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Sudoscan is an effective screening method for asymptomatic diabetic neuropathy in Chinese type 2 diabetes mellitus patients

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ABSTRACT

Aims/Introduction: The aim of the present study was to use the sudomotor function test, Sudoscan, as a screening method for the evaluation of asymptomatic diabetic distal symmetric polyneuropathy in Chinese type 2 diabetes patients. As a result, more attention could be paid to those asymptomatic patients who could be easily neglected and under-diagnosed in everyday clinic.

Materials and Methods: A total of 394 Chinese type 2 diabetes patients were enrolled and tested for symptoms and clinical signs of neuropathy using the Neurological Symptom Score, Neuropathy Disability Score, and vibration perception threshold. Sudoscan was carried out, and the results were collected as the measurement of the electrochemical skin conductance of both hands and feet.

Results: In the present study, we found that the abnormal rate of Sudoscan results in patients with asymptomatic neuropathy was higher than those without neuropathy and those with symptomatic neuropathy. This study also showed that lower electrochemical skin conductance at the feet was significantly associated with increasing symptoms, Neurological Symptom Score ($r = -0.124$, $P < 0.05$), Neuropathy Disability Score ($r = -0.3$, $P < 0.01$) and vibration perception threshold value ($r = -0.18$, $P < 0.05$). Logistic analysis showed that age (odds ratio 1.042, 95% confidence interval 1.014–1.071, $P < 0.05$) and feet electrochemical skin conductance levels (odds ratio 0.98, 95% confidence interval 0.962–0.993, $P < 0.01$) were independently associated with diabetic distal symmetric polyneuropathy.

Conclusions: Sudoscan might be a promising tool to screen asymptomatic diabetic distal symmetric polyneuropathy in Chinese patients with type 2 diabetes mellitus.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) can remain undetected and dormant, leading to serious complications[1,2]. The most common variety of diabetic peripheral neuropathy is a chronic, symmetrical, length-dependent, sensorimotor polyneuropathy defined as distal symmetric polyneuropathy (DSPN). However, symptoms and presentations of DSPN can vary greatly[3]. It often involves distal small nerve fibers and presents as painful neuropathy, but up to 50% of patients with neuropathy might be asymptomatic – easily resulting in delayed diagnosis, reduced quality of life and increased mortality[4,5].

Clinical diabetic neuropathy is usually diagnosed according to symptoms including anesthesia, burning or prickling sensation, as well as by testing tools including vibration sensation (tuning fork) or touch (Semmes–Weinstein monofilament examination)[6–9]. Conventional screening methods for DSPN consist of different questionnaires including the Michigan Neuropathy Screening Instrument, Neurological Symptom Score (NSS), Neuropathy Disability Score (NDS), Neuropathy Impairment Score–Lower Limb, Utah Early Neuropathy Scale and so on[10–14]. Each of these questionnaires emphasizes different clinical manifestations, and proves to be quite time-consuming in everyday clinical use. However, it still remains to be a huge challenge for screening asymptomatic diabetic neuropathy in

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Chinese type 2 diabetes mellitus patients concerning the low detecting rate in everyday clinic. Although a definite neuropathy diagnosis is based on confirmatory tests, exemplified by nerve conduction studies (NCS), NCS such as electromyography aim to reflect the impairment of large myelinated fibers, and are difficult to carry out in everyday clinic because of the obvious disadvantage of being invasive and inconvenient. Therefore, selecting a effective, non-invasive screening method to detect asymptomatic DSPN in the early stage still remains a problem.

