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Evaluation of Sympathetic Skin Response Test for The Diagnosis of Diabetic Neuropathy

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Abstract

Aim: Diabetes mellitus (DM) is a very common cause of peripheral neuropathy (PN). The aim of this study was to evaluate the sympathetic skin response (SSR) for the diagnosis of PN in DM patients. **Material and Methods:** We enrolled 101 patients with either type 1 or type 2 DM and 26 age, gender and BMI-matched control subjects. For PN evaluation we used the neuropathy symptom score (NSS), neuropathy disability score (NDS) and vibration perception threshold (VPT); SSR was measured in both palms and soles. **Results:** Patients had significantly lower SSR amplitude in the palms and soles, shorter SSR duration and lower SSR area in the soles compared with the control group. SSR amplitude and area in the soles, correlated strongly with NSS and VPT scores. Measurements of SSR were independent of age, body mass index (BMI), DM duration, as well as ankle-brachial blood pressure index. DM patients with PN had significantly lower SSR amplitude in the palms and longer latency and lower amplitude and area in the soles than patients without PN ($p<0.05$). Moreover, according to receiver and characteristic analysis, an SSR lower and upper limb area of 1.601- 2.811 mV*ms, respectively, as well as an SSR lower and upper limb amplitude value of 0.65-2.64mV, respectively, had good sensitivity and specificity to detect PN. **Conclusion:** We found impaired SSR in patients with DM. SSR area and amplitude in soles, detected PN with good sensitivity and specificity in DM patients. SSR might be used for the evaluation of PN in DM.

Keywords: Diabetes mellitus; Sympathetic skin response; Peripheral neuropathy; Sudomotor function

Introduction

Diabetes mellitus (DM) is the most common cause of peripheral neuropathy (PN) worldwide with an ever-increasing incidence [1]. Painful PN can affect seriously quality of life [2]. On the other hand, almost half of patients with diabetic PN may be asymptomatic, and hence at risk for injuries and diabetic foot complications [2]. For these reasons all patients with DM should be tested annually for PN, starting at the time of diagnosis in type 2 DM (T2DM) and 5 years after the diagnosis of type 1 DM (T1DM) [2].

Apart from peripheral, autonomic nervous system can also be affected in patients with DM and autonomic neuropathy, a kind of small nerve fiber neuropathy, is also one severe complication of DM [1]. Patients with diabetic autonomic neuropathy may experience devastating symptoms, such as hypoglycemia unawareness, orthostatic hypotension, erectile dysfunction, gastroparesis, and diarrhea or constipation [3]. Furthermore, the development of diabetic cardiac autonomic neuropathy (DCAN) increases the risk for painless myocardial ischemia, myocardial infarction, sudden cardiac death, and cardiovascular mortality [4]. Therefore, the American Diabetes Association (ADA) recommends that the clinical screening for DCAN should be routinely performed in patients with diabetes who have microvascular complications [2].

For the diagnosis of diabetic neuropathy, it is essential to exclude other causes that can affect peripheral and autonomic nervous system and may coexist with DM [2]. Several tests can be used to assess patients with DM and neuropathy. Nerve conduction studies are a reliable and easy-to-perform tool for the diagnosis of large nerve fiber peripheral neuropathy in every laboratory of clinical neurophysiology [5].

However, for the investigation and early diagnosis of small fiber neuropathy and especially autonomic neuropathy, several special tests have been proposed, such as cardiovascular autonomic function tests (Ewing test), heart rate variability (HRV), quantitative sudomotor axon reflex test (QSART) and quantification of sweat gland innervation [3]. These procedures, nevertheless, require the cooperation of the patients, are time consuming, and usually are performed in specialized centers with expensive equipment and experienced investigators.

However, one of them, the sympathetic skin response (SSR), is relatively easy to perform with the same apparatus as the nerve conduction studies and parameters like amplitudes or latency has been associated with small nerve fiber neuropathy [6] but also with DCAN and foot ulceration in diabetic foot [7].

This study was designed to investigate the performance of parameters obtained during SSR testing like amplitude and area of the responses in the diagnosis of diabetic PN.

