body mass index. ROC curve analysis, used to evaluate sensitivity and specificity of Sudoscan in detecting DN showed significant results for both hands and feet ESC (area under the curve of 0.86 and 0.88, respectively; $P < 0.0001$) with sensitivity of 78% and specificity of 92% for feet. The NIS-LL total score showed an area under the curve of 0.8429 with sensitivity of 76% and specificity of 86% (Table 2 and Fig. 3).

Test-retest reliability in 112 HCs was excellent for the feet with a correlation coefficient of 0.814 ($P < 0.0001$) and a mean percentage change of 1.15% after the maximum O_2 intake volume ($\text{VO}_{2\text{max}}$) test (Supplementary Fig. S4). Association between left and right side measurements of ESC in feet and

FIG. 2. Motor, sensory, and total Neurologic Impairment Score—Lower Legs M-NISLL, S-NISLL, and T-NISLL, respectively; scores in patients with normal ($\geq 60 \mu\text{S}$) versus abnormal ($<60 \mu\text{S}$) electrochemical skin conductance (ESC) of the feet. Data are mean $\pm$ SEM data. $*P < 0.0001$ by analysis of variance.

TABLE 1. SIGNIFICANT SPEARMAN'S RHO RANKED CORRELATIONS OF HAND AND FEET ELECTROCHEMICAL SKIN CONDUCTANCE VALUES WITH QUANTITATIVE AUTONOMIC FUNCTION TESTING RESULTS, NEUROPATHY IMPAIRMENT (LOWER LEGS) SCORES, AND PAIN SCORES IN 83 DIABETES MELLITUS PATIENTS

<i>Traditional tests for DN</i>	<i>Mean ESC</i>	<i>Spearman's rho</i>	<i>P value</i>
Clinical neuropathy scores			
NIS-LL motor score	Feet	-0.4773	<0.0001
	Hands	-0.3144	0.0064
NIS-LL sensory score	Feet	-0.2951	0.0107
	Hands	-0.2612	0.0246
NIS-LL total score	Feet	-0.3969	0.0005
	Hands	-0.3256	0.0046
QST (big toe)			
Pressure	Feet	-0.4048	0.0064
CS threshold	Feet	-0.3041	0.0336
WS threshold	Feet	-0.2841	0.0500
CP threshold	Feet	-0.3028	0.0345
Autonomic function measures ^a			
E/I ratio	Feet	0.2744	0.0175
	Hands	0.3708	0.0012
DB LFA	Feet	0.2635	0.0299
	Hands	0.3921	0.0009
DB RFA	Feet	0.3620	0.0018
	Hands	0.4726	<0.0001
DB TSP	Feet	0.2859	0.0149
	Hands	0.3694	0.0014
DB sdNN	Feet	0.2424	0.0402
	Hands	0.3374	0.0038
Val LFA	Hands	0.2778	0.0181
Val RFA	Feet	0.2480	0.0357
	Hands	0.2985	0.0109
Pain scores			
Average pain score	Feet	-0.3663	0.0170

^aData are log transformed.

CP, cold pain; CS, cold sensation; DB, deep breathing; DN, diabetic neuropathy; E/I ratio, expiration/inspiration ratio; ESC, electrochemical skin conductance; LFA, low-frequency band; NIS-LL, Neurologic Impairment Score—Lower Legs; QST, quantitative sensory testing; RFA, high-frequency band; sdNN, sample difference of the beat-to-beat (NN) variability; TSP, total spectral power; Val, Valsalva; WS, warm sensation.

hands in 210 HCs was excellent. The mean percentage difference between measurements on the right and left side was 0.8% for hands and 0.15% for feet, with correlation coefficients of 0.91 and 0.93, respectively ($P < 0.0001$) (Supplementary Fig. S5).

Discussion

This study shows that:

1. ESC of hands and feet is decreased in patients with DN diagnosed using the current Toronto classification of DPN,¹ compared with HCs and DM patients without neuropathy.
2. Sudoscan results correlate significantly with clinical measures of neuropathy, somatic and autonomic function testing, and pain scores.
3. Sudoscan is a sensitive tool to detect neuropathy in patients with DM, with a sensitivity of 78% and a specificity of 92%, equivalent to or better than clinical neuropathy scores.
4. Feet ESC was significantly decreased in patients with painful DN compared with the value in patients with nonpainful neuropathy.
5. Test-retest reliability is excellent for the feet.

