



Research paper

Assessment of sudomotor function in hypertensive with/without type-2 diabetes patients using SUDOSCAN: An electrophysiological study



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ARTICLE INFO

Article history:

Received 24 July 2020

Received in revised form 30 October 2020

Accepted 7 December 2020

Available online 13 December 2020

Keywords:

Hypertension

Type-2 diabetes

Electrochemical skin conductance

Cardiometabolic risk factors

SUDOSCAN

ABSTRACT

Objective: Electrochemical skin conductance (ESC) test is a simple and non-invasive screening test can detect dysfunction of the peripheral sudomotor, and indirectly estimates the function of cardiac autonomic nerves. This study aimed to assess the ESC values in hypertensive patients with/without type-2 diabetes by using SUDOSCAN technology. Moreover, this study evaluated the role of cardiometabolic risk factors on the results of ESC test.

Methods: This cross-sectional study was carried on three groups of participants, including healthy subjects (Group I, n = 49), hypertensive without type-2 diabetes (Group II, n = 75) patients, and hypertensive with type-2 diabetes (Group III, n = 76) patients. Body mass index (BMI), blood pressure (systolic, diastolic and pulse pressure index), fasting serum glucose, and lipid profile were determined. ESC test as a measurement sudomotor function was determined by applying a small direct current at low voltage to hands and feet sensor plates through SUDOSCAN device.

Results: ESC values of the peripheral sudomotor nerves in the Group II and III patients were significantly lower than the corresponding values of Group I. SUDOSCAN results of Group II and III. Significant discriminators of cardiac autonomic neuropathy (≥ 30 score) that determined by the area under the curve (AUC) with 95% confidence interval (95% C.I.) were, duration of the disease, BMI, and mean blood pressure in Group II, while the duration of the disease and the BMI were significant discriminators in Group III.

Conclusions: SUDOSCAN is a simple, useful device, which can detect the impairment of peripheral autonomic small nerve fibers and the risk of cardiac autonomic neuropathy in hypertension. Moreover, the duration of the disease and the associated cardiometabolic risk factors are important predictors of significant SUDOSCAN findings.

Significance: ESC test is useful in detecting subclinical neuropathy in hypertensive patients as well as in type 2 diabetes.

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1. Introduction

SUDOSCAN™ (Impeto Medical, Paris, France) is a non-invasive technology that assessed the C-small sympathetic nerve fibers of the sweat gland (Casellini et al., 2013) via determination of chloride conductance across the skin (Mayaudon et al., 2010). A current of low voltage (<4 V) is applied via the electrodes on the palms and soles where the sweat glands are densely condensed. The voltage-current can attract the chloride ions from a sweat gland, and the nerve fiber conductance can be altered by this electrochemical

reaction (Brunswick et al., 2007). Sudomotor dysfunction is a feature of sympathetic impairment of the heart, therefore SUDOSCAN indirectly can identify the patients at risk of cardiac autonomic neuropathy (CAN). The score of CAN is based on an algorithm based the ESC value, age, and body weight, and it accounts ≥ 30 score as instructed by the manufacturer. There are many tests and procedures used to detect dysfunction of the autonomic nervous system (ANS). Low et al (1983) introduced Quantitative Sudomotor Axon Reflex Sweat Test (QSART), which assesses the responses of sweat glands to the stimulation of the sudomotor nerve fibers by acetylcholine analogues. The principle of this diagnostic test is to measure the volume of sweat output after stimulating the sudomotor nerve fibers by acetylcholine, and a decrease of the sweat volume indicating, an impairment of nerve fiber function (Vinik et al., 2015). Krieger et al (2018) found that there was no

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difference between controls and diabetic patients in the response latency by using QSART test.

Electrochemical skin conductance (ESC) test that achieved by SUDOSCAN is more sensitive, less expensive and easier than other tests (e.g. QSART) used to detect dysfunction of the sudomotor nerve (Novak, 2019).

Moreover, ESC test considered as a diagnostic test for detecting diabetic neuropathy and other clinical conditions that caused or associated with neuropathy (Selvarajah et al., 2015; Krieger et al., 2018; Popescu, 2019; Falcão de Campos et al., 2019; Lefaucheur et al., 2018). High sweat volume output correlates with high ESC values, and a decrease of sweat production due to small nerve fiber neuropathy leads to dry skin and low ESC values.