Materials and Methods

The participants

One hundred one Caucasian patients with diabetes; 68 males; age 61.22 ± 10.23 years; body mass index (BMI) 30.14 ± 5.31 kg⁄m2, 91 with T2DM, 10 with T1DM, mean diabetes

duration 14.34 ± 8.38 years, glycosylated hemoglobin A1c (HbA1c) 7.29 ± 0.91% were recruited from the outpatient diabetes and foot clinics of our hospital and 26 healthy age and BMI matched volunteers (age 58.50 ± 12.31 years; BMI 28.89 ± 5.46 kg/m^2) as control subjects.

Inclusion criteria required that participants were older than 18 years and were not diagnosed with cardiovascular diseases, peripheral vascular disease, active foot problems, malignancy, eGFR< 30 ml/min/1.73m^2 or severe liver disease. Subjects on treatment with medications known to effect cardiac autonomic nervous system like b-adrenergic receptor blockers or agonists, and systemic anticholinergic agents were excluded. Patients with other causes for PN apart from DM, such as B12 deficiency, alcohol abuse, hypothyroidism, history of exposure to chemotherapeutic agents, and paraproteinemia were also excluded.

Participants underwent a thorough clinical examination, and a detailed history was obtained. The study was approved by the ethics committee of our hospital, was conducted according to the recommendations of the Declaration of Helsinki [8] and participants provided written informed consent.

Evaluation for neuropathy

Assessment for PN included evaluation of symptoms, signs, and quantitative sensory testing using the neuropathy symptom score (NSS), the neuropathy disability score (NDS), vibration perception threshold (VPT), and Von Frey filament score [9]. Regarding Von Frey filament score, a small nylon filament 5.07 was gently applied on each metatarsal head and the dorsal aspect of the great toes, which corresponds to five sites for each foot. Sensation of the filament's touch would get one point for each site; hence the results could range between zero and ten points. Moreover, loss of sensation at least one site was considered abnormal [2]. A diagnosis of PN was made when NDS ≥ 6 or 3<NDS<5 and NSS ≥ 5, or VPT abnormal and NDS>3 or NSS>3 [10-12].

Participants were also assessed for the presence of peripheral arterial disease (PAD) with the measurement of ankle-brachial blood pressure index (ABI); a value below 0.9 was considered as PAD [13].

Measurement of the SSR

Subjects were sitting comfortable in a quiet and dim lighted room. Surface disk electrodes, 8 mm in diameter, were fixed over the palmar surface of the right hand and plantar surface of the right foot. Reference electrodes were placed at the dorsal aspect of the hand and the foot respectively. Skin impedance was measured using the Nihon Kohden (Tokyo-Japan) Neuropack-Σ (MEB-5500 series) device. The right median nerve was stimulated over the wrist with surface electrodes. Single supramaximal square electrical pulses were delivered with stimulus duration of 1 ms at irregular intervals separated by at least 1 min to avoid habituation with stimulus applied using a constant current stimulator Nihon Kohden (Tokyo-Japan) Neuropack-Σ (MEB-5500 series). Filter bandpass was 0.5-500 Hz, stimulus intensity 50 mA, stimulus duration 0.2 msec, sweep velocity 0.5 sec/division and sensitivity 0.2-0.5 mV/division. Latency was measured from the stimulus artifact to the first deflection from the baseline. The optimal SSR of five stimuli was determined and used in the analysis. SSR latency, amplitude from negative to positive peak and the area under the curve of the potential were also measured [6-7].

Statistical analysis

Student's t-test was used to access the difference of the SSR measurements between patients and control subjects, as well between patients with and without PN.

To test the correlation among the results of SSR and the other tests such as VPT and Filament score, as well with the clinical scales (NSS and NDS), Pearson or Spearman correlations were performed for parametric or non-parametric data, respectively, to examine for associations between the studied parameters.

Finally, the sensitivity and specificity of the significant SSR measurements were estimated by the area under receiver operating characteristic (ROC) curve, using the trapezoidal rule, and optimal cut-off values were calculated by Youden index analysis [11]. Analyses were performed using the SPSS 20.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

As expected from the inclusion criteria, no significant differences were observed in age and BMI between patients with DM and controls (data not shown).