These results suggest that sudomotor function, evaluated through reverse iontophoresis (Sudoscan), is a reliable option when evaluating diabetes patients for the detection of small fiber neuropathy and peripheral autonomic neuropathy. Combined with a simple bedside test as the NIS-LL, Sudoscan may increase the effectiveness in detecting neuropathy. Dyck et al.²⁴ have shown significant inconsistencies on clinical neurological evaluations performed by different blinded physicians; the advantage of incorporating Sudoscan for the detection of neuropathy is that it eliminates the subjective component of the clinician error.

Several studies have evaluated the efficacy and reproducibility of Sudoscan in detecting DN during the past 2–3 years. Yajnik et al.²⁵ evaluated different neuropathy assessments on 265 diabetes patients and found that ESC measurements between the left and right side varied by 9.5% for hands and 6.0% for feet, compared with 14.2% for the vibration perception threshold test. Lower measures of ESC were significantly associated with increasing symptoms on the Michigan Neuropathy Scoring Instrument A, which evaluates the presence of small and large fiber neuropathy symptoms; increasing physical abnormalities on the Michigan Neuropathy Scoring Instrument B, which includes feet inspection, vibration perception, ankle reflexes, and monofilament perception; and increasing scores on the vibration perception threshold test, reflecting impaired vibration perception. Patients with an ESC of $< 40 \mu S$ were more than four times as likely as patients with an ESC of $\geq 40 \mu S$ to have two or more abnormal cardiac autonomic neuropathy tests with an odds ratio of 4.41 (95% confidence interval, 1.72–11.29). Of note is that $40 \mu S$ is a much

TABLE 2. DIAGNOSTIC EFFICIENCY OF FEET AND HANDS ELECTROCHEMICAL SKIN CONDUCTANCE TO REFLECT DIABETIC NEUROPATHY (NEUROLOGIC IMPAIRMENT SCORE—LOWER LEGS)

	<i>Criterion^a</i>	<i>Sensitivity</i>	<i>Specificity</i>	<i>+LR</i>	<i>–LR</i>	<i>+PV</i>	<i>–PV</i>
Hands ESC	64	78.33	85.71	5.48	0.25	61.04	93.26
Feet ESC	77	78.34	92.38	10.28	0.23	74.6	93.72
Total NIS-LL	1.5	76.67	85.71	5.37	0.27	95.83	46.15

^aCriterion corresponding to the highest Youden index.

ESC, electrochemical skin conductance; +LR, positive likelihood ratio; –LR, negative likelihood ratio; NIS-LL, Neurologic Impairment Score—Lower Legs; +PV, positive predictive value; –PV, negative predictive value.

FIG. 3. Electrochemical skin conductance of (a) hands and (b) feet receiver-operator characteristic curve to reflect diabetic neuropathy. (a) Area under the curve=0.8563, $P<0.0001$. (b) Area under the curve=0.8755, $P<0.0001$.

lower value than what is defined as the normal cutoff value. Lower ESC was specifically associated with postural fall in blood pressure, a measure of sympathetic cardiac autonomic neuropathy.²⁵

Mayaudon et al.⁸ measured sensitivity, specificity, and reproducibility of Sudoscan among 133 type 2 DM patients compared with 41 HCs. ESC showed a sensitivity of 75% and a specificity of 100%, with an area under the ROC curve of 0.88, similar to our current report. These researchers also showed low coefficients of variation between the left and right on both hands and feet measurements (15% and 7%, respectively). A similar study among 142 French diabetes patients showed that reduction in foot ESC measurements from $66 \pm 17 \mu\text{S}$ to $43 \pm 39 \mu\text{S}$ correlated with an increasing vibration perception threshold from $<15\text{V}$ to $>25\text{V}$ ($P=0.001$), regardless of blood glucose levels.⁹ Another study on type 1 and type 2 DM patients from an outpatient clinic in Germany was conducted parallel to standard care. Fifty-two patients with type 1 DM and 115 patients with type 2 DM (69 receiving insulin) were observed for 1 year. Hand and foot conductances were lower in patients with type 2 DM compared with patients with type 1 DM at baseline. After 1 year, a slight decrease in hand and foot ESC was observed in patients with type 2 DM without insulin, whereas an increase was observed in patients receiving insulin (-3.8 ± 9.7 vs. $1.0 \pm 9.7 \mu\text{S}$ [$P=0.02$] for the hands and -2.2 ± 7.5 vs. $4.1 \pm 8.8 \mu\text{S}$ [$P<0.001$] for the feet). The question remains as to whether this improvement is related to better glycemic control or is an effect of insulin per se on nerve conduction or ion transport. Coefficient of correlation between measurements performed with two different devices was 0.85 for hands and 0.93 for feet ($P<0.001$).²³