The area under the curve (AUC) of ESC value is higher in diabetic patients compared with controls, but there is a non-significantly correlation between ESC values and the fasting serum glucose levels (Kim et al., 2019). Névoret (2019) suggested that the utility of the ESC test in uncontrolled diabetes will be more useful compared with controlled diabetes because diabetic neuropathy is a feature of poor glycemic control.

On the other hand, EZSCAN test is a non-invasive autonomic practical screening test evaluates the function of sudomotor nerve as with ESC. This test is alternative to QSART because it is non-invasive, easier, and time-saving. EZSCAN was used used to detect prediabetes (Yang et al., 2013), and the EZSCAN values were increased with an increased number of the components of metabolic syndrome (Sun et al., 2012).

Essential hypertension is one component of metabolic syndrome and is commonly associated with the dysfunction of the sympathetic nervous system (Li et al., 2020), which may be related to concomitant diseases like diabetes mellitus (DM) or evidence of metabolic syndrome (Nikolov et al., 2019). Dysfunction of ANS is common in patients with DM and essential hypertension, which detected by the heart rate variability test. Previous studies showed contradictory results of the heart rate variability between T2D patients with and without hypertension (Takahashi et al., 2001; Istenes et al., 2014; Solanki et al., 2017). Previous studies did not assess the ANS in hypertensive patients through measuring the ESC test.

We hypothesized that SUDOSCAN technology is not restricted to diagnose DM or to detect subclinical diabetic neuropathy. SUDOSCAN can be applied in any clinical condition associated with metabolic derangement. Therefore, detection of the ANS dysfunction in hypertension with/without T2D by SUDOSCAN in patients without clinical evidence of peripheral or autonomic neuropathy will be worth trying. Therefore, this cross-sectional non-invasive study aimed to assess the ESC values in hypertensive patients with/without T2D by using SUDOSCAN technology. Moreover, this study evaluated the role of cardiometabolic risk factors on the results of ESC.

2. Materials and methods

2.1. Study design and setting

This cross-sectional study was conducted from January to September 2019, in the Department of Physiology, College of Medicine, Al-Mustansiriyah University.

2.2. Ethical approval

The ethical committee of Faculty of Medicine granted approval for this study. Each participant willing to enroll in this study, he/she or his/her proxy signed a written consent form.

2.3. Inclusion and exclusion criteria

All patients diagnosed with essential hypertension, and both T2D and hypertension aged between 40 and 78 years, without clinical symptoms of neuropathy, were enrolled in the study. Exclusion criteria included T1D, T2D with complications, including diabetic nephropathy, diabetic foot syndrome, diabetic nephropathy, current using of drugs acting on the ANS, e.g. alpha and/or beta-blockers, nerve stabilizing agents, history of seizures or epilepsy, nutritional deficiency, hepatic and renal dysfunction.

2.4. Sample size

The sample size was calculated by using a margin of errors ($\alpha = 0.05$, $\beta = 0.2$), two tails and 95% confidence intervals. Therefore, the sample size is $= 1 + 2C \times (\text{Standard deviation/difference between means})^2$, where C represents a constant value that derived from the statistical tables which equals to 7.85 when the $1 - \beta = 0.8$ and $\alpha = 0.05$.

2.5. Physical and clinical assessments

The patients were recruited from three consultant clinics. A total number of 200 participants grouped into:

Group I: Healthy subjects (n = 49)

Group II: Hypertensive patients without T2D (n = 75): Known cases of essential hypertension without clinical evidence of peripheral neuropathy.

Group III: Type2 Diabetic patients without clinical evidence of peripheral neuropathy (n = 76). Eleven patients have also high systolic blood pressure (≥ 140 mmHg) and three of them have also high diastolic blood pressure (≥ 90 mmHg).