Sudoscan (Impeto Medical, Paris, France) is a non-invasive device for the assessment of sudomotor function through evaluation of sweat gland secretory function as an early reflection of sympathetic nerve impairment[15]. Sweat glands innervated by thin unmyelinated sympathetic C fibers could be easily affected in the early stage of diabetes, as well as prediabetes[16]. The electrical current applied to the patients automatically by the device (usually <4 V) could attract sodium chloride from sweat in the palms of their hands and soles of their feet. Results of the electrochemical skin conductance (ESC) values for hands and feet are generated from the device. As an easy and objective screening method for DSPN, SUDOSCAN has proved to be a sensitive and quantitative screening test in clinical use in Caucasian and Indian patients[17–19]. However, there was no relevant report regarding the screening of Sudoscan in Chinese asymptomatic patients. The present study was carried out to evaluate Sudoscan as a tool for assessing asymptomatic DSPN in Chinese patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

Study population

The study was carried out in Huashan Hospital, Shanghai, China, from September 2014 to September 2015. The ethics committee of Hua Shan Hospital approved the study. Voluntary outpatients diagnosed with type 2 diabetes aged between 18 and 80 years, with or without symptoms of neuropathy, were continually enrolled in the study. Exclusion criteria included undiagnosed hyperglycemia, type 1 diabetes mellitus patients, those under treatment with drugs that could have an effect on the sympathetic system (such as beta-blockers and antineoplastic drugs), implantation of electrical implantable devices, history of seizures or epilepsy, lumbar sciatic nerve lesion, severe varices of the lower limbs, other metabolic diseases including thyroid disease or vitamin B_{12} deficiency, and any other advanced systemic condition including severe hepatic and renal dysfunction.

Sample size estimation

In the pilot experiment, we carried out the Sudoscan test in 62 patients (34 with non-DPN and 28 with DPN). We assumed a two-sided α error of 5%, and a statistical power of 80% to determine that a total of 165 patients were required per group. Finally, 394 patients were consecutively enrolled in the present study.

Physical examination

One trained nurse examined all the patients and recorded the results. Basic physical characteristics were recorded including height, weight, waist circumference and hip circumference measured by using standard methods. Body mass index and waist-to-hip ratio were calculated. Blood pressure was recorded in the supine position after 5 min of rest. The complete medical history (diabetes, hypertension, dyslipidemia, cardiovascular disease and other) was recorded for each patient.

Laboratory examination

Glycosylated hemoglobin A_{1c} of all included patients was determined by high-pressure liquid chromatography.

Peripheral neuropathy examination

Symptoms and signs of lower limbs were recorded, respectively. A composite score was calculated separately for neuropathic symptoms using the NSS score questionnaire, and for clinical examination using the NDS score.

Vibration perception value was detected with a biothesiometer carried out by a trained nurse.

Sudoscan test procedure

The Sudoscan device is composed of two sets of electrodes for the feet and hands, both of which are connected to a computer for recording and data analysis. The whole process of the test is non-invasive, and no special preparation is required. Patients only need to place the palms of their hands and the soles of their feet on the electrodes for 2–3 min, and a low-voltage (<4 V) electrical current stimulus is automatically applied by the device. The device can measure ESC values expressed in micro-siemens (μS) for the hands and the feet (both right and left sides). We used the mean of the left and right ESC values for statistical analysis.

Diagnostic criterion for DSPN

According to previous standards, an NSS score of 3–4 points was considered as a mild neuropathy symptom, 5–6 points as a medium neuropathy symptom and 7–9 points as a severe neuropathy symptom. The results of the NDS score were divided into three classes as well. An NDS of 3–5 points was considered as mild neuropathy signs, 6–8 points as medium neuropathy signs and 9–10 points as severe neuropathy signs. The golden diagnosis standard of DSPN is dependent on both NSS and NDS scores (with an NDS score of ≥6, or an NDS score of 3–5 associated with an NSS score of ≥5)[20].

We further divided all the patients into three categories based on their symptoms and clinical signs. The 'no diabetic neuropathy' group (group 1) referred to the patients without DSPN according to the NSS/NDS standard. The 'asymptomatic neuropathy' group (group 2) referred to the patients with NSS score <4 and NDS score >6. The 'symptomatic neuropathy' group (group 3) was defined by an NSS score >5, as well as an NDS score >3.

As for the Sudoscan test, we used 60 μS of mean feet ESC as the cut-off for diagnosis of DSPN according to previous studies[18,19].

