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Early Detection of Peripheral Neuropathy in Type II Diabetes Mellitus by SUDOSCAN

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Abstract

Backgrounds*: Sudomotor dysfunction is one of the earliest neurophysiologic abnormalities to manifest in distal small fiber neuropathy. SUDOSCAN ® was developed to provide a non invasive, quick, simple and quantitative measurement of sweat function. The aim of this study is to evaluate the value of SUDOSCAN in the diagnosis of neuropathy and its early detection.*

Methods*: This is a case control study was conducted from March 2014 to December2014 on type2 diabetic patient in the center of diabetes and endocrine disease in AL-Najaf . Sweat function was evaluated by measuring the electrochemical skin conductance (ESC) of the hands and feet.*

Results*: 100 patients with type 2 diabetes mellitus including 55 patients with peripheral neuropathy and 45 patients without peripheral neuropathy were involved in this case control study. Hands and feet conductance were lower in patients with type 2 diabetes with peripheral neuropathy when compared to patients with type 2 diabetes without neuropathy (with p value<0.001 for hands mean electrochemical skin conductance and feet mean electrochemical skin conductance).*

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

Keywords: *SUDOSCAN, Neurophysiologic abnormalities etc.*

List of abbreviations

ESC: Electrochemical skin conductance
HMESC: Hand mean ESC
FMESC: Feet mean esc
PN: Peripheral neuropath
CANP: Cardiac autonomic neuropathy
µS : microsimister
RCANP: Risk CANP
BMI: Body mass index
DN: Diabetic neuropathy

Introduction

Peripheral neuropathy is damage to or disease affecting nerves, which may impair sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected. Common causes include systemic diseases (such as diabetes or leprosy), vitamin deficiency, medication (e.g., chemotherapy), traumatic injury, radiation therapy, excessive alcohol consumption, immune system disease or viral infection. It can also be genetic (present from birth) or idiopathic (no known cause).[1][2][3] .

Neuropathy affecting just one nerve is called "mononeuropathy" and neuropathy involving multiple nerves in roughly the same areas on both sides of the body is called "symmetrical polyneuropathy" or simply "polyneuropathy." When two or more (typically just a few, but sometimes many) separate nerves in dicretete areas of the body are affected it is called "mononeuritis multiplex," "multifocal mononeuropathy," or "multiple mononeuropathy."[1][2][3]

Peripheral neuropathy may be chronic or acute. Acute neuropathies demand urgent diagnosis. Motor nerves (that control muscles), sensory nerves, or autonomic nerves (that control automatic functions such as heart rate, body temperature, and breathing), may be affected. More than one type of nerve may be affected at the same time. Peripheral neuropathies may be classified according to the type of nerve predominantly involved, or by the underlying cause. Where the cause is unknown it is described as idiopathic neuropathy.[1][2][3]

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Neuropathy may cause painful cramps, fasciculation (fine muscle twitching), muscle loss, bone degeneration, and changes in the skin, hair, and nails. Additionally, motor neuropathy may cause impaired balance and coordination or, most commonly, muscle weakness; sensory neuropathy may cause numbness to touch and vibration, reduced position sense causing poorer coordination and balance, normally.[1][2][3]organs, but common symptoms are poor bladder control, abnormal blood pressure or heart rate, and reduced ability to sweat reduced sensitivity to temperature change and pain, spontaneous tingling or burning pain, or skin allodynia (severe pain from normally non-painful stimuli, such as light touch); and autonomic neuropathy may produce diverse symptoms, depending on the affected glands.

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, 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[5] .The course of a diabetic sensorimotor polyneuropathy is insidious, however, and up to 50% of patients with neuropathy may be asymptomatic[6] 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[4]. 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 response. Skin biopsies have confirmed that numbers of epidermal C-nerve fibers are reduced in patients with diabetes [7]. 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[8] .Thus, sudomotor function represents an attractive tool to evaluate the peripheral autonomic system in people with DM[9]. The various techniques of sudomotor function testing are variably sensitive and specific for the detection of distal small fiber neuropathy[10]. 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[11-13]. 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 [14-15]. 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[16]. The aim of this study was to evaluate Sudoscan as a tool for assessing neuropathy in patients with DM.