The authors interviewed the participants and basic characteristics were recorded. Physical characteristics were measured, including height (m), weight (kg) and waist circumference (cm) using standard methods. Body mass index (BMI) and waist-to-height ratio (WHeR) were calculated. WHeR simply calculated by dividing the waist (cm) by height measurement (cm). A cutoff value of ≥ 0.580 indicates that the patient is at risk of metabolic derangement (Bohr et al., 2016). Blood pressure (BP) was recorded in the supine position after 5 min of rest. A mean value of three readings was considered. Pulse pressure (PP), mean arterial blood pressure (MAP), and arterial stiffness was determined by using the following equations:

$$\text{Pulse pressure(PP)} = \text{Systolic BP} - \text{Diastolic BP}$$

$$\text{Mean arterial BP(mmHg)} = \text{diastolic BP} + \frac{1}{3} \times (\text{PP})$$

Pulse pressure index (PPI) as a measurement of arterial stiffness = PP divided by Systolic BP

Fasting serum glucose, high-density lipoprotein-cholesterol (HDL-c), triglyceride TG) and glycated hemoglobin (HbA_{1c}) were determined. Triglyceride glucose index (TyG-I) was calculated by using the following equation (Akbar et al., 2017)

$$\text{TyG} - \text{I} = \text{Ln} \frac{\text{Serumglucose(mg)} \times \text{Serumtriglyceride(mg)}}{2}$$

2.6. Assessment of peripheral nerves

The authors asked the patients about the subjective complained symptoms that related to peripheral neuropathy including, numbness, decrease pain sensation, thermal changes, burning sensation, pain, and muscle cramp on walking. Then, the neurological examination and the following tests were carried: vibration sensation test using 128 Hz fork, thermal sensation test using warm and cold

objects, pinprick test for pain, and ankle reflex test using the scoring of 0 = absent and 1 = reduced or present. Then the revised neuropathy disability score was calculated (Weintrob et al., 2007). Then summation of the total scores of the above-mentioned tests (vibration sensation, impaired thermal sensation, pinprick, and ankle reflex) represented the Revised Neuropathy Disability Score (RNDS). Patients with RNDS of six points or more are considered to show abnormal reaction. Patients with ≤ 3 points, which indicated no evidence of neuropathy, were included in this study.

2.7. SUDOSCAN device

Patients were asked to place both palms and soles on the electrodes for a period of 2–3 min, then an electrical stimulus by a device was automatically running at a low-voltage (<4 V). The electrochemical skin conductance (ESC) values were measured by the device, which expressed in micro-Siemens (μS) for both hands and the feet. Sudomotor function for feet is categorized according to the value of ESC as normal (70–100μS), moderately reduced (50–70 μS), and severely reduced (0–50 μS); and for hands normal (60–100μS), moderately reduced (40–60 μS), and severely reduced (0–40 μS). The SUDOSCAN manufacturer found that a score of ≥ 30 calculated from the algorithm of ESC, age, and body weight, indicates the patients at risk of developing CAN. The mean values were considered for statistical analysis. The mean value of CAN score of healthy subjects (Group I) according to the age group are: 18, 12,

8.5 for age groups (years); 40–49 (n = 19), 50–59 (n = 25), 60–69 (n = 4), respectively. One healthy subject aged 73 year has a score of 33.

2.8. Statistical analyses

Continuous data are presented as mean ± standard deviation and categorical variables as number (percentages). Analysis of variance (One Way ANOVA) with the *post hoc Tukey* test was used to compare mean differences of ESC values between the groups. Categorical variables were compared by Chi-squared test. Multivariate regression analysis and receiving operating characteristics were used to determine the prediction of the ESCs values using β-coefficient of each cardiometabolic factors, and to determine the ESC value as a discriminator for these cardiometabolic risk factors by calculating the AUC with 95% confidence intervals. SPSS (version 20) software was used for the analysis of the data. Significance was accepted at the p-value of ≤0.05.

3. Results

3.1. Characteristics of the participants

Table 1 shows the characteristics of the participants enrolled in the study significant differences in the distribution of gender and the mean of age. There are no significant differences in the

Table 1 Characteristics of the participants.