Beyond its potential for diabetes screening, Sudoscan may play an important role in following patients' response to clinical intervention or investigational therapies. A large study was recently completed in Finland using Sudoscan to assess cardiometabolic disease risk status and its change in response to lifestyle intervention. Of 537 women and 113 men who underwent a cardiovascular risk evaluation and ESC measurement at baseline, those with the highest cardiovascular risk were invited to participate in a 12-month physical activity program. For the 154 women with the lowest fitness level at baseline, a statistically significant change in waist

circumference, weight, body fat percentage, $\text{VO}_{2\text{ max}}$, and hands and feet ESC was observed after 1 year. The increase in $\text{VO}_{2\text{ max}}$ and ESC were highest in subjects with the highest weekly activity level. Correlation between Sudoscan risk score and $\text{VO}_{2\text{ max}}$ was $r=-0.57$, $P<0.0001$ for women and $r=-0.48$, $P<0.0001$ for men.²⁶ Although larger studies that include more men are required to confirm these results, the outcome of this study suggests not only that lifestyle intervention using moderate physical activity can have a significant impact on cardiovascular risk, but also that a simple tool like Sudoscan can be used in interventional programs to assess and monitor changes in cardiovascular risk.

Our results are in accordance with those of others, as discussed above. Moreover, in our study we found a significant correlation between ESC and pain scores, with feet ESC being significantly decreased in patients with painful DN compared with patients with nonpainful neuropathy. Although the number of patients included was small, these observations warrant further study.

Several reliable and validated techniques of sudomotor function testing are currently available.⁶ However, most are actually underutilized in the clinical setting. This is owing, in part, to requirements of very specialized equipment, complicated patient preparation, highly trained technicians for test performance and/or interpretation, and prolonged testing time. Sudoscan appears to address all these shortcomings.⁷

In conclusion, Sudoscan is a promising, sensitive tool to detect neuropathy in patients with DM. Sudoscan testing is entirely painless, can be conducted in 3 min, and requires no special patient or equipment preparation. Test administration and result interpretation also demand no special training. It is objective, reproducible, and quantitative, requiring no patient cooperation. Further larger studies including different age groups and ethnic populations are needed to confirm these findings, as well as interventional studies to assess the utility of this tool as an objective measure of small fiber neuropathy and peripheral autonomic dysfunction. Sudoscan may become an invaluable tool for today's clinicians, whether the potential applications are screening for early diagnosis of DN, assessing response to different therapeutic interventions in diabetes subjects, or even as a predictive tool for the development of insulin resistance and diabetes.

Acknowledgments

This research study was supported by a grant from Impeto Medical.

Author Disclosure Statement

No competing financial interests exist.