Statistical analysis

Continuous data are presented as mean ± standard deviation, and categorical variables as percentages, respectively. Analysis of variance was used to compare mean differences of ESC values between the groups. Categorical variables were compared by the χ^2-test. Correlation was determined using Spearman's rho rank tests. Logistic regression analysis was used to determine the association between biological determinants (age, sex, body mass index, waist-to-hip ratio, duration of type 2 diabetes mellitus etc.), feet ESC, hands ESC and DSPN. Spss 16.0 software (Spss, Chicago, IL, USA) was used for all statistical analyses. Significance was accepted at the $P < 0.05$ level.

RESULTS

A total of 394 type 2 diabetic patients (244 men and 150 women) were enrolled in the study. We excluded the 37 patients who had been diagnosed as DPN and treated with neurotrophic drugs, and further divided patients into three groups according to their clinical symptoms and signs (as described in the diagnostic criterion).

The clinical and biochemical characteristics of the three groups of the remaining 357 participants are described in Table 1. Type 2 diabetes mellitus patients with symptomatic diabetic neuropathy had higher age, longer duration of diabetes and higher glycosylated hemoglobin A_{1c} levels among the three groups. However, among the three groups, the asymptomatic neuropathy group had the highest rate of Sudoscan detecting abnormal results at up to 69%, compared with 34.6% in the no diabetic neuropathy group and 61.7% in symptomatic neuropathy group (Figure 1).

An association was detected between NSS and NDS with both hands and feet ESC values, respectively. Increasing scores among the different evaluation scales were associated with decreasing ESC. Lower ESC was significantly associated with increasing symptoms by using the NSS score ($r = –0.124$, $P < 0.05$), increasing score on physical examination by using the NDS score ($r = –0.3$, $P < 0.05$) and increasing vibration threshold test value ($r = –0.18$, $P < 0.05$; Table 2). The association between traditional tests with feet ESC was higher in the subgroup of newly diagnosed DSPN patients than those who had already been diagnosed and treated with neurotrophic drugs. Lower ESC was associated with NSS score ($r = –0.181$, $P < 0.01$) and NDS score ($r = –0.324$, $P < 0.01$).

On logistic regression analysis, we found that feet ESC remained independently associated with DSPN diagnosed by NSS/NDS score (odds ratio 0.98, 95% confidence interval 0.962–0.993), as well as age (odds ratio 1.042, 95% confidence

Table 1 | Basic clinical and biochemical characteristics of 357 type 2 diabetes mellitus study participants

Clinical features	Group 1 ($n = 258$)	Group2 ($n = 29$)	Group 3 ($n = 60$)
Sex (male/female)	162/96	23/6	36/24
Age (years)	57.3 ± 12.3*	64.0 ± 13.4*	65.4 ± 9.3*
Duration of diabetes (years)	6 (1–10)*	9 (1–13)*	11 (6–18)*
Family history of T2DM (%)	38.4	34.5	35.0
Smoking (%)	28.3	24.1	16.7
Alcohol (%)	15.1	20.7	11.7
Dyslipidemia (%)	28.7	13.8	20.0
Height (cm)	166.5 ± 8.4	161.8 ± 12.3	166.3 ± 7.8
Weight (kg)	69.5 ± 13.1	68.2 ± 7.6	66.5 ± 10.1
BMI (kg/m^2)	24.5 ± 3.6	24.6 ± 2.36	23.5 ± 2.9
Waist (cm)	89.0 ± 10.1	89.0 ± 7.3	90.0 ± 8.7
Hip (cm)	96.4 ± 7.2	96.6 ± 5.0	96.1 ± 6.3
WHR	0.88 (0.8–0.9)	0.9 (0.85–0.95)	0.93 (0.89–0.97)
Systolic BP (mmHg)	125.9 ± 11.6	125.0 ± 14.5	129.3 ± 13
HbA1c (%)	8.0 ± 2.0*	7.5 ± 1.0*	9.0 ± 2.2*
NSS score	1 (0–4)*	1 (0–2.5)*	6 (5–7)*
NDS score	1 (0–2)*	7 (6–8)*	5 (4–6)*
VPT value	10.1 ± 5.8*	15.7 ± 9.6*	17.5 ± 8.5*
DSPN detected by Sudoscan (%)	34.6*	69.0*	61.7*
Feet ESC value (μS)	67.1 ± 16.6*	57.8 ± 20.8*	56.2 ± 20.3*
Hands ESC value (μS)	66.4 ± 16.0*	55.6 ± 20.0*	61.1 ± 16.9*