Variables	Group I (n = 49)	Group II (n = 75)	Group III (n = 76)	F-value	P-value	P-value between groups		
Gender (Female:Male)	32:17	57:18	46:30			*<0.196,	‡0.590,	‡ 0.041
Age (year)	51.5 ± 7.0	58.7 ± 9.2	58.7 ± 8.7	13	<0.001	*<0.001,	‡<0.001,	‡1.000
Body mass index (kg/m ²)	28.9 ± 5.3	32.2 ± 6.1	30.8 ± 5.4	4.95	0.008	* 0.005,	‡0.152,	‡0.316
Duration of diseases (year)	–	9.3 ± 4.7	8.3 ± 3.1	2.65				‡0.106
Blood pressure (mmHg)								
Systolic	125.1 ± 10.1	155.4 ± 27.1	128.2 ± 12.7	52.45	<0.001	*<0.001,	‡0.645,	‡<0.001
Diastolic	81.6 ± 6.6	89.6 ± 14.0	77.9 ± 9.8	22.09	<0.001	*<0.001,	‡0.154,	‡<0.001
Mean	96.1 ± 7.0	111.5 ± 16.4	94.7 ± 9.0	43.41	<0.001	*<0.001,	‡0.786,	‡<0.001
Pulse pressure	43.5 ± 8.0	65.8 ± 22	50.3 ± 12.7	32.58	<0.001	*<0.001,	‡0.054,	‡<0.001
Pulse pressure index	0.346 ± 0.039	0.415 ± 0.085	0.39 ± 0.08	13.53	<0.001	*<0.001,	‡ 0.003,	‡<0.001
Fasting serum glucose (mg/dL)	96.9 ± 20.4	97.5 ± 6.6	148.9 ± 48.5	62.00	<0.001	*0.995,	‡<0.001,	‡<0.001
Glycated hemoglobin (%)	5.54 ± 0.51	5.3 ± 0.75	7.79 ± 1.4	9.18	<0.001	*0.954,	‡<0.004,	‡<0.001
Glucose triglyceride index	9.57 ± 0.72	9.67 ± 0.38	10.29 ± 0.58	33.87	<0.001	*0.588,	‡<0.001,	‡<0.001

The results are expressed as mean ± SD. P-value was calculated by using one way analysis of variance, with *post hoc Tukey* *denotes comparison between Group I and Group II, †denotes comparison between Group I and III, and ‡denotes comparison between Group II and Group III. Group I: Healthy subjects, Group II: Hypertensive patients, Group III: hypertension with diabetes patients.

Table 2 Electrochemical skin conductance values of the peripheral nerves and the risk of cardiac autonomic neuropathy score using SUDOSCAN in hypertensive and diabetic patients compared with health subjects.

Electrochemical skin conduction (μS)	Group I (n = 49)	Group II (n = 75)	Group III (n = 76)	F-value	P-value	P-value between groups		
Peripheral small nerve fibers of the feet								
Left (μS)	78.8 ± 11.2	67.7 ± 16.1	62.7 ± 20.8	13.37	<0.001	* 0.001,	‡<0.001,	‡0.179
Right (μS)	79.7 ± 7.6	68.4 ± 16.2	65.1 ± 18.1	12.75	<0.001	* 0.001,	‡<0.001,	‡0.581
Mean (μS)	77.0 ± 15.5	67.8 ± 15.8	64.9 ± 18.4	8.01	<0.001	* 0.009,	‡<0.001,	‡0.525
Asymmetry (%)	4.7 ± 14.4	5.5 ± 9.4	7.6 ± 14.0	1.56	0.213	*0.817,	‡0.213,	‡0.446
Peripheral small nerve fibers of the hands								
Left (μS)	73.7 ± 11.3	59.6 ± 18.4	56.1 ± 18.1	17.37	<0.001	*<0.001,	‡<0.001,	‡0.404
Right (μS)	70.9 ± 11.4	56.4 ± 17.9	52.6 ± 18.3	19.00	<0.001	*<0.001,	‡<0.001,	‡0.340
Mean (μS)	71.9 ± 11.2	57.7 ± 18.2	54.1 ± 17.8	18.12	<0.001	*<0.001,	‡<0.001,	‡0.361
Asymmetry (%)	4.3 ± 4.3	7.6 ± 7.0	10.3 ± 11.4	7.48	0.001	*0.091,	‡<0.001,	‡0.124
Cardiac autonomic neuropathy score	14.5 ± 10.0	33.2 ± 10.8	33.1 ± 12.9	49.34	<0.001	*<0.001,	‡<0.001,	‡1.000

The results are expressed as mean ± SD. P value was calculated by using one way analysis of variance, with *posthoc Tukey* *denotes comparison between Group I and Group II, †denotes comparison between Group I and III, and ‡denotes comparison between Group II and Group III. Group I: Healthy subjects, Group II: Hypertensive patients, Group III: Diabetic patients.