Different forms of somatic and autonomic neuropathy can function as predictors or contributors to a number of chronic diseases, but the disparity between the association of intensive therapy, mortality, and the expression of chronic disease remains unclear[17-18]. Changes in peripheral autonomic nervous system function may be the earliest manifestation of distal small fiber neuropathy[19]. The eccrine glands are innervated by a rich supply of blood vessels and sympathetic C nervefibers and are responsible for the sweat response. Thus, sudomotor function can represent an attractive tool to evaluate the peripheral autonomic system[20]. Low et al., using the quantitative sudomotor axon reflex test (QSART), showed that sudo-motor function decreases in patients with diabetes[21]. Studying skin biopsies, it was confirmed thatthe density of epidermal C-nerve fibers is decreased in patients with diabetes[22]. The evaluation of sudomotor function therefore can be adirect and indirect indicator for the degree of neuropathy in diabetes patients or those at risk.This is especially important because it is known that intensive therapy with insulin can delay the onset and slow the progression of retinopathy, nephropathy and peripheral neuropathy [23]. Additionally, lifestyle change can improve impaired nerve function [24-25].

Patients & methods

The case control study was conducted from march 2014 to December 2014 on 100 patient type2 diabetes and 50 person as healthy control in the centre of diabetes and endocrine disease in al najaf. All participants gave their oral agreement. The study was performed parallel to the patient standard care, General examination was performed together with weight, height, gender and biochemistry, including HbA1C.Type 2 diabetes patients between 45 and 75 yrs of age, with or without symptoms of neuropathy were enrolled in the study. Exclusion criteria included treatment with drugs that would have an effect on the sympathetic system such as beta blockers (to avoid interference in CAN testing), amputation of arms or legs, implantation of electrical implantable devices (pacemaker/defibrillator), sensitivity to nickel or any other standard electrodes, and history of seizures or epilepsy.

Sweat function assessment

SUDOSCAN ® (Impeto Medical, Paris, France) is a new patented device designed to perform a precise evaluation of sweat gland function based on the electrochemical reaction between the chlorides in sweat

and stainless-steel electrodes at low DC voltage [23-27]. The apparatus consists of 2 sets of electrodes in contact with the palms of the hands and soles of the feet, where sweat gland density is the highest, connected to a computer for recording and data management purposes. To conduct the test, the individual is required to stand still for 3 min. During the test,4 combinations of 15 different low direct current (DC) incremental voltages ≤ 4 volts are applied. A time/ampere curve is recorded for each derivation. Electrochemical skin conductance(ESC) in the hands and feet, i. e., the ratio between current generated and the constant DC stimulus, are displayed on a monitor immediately after the test. Sudomotor dysfunction is evaluated according to the ESC measured on the feet: >60 µS=no dysfunction; 60–40 µS=moderate dysfunction; and <40 µS=severe dysfunction. Neither special subject preparation nor specially trained medical personnel are required.

Figure 1: General presentation of the SUDOSCAN with the hands and feet electrodes and the master unit.

Aim of study

To investigate the value of SUDOSCAN in the diagnosis of neuropathy and its early detection

Results

This study involves one hundred patients with type 2 diabetes mellites fifty-five patients of them having neuropathy and forty-five diabetic patients without neuropathy regardless of the symptom and fifty persons as healthy control, for each patient HMESC and FMESC were measured by SUDO SCAN,the results were statistically analyzed by Chi-Squared test and analysis of variance (ANOVA) in Microsoft Excel at a level of significance of P < 0.05. There is a significant difference in Mean FMESC (83.62 ± 5.54) and Mean HMESC (74 ± 6.88) with P value of 0.05) as shown in table-1).

Table 1 Mean FMESC and HMESC in diabetic patient with and without peripheral neuropathy

Diabetes	No. patients	Mean FMESC (µs)	Mean HMESC(µs)
No neuropathy	45	83.62 ± 5.54	74 ± 6.88
With neuropathy	55	61.94 ± 20.90	49.45± 13.8
P value		<0.0001	<0.0001

P value<0.05(significant

There is a significant difference between mean FMESC and HMESC in diabetic patients with peripheral neuropathy and normal control patients as shown in table-2

Table 2 Mean FMESC and HMESC in diabetic patients with peripheral neuropathy and normal control patient

	Mean FMESC(µs)	Mean HMESC(µs)
Normal control	82.33± 7.265	75.83 ± 13.55
Diabetes With neuropathy	61.94 ± 20.90	49.45± 13.80
P value	<0.0001	<0.0001

P value<0.05(significant)

There is no significant difference in FMESC measures in diabetic patient with peripheral neuropathy in relation to BMI (body mass index) as shown in table-3.