The results of the neurological examination of the participants are presented in Table 1.

	Number	Mean	Minimum	Maximum	SD.
NSS	101	4.40	0	9	3.01
NDS	101	3.86	0	10	2,74
VPT Right	101	24.30	5	50	13,6
VPT Left	101	25.30	0	50	14,32
FILAMENT Right	101	7.02	0	9	2,73
FILAMENT Left	101	6.90	0	9	2,79

NSS: neuropathy symptom score, NDS: neuropathy disability score, VPT: vibration perception threshold, SD: standard deviation

Table 1: The results of the neurological examination of the study subjects with type 2 diabetes mellitus.

Significant differences between patients and control subjects were found using student's t-test regarding the amplitude and area under the curve of the potential of the palm response ($p<0.01$ and $p<0.02$, respectively) and amplitude, area under the curve of the potential and duration of the sole SSR measurements ($p<0.01/p<0.01/p<0.01$, respectively). In contrary, latency did not differ significantly in patients and controls in either palms or soles. In Table 2 are summarized the Data regarding SSR the results of SSR measurements are shown in Table 2.

Patients/controls	**Valid N**	**Mean**	**Minimum**	**Maximum**	**SD**
SSR Latency palm (s)	101/ 26	1.50/1.37	1.1/1.04	4.18/2.48	0.37/0.29
SSR Duration palm (s)	101/ 26	5.44/5.04	2.54/3.42	7.24/6.78	1.17/1.05
SSR Amplitude palm (mV)	101/ 26	2.94/4.62*	0.01/1.05	9.80/10.10	2.21/2.38
SSR area Palm (mV*ms)	101/ 26	3499/ 4827	23/1754	14273/ 10350	2813/ 2429
SSR Latency sole (s)	101/ 26	2.19/2.05	1.54/1.62	5.02/3.90	0.49/0.51
SSR Duration sole (s)	101/ 26	5.27/4.78*	1.78/3.18	6.78/6.36	0.96/0.89
SSR Amplitude sole (mV)	101/ 26	1.05/1.72*	0.02/0.19	5.09/3.4	1.03/0.97
SSR area sole (mV*ms)	101/ 26	1665/ 2450*	24/25	8160/5682	1486/ 1399

*Significant differences ($p<0.050$) for measurements between the two groups. SSR: sympathetic skin response, N: number, SD: standard deviation.

Table 2: SSR parameters measured in the right palms and soles of the participants with diabetes mellitus and controls.

Moreover, the correlations of the above significant SSR measurements and the clinical scales, as well as the VPT and Filament scores are given in Table 3. There is a very strong correlation of the SSR amplitude and area but not of the duration in the sole with NDS, VPT and Filament score. In contrary a weak correlation was observed for the measurements of SSR amplitude and area in the palms with NDS and Filament score. No significant correlations were found between the SSR measurements and age, BMI, duration of diabetes or ABI score neither in the palms nor in the soles of the participants. HbA1c correlated significantly with SSR area in the palm ($r= -0.208$, $p=0.042$).

Linear correlation R/p	**SSR Amplitude Palm**	**SSR Area Palm**	**SSR Amplitude Sole**	**SSR Area Sole**	**SSR Duration Sole**
NSS	-0.10/ 0.27	-0.10/ 0.30	-0.13/ 0.17	-0.07/ 0.45	0.15/ 0.13
NDS	**-0.22/ 0.02**	-0.18/ 0.07	**-0.34/ <0.001**	**-0.29/ 0.002**	-0.07/ 0.47
VRT Right	-0.16/ 0.10	-0.12/ 0.20	**-0.30/ 0.002**	**-0.31/ 0.001**	-0.12/ 0.22
VPT Left	**-0.26/ 0.007**	**-0.23/ 0.02**	**-0.35/ <0.001**	**-0.33/ <0.001**	-0.08/ 0.40
Filament Right	**0.19/ 0.04**	0.16/ 0.10	**0.31/ 0.001**	**0.35/ <0.001**	0.16/ 0.09
Filament Left	**0.23/ 0.01**	0.18/ 0.06	**0.32/ 0.001**	**0.34/ <0.001**	0.11/ 0.23

r: Pearson correlation coefficient; p: p value; NSS: neuropathy symptom score, NDS: neuropathy disability score, VPT: vibration perception threshold; SD: standard deviation, SSR: sympathetic skin response.
The correlations of the statistically significant SSR measurements and the clinical scales, as well as the VPT and Filament scores only in patients with DM are marked in bold.