References

1. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Lauria G, Malik RA, Spallone V, Vinik A, Bernardi L, Valensi P: Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010;33:2285–2293.
2. Alport AR, Sander HW: Clinical approach to peripheral neuropathy: anatomic localization and diagnostic testing. *Continuum (Minneapolis)* 2012;18:13–38.
3. Vinik A, Nevoret M-L: Neuropathy in prediabetes and the metabolic syndrome. Prevention of type 2 diabetes. In: LeRoith D, ed. *Prevention of Type 2 Diabetes: From Science to Therapy*. New York: Springer Science & Business Media, 2012:117–142.
4. McArthur JC, Stocks EA, Hauer P, Cornblath DR, Griffin JW: Epidermal nerve fiber density: normative reference range and diagnostic efficiency. *Arch Neurol* 1998;55:1513–1520.
5. Fealey RD, Low PA, Thomas JE: Thermoregulatory sweating abnormalities in diabetes mellitus. *Mayo Clin Proc* 1989;64:617–628.
6. Illigens BM, Gibbons CH: Sweat testing to evaluate autonomic function. *Clin Auton Res* 2009;19:79–87.
7. Vinik AI, Nevoret ML, Casellini CM, Parson HK: Neurovascular function and sudorimetry in health and disease. *Curr Diab Rep* 2013 May 17 [Epub ahead of print]. doi: 10.1007/s11892-013-0392-x.
8. Mayaudon H, Miloché PO, Bauduceau B: A new simple method for assessing sudomotor function: relevance in type 2 diabetes. *Diabetes Metab* 2010;36:450–454.
9. Gin H, Baudoin R, Raffaitin CH, Rigalleau V, Gonzalez C: Non-invasive and quantitative assessment of sudomotor function for peripheral diabetic neuropathy evaluation. *Diabetes Metab* 2011;37:527–532.
10. Hubert D, Brunswick P, Calvet JH, Dusser D, Fajac I: Abnormal electrochemical skin conductance in cystic fibrosis. *J Cyst Fibros* 2011;10:15–20.
11. Schwarz P, Brunswick P, Calvet J-H: EZSCAN a new technology to detect diabetes risk. *Br J Diabetes Vasc Dis* 2011;11:204–209.
12. Brunswick P, Mayaudon H, Albin V, Lair V, Ringuede A, Cassir M: Use of Ni electrodes chronoamperometry for improved diagnostics of diabetes and cardiac diseases. *Conf Proc IEEE Eng Med Biol Soc* 2007;2007:4544–4547.
13. Ayoub H, Grivewau S, Lair V, Brunswick P, Cassir M, Bedioui F: Electrochemical characterization of nickel electrodes in phosphate and carbonate electrolytes in view of assessing a medical diagnostic device for detection of early diabetes. *Electroanalysis* 2010;22:2483–2490.
14. Dyck PJ: Detection, characterization and staging of polyneuropathy: assessed in diabetes. *Muscle Nerve* 1988;11:21–32.
15. Casellini CM, Barlow PM, Rice AL, Casey M, Simmons K, Pittenger G, Bastyr EJ III, Wolka AM, Vinik AI: A 6-month, randomized, double-masked, placebo-controlled study evaluating the effects of the protein kinase C- β inhibitor ruboxistaurin on skin microvascular blood flow and other measures of diabetic peripheral neuropathy. *Diabetes Care* 2007;30:896–902.
16. Vinik AI, Erbas T, Park TS: Methods for evaluation of peripheral neurovascular dysfunction. *Diabetes Technol Ther* 2001;3:29–50.
17. Witzke K, Vinik A, Grant L, Parson H, Pittenger G: Loss of RAGE defense: a cause of Charcot neuroarthropathy? *Diabetes Care* 2011;34:1617–1621.
18. Vinik AI, Ziegler D: Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007;115:387–397.
19. Lieb DC, Parson HK, Mamikunian G, Vinik AI: Cardiac autonomic imbalance in newly diagnosed and established diabetes is associated with markers of adipose tissue inflammation. *Exp Diabetes Res* 2012;2012:878760.
20. La Rovere MT, Pinna GD, Maestri R, Sleight P: Clinical value of baroreflex sensitivity. *Neth Heart J* 2013;21:61–63.
21. Moak JP, Goldstein DS, Eldadah BA, Saleem A, Holmes C, Pechnik S, Sharabi Y: Supine low-frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. *Heart Rhythm* 2007;4:1523–1529.
22. Moak JP, Goldstein DS, Eldadah BA, Saleem A, Holmes C, Pechnik S, Sharabi Y: Supine low-frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. *Cleve Clin J Med* 2009;76(Suppl 2):S51–S59.
23. Calvet JH, Dupin J, Winiecki H, Schwarz PEH: Assessment of small fiber neuropathy through a quick, simple and non invasive method in a German diabetes outpatient clinic. *Exp Clin Endocrinol Diabetes* 2012;120:1–4.
24. Dyck PJ, Overland CJ, Low PA, Litchy WJ, Davies JL, Dyck PJB, O'Brien PC, Albers JW, Andersen H, Bolton CF, England JD, Klein CJ, Llewelyn JG, Mauermann ML, Russell JW, Singer W, Smith AG, Tesfaye S, Vella A: Signs and symptoms versus nerve conduction studies to diagnose diabetic sensorimotor polyneuropathy: CI vs. NPhys trial. *Muscle Nerve* 2010;42:157–164.
25. Yajnik CS, Kantikar VV, Pande AJ, Deslypere JP: Quick and simple evaluation of sudomotor function for screening of diabetic neuropathy. *ISRN Endocrinol* 2012;2012:103714.
26. Calvet JH, Rasanen A, Eklund J, Brunswick P, Schwarz P: Assessment of sudomotor function as a tool for cardiorepiratory fitness level evaluation: comparison with VO2 max. Presented at the European Association for the Study of Diabetes Meeting, Lisbon, Portugal, September 2011.

Address correspondence to:

Aaron I. Vinik, MD

Strelitz Diabetes Center for Endocrine and Metabolic Disorders
855 West Brambleton Avenue
Norfolk, VA 23510

E-mail: vinikai@evms.edu