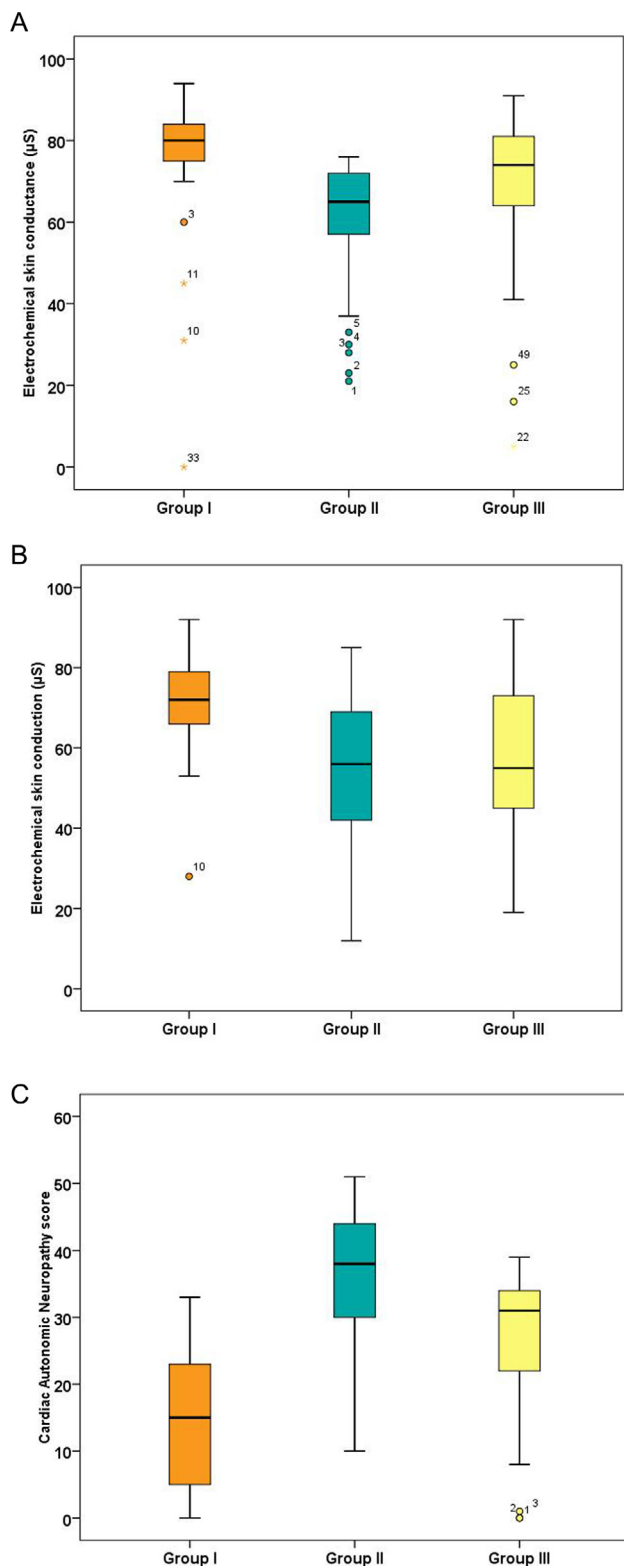


Fig. 1. Boxplot of Sudoscan values in healthy subjects (Group I), Hypertensive patients (Group II), and type-2diabetes with hypertension (Group III). Sudoscan mean value of feet (A), Hands (B), and the score of cardiac autonomic neuropathy risk (C).

duration of disease and the body mass index between hypertensive (Group II) and T2D with hypertension (Group III) patients. Pulse pressure index, as a measurement of arterial stiffness, is significantly higher in the Group II patients than the corresponding

values of the Group I and Group III participants (Table 1). Group III patients have significantly higher values of glycemic indices including, fasting serum glucose, HbA_{1c} and TyG-I than the corresponding values of the healthy subjects and hypertensive patients (Table 1).