Continuous data are presented as mean ± standard deviation values and quartiles. *Significant difference between three groups ($P < 0.05$). Group 1, no diabetic neuropathy group; Group 2, asymptomatic neuropathy group; Group 3, symptomatic neuropathy group. BMI, body mass index; BP, blood pressure; DSPN, distal symmetric polyneuropathy; HbA1c, glycosylated hemoglobin A_{1c}; NDS, Neuropathy Disability Score; NSS, Neuropathy Symptom Score; T2DM, type 2 diabetes mellitus; VPT, vibration threshold test; WHR, waist-to-hip ratio.

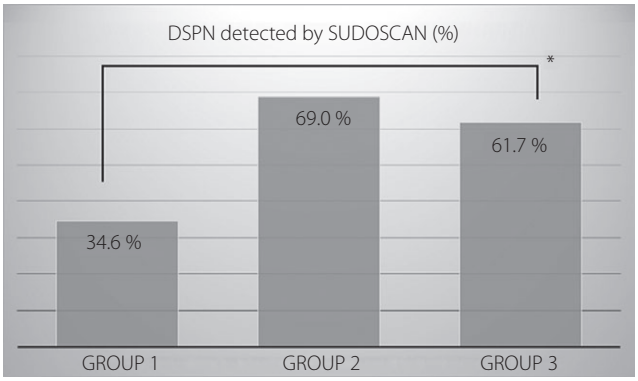

Figure 1 | Distal symmetric polyneuropathy (DSPN) detected by Sudoscan in three groups divided according to symptoms and signs of lower limbs as described previously. Group 1, no diabetic neuropathy group; Group 2, asymptomatic neuropathy group; Group 3, symptomatic neuropathy group. *$P < 0.01$

Table 2 | Spearman's correlations of hands and feet electrochemical skin conductance values with Neuropathy Symptom Score, Neuropathy Disability Score and vibration threshold test value in 357 Chinese type 2 diabetes mellitus patients

Traditional Tests for DSPN	ESC value	Spearman's rho	*P*-value
NSS score	Feet	–0.12*	0.015
	Hands	–0.11	0.290
NDS score	Feet	–0.30*	<0.001
	Hands	–0.29*	<0.001
VPT value	Feet	–0.18*	<0.001
	Hands	–0.23*	<0.001

*Significant difference of Spearman's rho between Neuropathy Symptom Score (NSS), Neuropathy Disability Score (NDS), vibration threshold test (VPT) value and electrochemical skin conductance (ESC) value ($P < 0.05$). DSPN, distal symmetric polyneuropathy.

interval 1.014–1.071). However, duration of diabetes, glycosylated hemoglobin A_{1c} level, body mass index, waist-to-hip ratio and other factors were not independently associated with DSPN (Table 3).

All the participants accepted Sudoscan without any complaint of discomfort, and no safety event was ever reported.

DISCUSSION

The early detection of DSPN in clinical work has been a difficult problem, especially for those patients without obvious clinical symptoms[21]. Traditional screening tools for DSPN, such as the tuning fork and the 10-g monofilament, are subjective and require the patient's full attention and cooperation, but are not quantitative to measure[22,23]. Although a definite neuropathy diagnosis is based on confirmatory tests exemplified by the NCS, NCS such as electromyography aim to reflect the impairment of large myelinated fibers. The results are often normal in patients with early or small fiber predominant neuropathy[21,24].