Table 3 Relation of FMESC to body mass index in diabetic patient with peripheral neuropathy

BMI	FMESC (µs)			Total
	>60	40-60	<40	
18-23.9	5	2	4	11
24-29.9	12	4	5	21
≥30	15	5	3	23
Total	32	11	12	55
P value	0.647			

P value>0.05(not significant

There is no significant difference in HMESC measures in diabetic patient with peripheral neuropathy in relation to BMI (body mass index) (p value > 0.05) as shown in table-4.

Table 4 Relation of HMESC to body mass index in diabetic patient with peripheral neuropathy

BMI	HMESC (µs)			Total
	>60	40-60	>40	
18-23.9	1	6	4	11
24-29.9	3	11	8	22
≥30	3	12	7	22
Total	7	29	19	55
P value	0.991			

P value>0.05(not significant)

There is no significant differences in FMESC measures in diabetic patient without peripheral neuropathy in relation to BMI (body mass index) (p value > 0.05) as shown in table-5.

Table 5 Relation of FMESC to body mass index in diabetic patient without peripheral neuropathy

BMI	FMESC (µs)			Total
	>60	40-60	<40	
18-23.9	5	0	0	5
24-29.9	20	0	0	20
≥30	18	1	1	20
Total	43	1	1	45
Yat`s p value	0.592			

P value>0.05(not significant)

There is no significant difference in HMESC measures in diabetic patient without peripheral neuropathy in relation to BMI (body mass index) (p value > 0.05) as shown in table-6.

Table 6 Relation of HMESC to body mass index in diabetic patient without peripheral neuropathy

BMI	>60	40-60	<40 *	Total
18-23.9	5	1	0	6
24-29.9	20	1	0	21
≥ 30	17	1	0	18
Total	42	3	0	45
P value	0.571			

*Not included in analysis
P value>0.05(not signifigant)

There is a significance difference in FMESC measures in diabetic patient with peripheral neuropathy in relation to Hb A1C (control of diabetes) (p value < 0.05) as shown in table-7.

Table7 Relation of FMESC to HbA1C in diabetic patient with peripheral neuropathy

	FMESC(µs)			
HbA1c	>60	40-60	<40	Total
<7	7	3	9	19
>7	16	8	12	36
Total	23	11	21	55
P value	0.007			

P value<0.05(significant)

There is a significant differences in HMESC measures in diabetic patient with peripheral neuropathy in relation to Hb A1C (control of diabetes) (p value < 0.05) as shown in table-8.

Table 8 Relation of HMESC to HbA1Cin diabetic patient with peripheral neuropathy

	HMESC(µs)			
HbA1c	>60	40-60	<40	Total
<7	1	16	2	19
>7	5	19	12	36
Total	6	35	14	55
P value	0.001			

P value<0.05(significant)

There is no significant difference in FMESC measures in diabetic patient without peripheral neuropathy in relation to Hb A1C (control of diabetes) (p value 0.05) as shown in table-9.

Table 9 Relation of FMESC to HbA1C in diabetic patient without peripheral neuropathy

	FMESC(µs)			
HbA1c				Total
	>60	40-60	<40	
<7	23	1	0	24
>7	20	0	1	21
Total	43	1	1	45
P value	0.36			

P value>0.05(not significant

There is no significant difference in HMESC measures in diabetic patient without peripheral neuropathy in relation to HbA1C (control of diabetes) (p value 0.05) as shown in table-10.

Table10: Relation of HMESC to HbA1Cin diabetic patient without peripheral neuropathy

	HMESC(µs)			
HbA1c				Total
	>60	40-60	<40	
<7	21	2	0	23
>7	21	0	1	22
Total	42	2	1	45
P value	0.22			

P value>0.05(not significant)

There is no significant difference in FMESC measures in diabetic patient with peripheral neuropathy in relation to patients gender (p value 0.05) as shown in table-11.