Table 3: Linear correlation of the SSR parameters with the neuropathy signs in subjects with diabetes mellitus.

The SSR amplitude in the palms was significantly lower in participants with, in comparison with those without PN (student's t-test $p<0.02$). Regarding the SSR responses in the soles the latency was significantly longer, and the amplitude and area significantly lower in the PN+ patients (student's t-test: $p<0.02$, $p<0.002$ and $p<0.001$ respectively).

ROC analysis revealed that the cutoff points of lower and upper limb area under the curve (AUC), which maximized both the sensitivity and specificity to indicate PN, were 1.601 mV*ms (AUC=0.76; 95% CI: 0.67–0.84; sensitivity, 74%; specificity, 63.3%, $P<0.001$) and 2.811 mV*ms (AUC = 0.67; 95% CI: 0.57–0.76; sensitivity, 62%; specificity, 66.2%, $P<0.001$), respectively. Similarly, the optimal cutoff points of lower and upper limb amplitude to indicate PN were 0.65 mV (AUC = 0.75; 95% CI: 0.66–0.84; sensitivity, 64%; specificity, 75.3%, $P<0.001$) and 2.64 mV (AUC=0.69; 95% CI: 0.60–0.79; sensitivity, 68%; specificity, 63.6%, $P < 0.001$), respectively (Figure 1).