3.2. Assessment of electrochemical skin conductance test

The results of SUDOSCAN study show that the ESC values of both sides of feet and hands are significantly impaired in hypertensive (Group II) and DM with hypertension (Group III) compared with healthy subjects (Group I) (Table 2, Fig. 1). The mean values of a sudomotor function of the feet and hands indicate moderate impairment of sudomotor nerve function in both Group II and III. The score of the CAN risk (>30) is significantly higher in Group II and III compared with healthy subjects, which accounted for more than two folds (Table 2, Fig. 1). There was no difference in the score of CAN risk was observed between Group II and III patients (Table 2, Fig. 1). Table 3 shows the distribution of participants according to the abnormal results of the SUDOSCAN investigational study. Severe impairment of the small nerve fibers of the feet and hands observed in the 13.3% and 17.3% of Group II patients, and in the 15.8% and 21.1% of Group III patients, respectively.

3.3. Relationships between electrochemical skin conductance value with cardiometabolic risk factors

Multivariate regression analysis showed that cardiometabolic factors, including BMI, MAP, fasting level of serum TG, HDL-c, glucose and HbA_{1c} predict significant impairment of the conduction of sudomotor nerve fibers of hands and feet in the Group II compared with Group III (Table 4). These cardiometabolic factors significantly predict a higher percentage of patients having a higher score of CAN risk in Group II (37.4%) and Group III (41.6%). In respect to the duration of disease, as long duration of illnesses is associated with low values of ESCs (negative β coefficient), indicating impairment of the sudomotor function of feet and hands, while the positive β -coefficient of multivariate regression analysis of CAN risk, indicating significant high score values (≥ 30) and at risk of CAN. The other cardiometabolic risk factors showed variable correlations with the ESC or CAN risk score.

Table 5 shows that the AUC with 95% confidence intervals for the duration of the disease, BMI, and MAP are significantly discriminators of the CAN risk (i.e. patients with a cutoff value of ≥ 30 scores). This means that phenotype of patients who are at risk CAN are those with long duration of illness, having higher BMI and BP. The score of CAN risk does not significantly discriminate the patients with abnormal lipid profile, indicating that patients with CAN risk could be observed in hypertensive patients with normal or abnormal lipid profile.

The AUCs with 95% C.I. of the duration of diabetes, BMI, HbA_{1c} are higher than 0.5, and the AUC of HDL-c is than 0.5 value, indicating these variables are significant discriminators of CAN risk in Group III patients (Table 5). In Group II patients, the AUCs with 95% C.I. of the duration of disease, BMI and MBP are significantly higher than 0.5 value (Table 5).

4. Discussion

The results of this study show significant impairment of ESC of sudomotor nerve fibers is present in hypertensive as well as in diabetic patients. The values of ESC are related to cardiometabolic factors and act as predictors and discriminators. Moreover, low serum HDL-c level is a laboratory finding of the CAN risk in Group III.

Table 3

Distribution of participants according to the impairment of the sudomotor function of peripheral small nerve fibers and the algorithm of the risk of cardiac autonomic neuropathy using SUDOSCAN.

	Group I (n = 49)			Group II (n = 75)			Group III (n = 76)			P-value		
	Normal	Moderately reduced	Severely reduced	Normal	Moderately reduced	Severely reduced	Normal	Moderately reduced	Severely reduced			
Feet												
Left	46	2	1	45	20	10	36	24	16	* <0.001 ,	† <0.001 ,	‡0.253
Right	47	1	1	45	21	9	39	26	11	* <0.001 ,	† <0.001 ,	‡0.561
Mean	46	2	1	43	22	10	37	27	12	* <0.001 ,	† <0.001 ,	‡0.569
Hands												
Left	46	2	1	43	21	11	33	28	15	* <0.001 ,	† <0.001 ,	‡0.233
Right	43	5	1	34	28	13	26	32	18	* <0.001 ,	† <0.001 ,	‡0.344
Mean	46	2	1	38	24	13	27	33	16	* <0.001 ,	† <0.001 ,	‡0.166
Heart	48	1	0	28	45	2	24	50	2	* <0.001 ,	† <0.001 ,	‡0.754

P-value is calculated by Chi-squared *t* test. * compared between Group I and II, † compared between Group I and III, ‡ compared between Group II and III. Group I: healthy subjects, Group II: hypertensive patients, Group III: hypertension and diabetes patients. The electrochemical skin conductance (μS) of feet sudomotor nerve function indicates normal: 70–100, moderately impaired: 50–70, and severely impaired: 0–50, while for hands normal: 60–100, moderately impaired: 40–60, and severely impaired: 0–40. The algorithm of cardiac autonomic neuropathy risk is a score of ≥ 30.