Table 3 | Logistic analysis of clinical factors with the diagnosis of distal symmetric polyneuropathy by Neuropathy Symptom Score/Neuropathy Disability Score

	B-value	OR ratio	CI	*P*-value
Age (years)	0.04	1.04	1.01–1.07	0.003*
Duration of diabetes (years)	0.02	1.02	0.98–1.07	0.173
BMI (kg/m^2)	–0.07	0.93	0.83–1.05	0.254
Systolic BP (mmHg)	0.00	0.99	0.97–1.03	0.960
HbA1c (%)	0.13	1.14	0.98–1.01	0.091
Feet ESC (μS)	–0.023	0.98	0.962–0.993	0.004*
Hands ESC (μS)	–0.011	0.99	0.97–1.01	0.35

*Significant difference of logistic analysis of clinical factors ($P < 0.05$). BMI, body mass index; BP, blood pressure; DSPN, distal symmetric polyneuropathy; HbA1c, glycosylated hemoglobin A_{1c}; WHR, waist-to-hip ratio.

As we know, clinical tests of diabetic neuropathy are mostly based on testing of different peripheral nerves, usually involving the large type A alpha and beta myelinated nerve fibers. However, the unmyelinated, thin type C fibers of the sympathetic nervous system are usually neglected because of the limited evaluation methods. Sweat gland function controlled by sympathetic C fibers might be affected in the early pathological process of diabetes or prediabetes, as has been shown in patients with early diabetes by the use of different methods, including skin biopsies[4,25].

Sudoscan, reflecting the function of sympathetic C fibers, does not require patient preparation or full attention, and can be easily carried out by any non-medical person in the outpatient clinic, and thus predicts early detection of DSPN. It has proven in several previous studies during the past 2–3 years to be much easier and more rapid to carry out, and is non-invasive and well tolerated. However, there were no related studies of Sudoscan in screening Chinese type 2 diabetes mellitus patients without typical symptoms of DSPN[15,25], so the present study focused on those asymptomatic type 2 diabetes mellitus patients, possibly resulting in a delay in treatment due to their negligible manifestations.

In the present study, we investigated the results of the Sudoscan test in type 2 diabetes mellitus patients without any clinical manifestation of the lower limbs, and discovered a relatively higher detection rate by SUDOSCAN in asymptomatic DSPN patients, indicating that SUDOSCAN might be more sensitive in screening DSPN in asymptomatic DSPN patients. We found in the present study that lower ESC was associated with symptoms of peripheral neuropathy and conventional clinical tests. We further divided patients into subgroups according to their previous use of neurotrophic drugs, and showed a lower association between traditional tests with feet ESC in those who had previously been diagnosed with DPN and treated with neurotrophic drugs, such as Methycobal® and methylcobalamin, compared with type 2 diabetes mellitus patients who have never been diagnosed with DPN before. This finding might as a result of the recovery of small fibers after the use of

neurotrophic medicine. Freedman[17] studied the relationship between ESC and kidney disease in African and European American type 2 diabetes patients, and revealed different results due to racial difference, showing that ethnic difference might be one of the impact factors of ESC values. Previous studies mainly focused on the comparison of Sudoscan and other detecting methods, and showed a significant correlation between ESC value and other detecting methods including Michigan Neuropathy Screening Instrument score, vibration threshold test and electromyography results in Caucasian and African populations[18,19]. Yet previous studies did not provide a perspective into the screening of Sudoscan in asymptomatic diabetic neuropathy patients, which proved to be equally important and easily neglected. Therefore, the present study is considered to be a pilot study in Chinese type 2 diabetes mellitus patients.

A number of limitations of the present study need to be clarified. Unlike previous published studies, which included a certain population of diabetic patients with established DSPN by diagnostic methods, such as skin biopsy, the present study did not provide a confirmed diagnosis of these type 2 diabetes mellitus patients. We used NSS/NDS score as the gold standard of DSPN, and further divided the whole group into three categories based on the cut-off point in NSS and NDS scores. Also, the sample size of the present study was not large enough to provide the clinical risk factors of DSPN as described in previous studies. To further elucidate the diagnostic value of Sudoscan in screening asymptomatic diabetic DSPN patients, we need to establish a more confirmatory method as the gold standard instead, as well as expand the sample size.

The results suggested that the assessment of sudomotor function using Sudoscan through detection of impaired sudomotor function might provide a screening method for the detection of asymptomatic diabetic DSPN in Chinese type 2 diabetes mellitus patients.

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DISCLOSURE

The authors declare no conflict of interest.

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