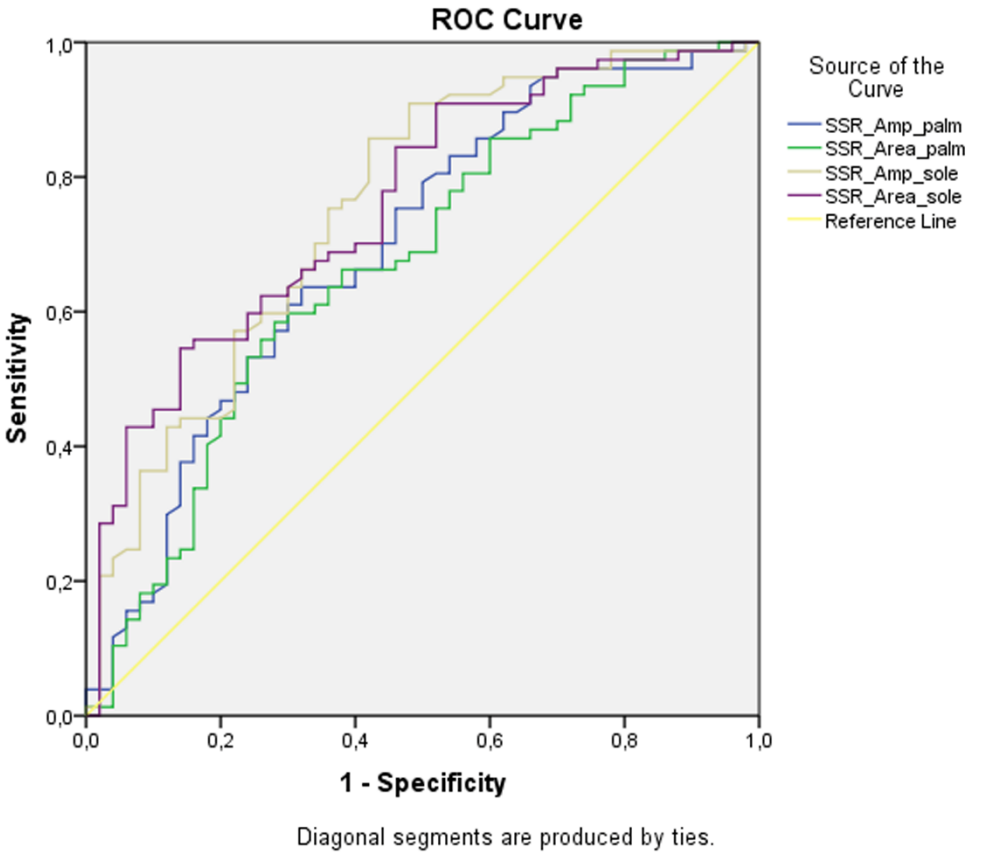

Figure 1: ROC analysis reveals the sensitivity and specificity of SSR area and amplitude for neuropathy detection in patients with DM; Blue line: SSR area for soles, Green line: SSR area for palms, Orange line: SSR amplitude for palms, Purple line: SSR amplitude for soles, SSR: Sympathetic Skin Response.

Discussion

This study has shown impaired sudomotor function assessed by SSR testing in patients with DM in comparison with non-diabetic subjects. In addition, we found that the amplitude and the area of the SSR responses especially in the lower extremities can be used to assess PN with adequate sensitivity and specificity.

The SSR response has been used in the past to assess patients with diabetic polyneuropathy and has been associated with PN [14] and especially with its complications such as diabetic foot, like in an older study of our team [7]. But in that study the correlations were based more in the presence or not of the SSR response in the foot. On the contrary, in the present study using patients with less severe neuropathy we had responses from all patients in both the upper and lower limbs which helped to complete the raw data statistical analysis and to draw more useful and precise conclusions.

First, it was found that the amplitude and the area of SSR response were significantly lower in patients compared to age, gender and BMI index matched control subjects. This observation confirms that the sudomotor function in diabetic patients is affected, as has been shown in previous research even with normal nerve conduction studies [15]. This disorder is important not only because of the dry skin caused by diminished sweating with a risk of developing ulcers in foot (diabetic foot) but also because of the concomitant reduced thermoregulation that affects the quality of life of patients with DM [16]. It is also important that it can be assessed using a relatively simple and sensitive test without the need of more complicated tests available only in specialized centers.

Additionally, the above SSR measurements correlated significantly with the patients' clinical scales and tests evaluating vibration and mechanical pressure threshold, that is VPT and Filament test. This approves that sudomotor dysfunction worsens in diabetic patients in parallel with the deterioration of peripheral neuropathy, increasing the risk for complications such as diabetic foot or those arising from the autonomic nervous system damage including DCAN [2].

Dividing our patients by the clinical criteria of PN, we found that SSR responses were significantly lower in the group of patients with PN, showing that these responses can differentiate patients at increased risk for polyneuropathy and its complications.

To define the optimal cut-off that determines the values of the measurements that could separate patients with or without polyneuropathy, we proceeded to the ROC curve analysis for the amplitude and the area of the SSR responses under the palms and soles. According to the results, all the above measurements could be used with significant sensitivity and specificity to identify each one of the patients with a significantly increased risk to develop PN. Our results are in consistent with recently reported usefulness of the SSR response to predict DCAN [17].

There are limitations in our study; the cross-sectional design does not allow us to establish causality between DM and sudomotor dysfunction. Moreover, the control cohort was small, although well matched with the patients' group; T1DM

was underrepresented too. We should also mention that SSR is not a tool widely available in clinical practice.

In conclusion, we found an impaired sudomotor function assessed by SSR testing in patients with DM compared with matched controls. In addition, SSR area and amplitude in soles had good sensitivity and specificity for the diagnosis of PN. These observations favor the use of SSR for the assessment of PN in patients with DM. Nevertheless, more research is needed before SSR can be used in clinical practice.

Conflict of interest and Funding

There was no funding for this study and no authors have conflicts of interest pertaining to the information in this manuscript.

Declarations of interest

None

Authors' Contributions

Substantial contributions to the design or development of the study; P.K., N.T.; Substantial contributions in the collection, analysis and interpretation of data; P.K., N.T., E.S., E.T.; Substantial contributions in the writing of the article or in its critical revision; P.K., N.T., E.S., E.T. Substantial contributions in the approval of the final version: P.K., N.T., E.S., E.T.

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