Table 4

Prediction of the electrochemical skin conduction values at feet and hands, and risk of cardiac autonomic neuropathy score in hypertensive (Group II) and hypertension with diabetes (Group III) patients using SUDOSCAN.

Groups	Location of nerve fiber	R	R ²	Adjusted prediction (%)	F-value	P-value	β-coefficient						
							Duration (year)	MBP (mmHg)	BMI (kg/m ²)	HbA1c (%)	FSG (mg/dl)	TG (mg/dl)	HDL (mg/dl)
Group II	Feet	0.450	0.203	11.9	2.435	0.028	-1.458	-0.071	0.433	0.797	0.138	-0.020	0.040
	Hands	0.445	0.198	11.4	2.365	0.032	-1.622	-0.173	0.483	1.358	0.468	-0.027	-0.234
	Heart	0.612	0.374	30.9	5.721	<0.001	0.825	0.153	0.586	-1.124	0.083	0.030	-0.081
Group III	Feet	0.329	0.108	1.6	1.178	0.327	-0.750	-0.475	0.533	-0.095	-0.033	-0.006	-0.032
	Hands	0.374	0.140	5.2	1.583	0.155	-0.872	0.039	0.786	0.015	-0.052	0.010	-0.152
	Heart	0.686	0.471	41.6	8.639	<0.001	2.065	0.162	0.922	-0.170	0.007	0.005	-0.201

R: correlation factor, MBP: mean blood pressure, BMI: body mass index, HbA1c: glycated hemoglobin, FSG: fasting serum glucose, TG: fasting serum triglyceride, and HDL: fasting serum high-density lipoprotein-cholesterol. Negative value of β-coefficient indicated inverse correlation, while positive value indicated direct correlation.

Table 5

The area under the curve (AUC) with 95% confidence intervals (C.I.) of the determinants related to the risk of cardiac autonomic neuropathy taking a score of ≥ 30 as a discriminator in hypertensive without diabetes patients (Group II) and hypertensive with diabetes patients (Group III).

Determinants	Group II			Group III		
	AUC	95% C.I.	P-value	AUC	95% C.I.	P-value
Duration of disease (year)	0.725	0.599–0.852	0.001	0.803	0.697–0.909	<0.001
Body mass index (kg/m ²)	0.703	0.581–0.824	0.004	0.665	0.520–0.810	0.022
Mean blood pressure (mmHg)	0.686	0.565–0.807	0.008	0.498	0.353–0.644	0.982
Pulse pressure index	0.555	0.420–0.690	0.433	0.501	0.366–0.637	0.987
Glycated hemoglobin (%)	0.556	0.409–0.702	0.424	0.706	0.580–0.833	0.004
Fasting serum glucose (mg/dl)	0.526	0.373–0.680	0.707	0.574	0.441–0.707	0.301
Fasting serum triglyceride (mg/dl)	0.550	0.408–0.693	0.473	0.534	0.392–0.677	0.631
Triglyceride-glucose index	0.546	0.402–0.689	0.515	0.547	0.406–0.687	0.513
Fasting high density lipoprotein-cholesterol (mg/dl)	0.461	0.325–0.598	0.581	0.353	0.218–0.489	0.041

The basic characteristics of Group II and Group III patients are not significantly different indicating that these factors do not bias the results of this study.

The score of the ESC in the Group III patients is higher than the corresponding data of Group II patients, while the scores of CAN are similar in Groups II and III patients. The mean ESC values of feet and hands in the Group III patients are significantly lower than the corresponding values of Group I, which agreed with the results of Carbajal-Ramírez et al. study on the T2D of variable duration of disease (Carbajal-Ramírez et al., 2019).

As shown in Table 2 and Fig. 1, the SUDOSCAN values of feet and hands of Group II patients are non-significantly different from the corresponding values of Group III, indicating that the sudomotor

nerve fibers are impaired in hypertension. Therefore, SUDOSCAN is a useful diagnostic screening test, which can detect dysfunction of sudomotor nerve fibers. The literature survey did not report the ESC values in hypertension.