Table11 Relation of gender to FMESC in diabetic patient with neuropathy

	FMESC(µs)			
gender				Total
	>60	40-60	<40	
Male	21	5	8	34
Female	12	6	3	21
Total	33	11	11	55
P value	0.39			

P value>0.05(not significant)

There is a significant difference in HMESC measures in diabetic patient with peripheral neuropathy in relation to patient's gender (p value < 0.05) as shown in table-12.

Table12 Relation of gender to HMESC in diabetic patient with neuropathy

	HMESC(µs)			
gender				Total
	>60	40-60	<40	
Male	2	25	8	34
Female	7	10	3	21
Total	9	35	11	55
P value	0.018			

P value<0.05(significant)

There is no significant difference in FMESC measures in diabetic patient without peripheral neuropathy in relation to patient's gender (p value 0.05) as shown in table-13.

Table13 Relation of gender to FMESC in diabetic patient without neuropathy

	FMESC(µs)			
gender				Total
	>60	40-60	<40	
Male	31	1	1	33
Female	10	1	1	12
Total	41	2	2	45
P value	0.54			

value>0.05(not significant)

There is no significant difference in HMESC measures in diabetic patient without peripheral neuropathy in relation to patient's gender (p value 0.05) as shown in table-14.

Table 14 Relation of gender to HMESC in diabetic patient without neuropathy

	HMESC(µs)			
gender				Total
	>60	40-60	<40	
Male	30	2	1	33
Female	9	1	2	12
Total	39	3	3	45
P value	0.54			

P value>0.05(not significant)

Gender distribution in different studied groups

Our study show that ESC values of hand and feet decrease in diabetic patient with peripheral neuropathy than those without peripheral neuropathy. There is no significant difference in FMESC and HMESC measure in diabetic patient with and without peripheral neuropathy in relation to BMI. There is a significant difference in FMESC and HMESC measures in diabetic patient with peripheral neuropathy(p value 0.007,p value 0.001) respectively in relation to HbA1c. there are no significant difference in FMESC and HMESC measures in diabetic patient without peripheral neuropathy P-value(0.36,0.22) respectively in relation to HbA1c. Sweat gland function is controlled by sympathetic C fibers which might be affected early in the process of pathogenesis of diabetes. Sweat gland dysfunction has been demonstrated in patients with early diabetes using different methods including skin biopsies [26–27,28–29].

Subjects with impaired glucose tolerance have lower ESC compared to those with normal glucose tolerance, and subjects with diabetes have even lower conductance [30],HbA1C is used to monitor glycemic levels for the past 3 month period. SUDOSCAN is not a blood-based test but focuses on the assessment of the small C nerve fibers. As such, SUDOSCAN is a test that can be performed in complement to HbA1c.

There are no significant difference in FMESC values in diabetic patient with and without peripheral neuropathy (p value 0.39,0.54) respectively in relation to gender, measurements performed by SUDOSCAN don't depend on sweat rate. A study performed on more than 500 women and more than 200 men show no significant differences in hands' and feet' ESC. This will be confirmed in future pending studies on larger group populations.ESC values of both feet and hands are significantly better in healthy control and those without diabetes DN compared to those with DN.

SUDOSCAN evaluates sudomotor function by measuring ESC resulting from an electrochemical reaction between sweat chloride and nickel electrodes after a low DC stimulation. Importance of sweat chloride in this reaction was well demonstrated in a study performed with cystic fibrosis (CF) patients who had significantly higher conductance compared with healthy subjects [31]. Sweat gland function is controlled by sympathetic C fibers which might be affected early in the process of pathogenesis of diabetes. Clinical tests of diabetic neuropathy are mostly based on testing of peripheral. Nerves, usually involving the large type A alpha and beta-myelinated nerve fibers (vibration and touch sense). However, the unmyelinated, thin type C fibers of sympathetic nervous system are not tested. SUDOSCAN offers a simple test to evaluate these fibers. So one important limitation of this preliminary study is that peripheral neuropathy was not confirmed by complete neurological clinical examination, which generally assesses large fiber neuropathy.

Conclusions

SUDOSCAN is a promising, screening 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.

Recommendations

1-Comparing the results of SUDOSCAN with other standard measure to predict its sensitivity and specificity for diagnosis of neuropathy.
2-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
3-Performing a follow up study with SUDOSCAN 6 months later after regulation of blood sugar.

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