The duration of the disease is an important risk factor of CAN. The prevalence of CAN is higher in diabetic patients with a longer duration of illness than newly diagnosed patients (Dimova et al., 2017; Bhuyan et al., 2019). This observation could be attributed to the microvascular complications that occurred with a longer duration of diabetes (Zoungas et al., 2014). The other explanation of abnormal CAN score in Group III patients could be due to mitochondrial injury (Fisher and Tahrani, 2017) as a result of the generation of reactive oxygen and nitrogen species (Ansley and

Wang, 2013). The risk of CAN is significantly higher in Groups II and III patients compared with the corresponding score of Group I subjects. Hypertension is a risk factor of developing CAN in diabetes, which explained a higher score of CAN in Group III patients (Serhiyenko and Serhiyenko, 2018). In Group II patients, the score of CAN is approximately equal to the CAN score of the Group III patients, which due to a higher mean level of blood pressure in Group II compared with Group III. There is evidence that it is possible to halt the progression of CAN with early therapeutic intervention, including vasodilators (Serhiyenko and Serhiyenko, 2015; 2018).

Previous studies showed that there is an association between the number of components of metabolic syndrome, including the BMI, high blood pressure, high blood sugar, and dyslipidemia with autonomic dysfunction in patients without clinical evidence of peripheral or CAN (Zhu et al., 2016).

Obesity indicated by a BMI of ≥ 30 kg/m² is the cause of abnormal SUDOSCAN values in both Groups II and III. This finding agreed with other studies that CAN is associated with obesity, hypertension, and pre-diabetes (Williams et al., 2019). Obesity itself can cause dysfunction of the parasympathetic autonomic nervous system which manifested as abnormal heart rate response and heart rate variability (Laitinen et al., 2011; Akhter et al., 2011). Our study added more information that obesity is a significant discriminator of neuropathy in both hypertensive and T2D patients as shown in Table 5. Recent review highlight the importance of considering obesity as a risk factor for diabetic neuropathy and a reduction of the body weight is a good strategy in the treatment or prevention of T2D neuropathy (Callaghan et al., 2020).

High blood pressure is a significant discriminator of the CAN risk in Group II (AUC is 0.686, $p=0.008$), while it is a non-significant discriminator in Group III (AUC is 0.498, $p=0.982$), which related to the status of controlled blood pressure. Our finding is compatible with other studies carried on a small sample size of 18 hypertensive patients without diabetes and 10 hypertensive patients with diabetes, which assessed CAN by performing cardiovascular tests including the variability of the heart rate (Legrady et al., 2013). Moreover, a cross-sectional-study showed that the percentage of hypertension among T2D patients with CAN was higher than those without CAN (57% versus 49%), indicating that high blood pressure is adversely affecting the ANS (Chung et al., 2017).

On the other side, the AUC of the HbA1c in Group III is a significant determinant of CAN risk, while in Group II patients is a non-significant determinant of developing CAN. A low serum level of HDL-c is a weak determinant of the CAN risk in Group III, but not in Group II. According to the cardiometabolic risk factors, the predicted percentages of the peripheral nerve dysfunction are higher in Group II while the percentage of the CAN is higher in Group III (Table 4).

Therefore, our findings suggested that cardiometabolic risk factors contributed to the abnormal values of the SUDOSCAN in hypertension and/or diabetes (Kseneva et al., 2019).

The strength of the study is the demonstration of peripheral and cardiac autonomic neuropathy in hypertensive patients without pre-diabetes or diabetes in a large sample size. One of the most important limitations of the study is the heart rate variability testing was not carried on.

5. Conclusions

We conclude that SUDOSCAN testing is a simple, useful device, which can detect the impairment of peripheral autonomic small nerve fibers and cardiac autonomic neuropathy in hypertension. Moreover, the duration of the disease and the associated car-

diometabolic risk factors are important predictors of significant SUDOSCAN findings.

Financial support and sponsorship

This study was financially supported by the Al-Mustansiriya University.

CRedit authorship contribution statement

Ismail Ibrahim Hussein: Data curation, Funding acquisition, Investigation, Project administration, Resources, Writing-review & editing. **Safaa Hussein Ali Alshammary:** Data curation, Funding acquisition, Methodology, Resources, Writing-review & editing. **Marwan S.M. Al-Nimer:** Conceptualization, Formal analysis, Software, Supervision, Validation, Writing-original draft, Writing-review & editing.

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.

Acknowledgements

The authors appreciate and extend their thanks to the healthy subjects and patients whose participation made this study possible.

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