The sympathetic skin response in diabetic neuropathy and its relationship to autonomic symptoms

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ABSTRACT

الأهداف: تقييم الاستجابة الودية للجلد عند السعوديين المصابين بمرض السكري باعتبارها المقياس الرئيسي للإصابة الودية العصبية الطرفية حيث لاتوجد دراسات في المملكة العربية السعودية في هذه الحالة.

الطريقة: أجريت هذه الدراسة في مستشفى الملك خالد الجامعي بالرياض, المملكة العربية السعودية خلال الفترة مابين حزيران 2006م و حزيران 2007م. سجلت الاستجابة الودية الجلدية عند 18 من الأصحاء، تبعها تسجيل مماثل مع تخطيط الأعصاب الطرفية عند 50 مريضا مصابا بمرض السكري يعاني جميعهم من اعتلال الأعصاب الطرفية. أجريت مقارنة بين الاستجابة الودية عند المصابين باعتلال الأعصاب الودية و غير المصابين بهذا الاعتلال.

النتائج: أظهرت الدراسة وجود استجابة ودية عند كل الأصحاء و عند 32من المصابين بالسكري، غياب الاستجابة لدى 14 من أصل 16 مريضا يعانون من أعراض الإصابة بالأعصاب الودية، غياب الاستجابة لدى 4 مرضى من أصل 34 مريضا لا يعانون من أعراض اعتلال بالأعصاب الودية. وجدنا علاقة قوية بين غياب الاستجابة الودية واعتلال الأعصاب الودية الطرفية وذلك باستخدام اختبار فيشر الإحصائي ($p<0.001$) دون وجود رابط مع عمر المريض أو مدة إصابته بالسكري. كما تبين أن لهذه العلاقة حساسية بنسبة 87.5%، خاصية بنسبة 88.2%، قيمة التكهن الإيجابي بنسبة 77.8% و قيمة التكهن السلبي بنسبة 93.7%.

خاتمة: يمكن اعتبار غياب الاستجابة الودية كمؤشر على اعتلال الأعصاب الودية الطرفية ويمكن اعتماده في متابعة مرضى السكري السعوديين.

Objective: To examine the utility of the sympathetic skin response (SSR) as a measure of impaired autonomic function among diabetic patients in Saudi Arabia.

Methods: In this case-control study, baseline SSR was obtained from 18 healthy subjects, followed by nerve conduction studies, and SSR testing on a consecutive cohort of 50 diabetic patients with peripheral neuropathy. The SSR in diabetic patients was compared between those with autonomic neuropathy and those without autonomic neuropathy. This study was conducted at the King Khaled University Hospital, Riyadh, Saudi Arabia, from June 2006 to June 2007.

Results: The SSR was present in all healthy subjects, and in 32 diabetic patients. Among 16 patients with autonomic neuropathy, the SSR was absent in 14 and present in 2, while 4 of 34 patients lacking evidence of autonomic neuropathy had absent SSR. Using Fishers' exact test, we found a strong association between absent SSR and autonomic neuropathy ($p<0.001$), however, not with age or duration of diabetes mellitus. As a diagnostic test of autonomic neuropathy, the SSR had a sensitivity of 87.5%, a specificity of 88.2%, a positive predictive value of 77.8%, and a negative predictive value of 93.7%.

Conclusions: Absence of the SSR is a reliable indicator of autonomic neuropathy among patients with diabetes mellitus in Saudi Arabia.

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Autonomic neuropathy is a recognized complication of diabetes mellitus,[1] in which it plays a pathogenic role in neuropathic pain, abnormalities of sweating, Charcot joints, foot ulcers, and bladder dysfunction.[2-4] A strong association has been observed also between autonomic neuropathy and increased cardiovascular

risks in diabetic subjects.[5] The prevalence of autonomic neuropathy among diabetics depends on the population studied, ranging from a third of randomly selected patients to as much as two-thirds in those with peripheral neuropathy.[6,7] Yet, early symptoms of autonomic dysfunction may be so subtle and non-specific that they may not be recognized.[8] Assessment of autonomic function may thus be of considerable significance in the care of patients with diabetes mellitus. While nerve biopsy or microneurography provide definitive evidence of autonomic neuropathy, non-invasive tests of autonomic function may be more appropriate for routine clinical use. The sympathetic skin response is a transient change in the electrical potential of the skin evoked by a variety of stimuli.[9,10] When elicited by electrical stimulation, the response uses a multi-synaptic reflex arc, which includes afferent large myelinated sensory fibers, central sympathetic relays, and efferent unmyelinated preganglionic and postganglionic sudomotor fibers.[10] Several studies have documented abnormalities in the sympathetic skin response (SSR) in peripheral sympathetic neuropathies,[7,11,12] as well as in lesions involving central sudomotor pathways.[13,14] However, a number of studies have questioned the validity of this technique as a reliable measure of autonomic function owing to its wide variability within the normal population,[15] a tendency to habituate with repeat testing,[16] and an inconsistent correlation with symptoms and signs of autonomic nervous system involvement in diabetic patients.[17] The aim of the present study was to examine the utility of the SSR as a measure of autonomic function in patients with diabetic polyneuropathy.

Methods. *Subjects.* Sixty-eight subjects were included in the study. Eighteen subjects (10 males, 8 females) were healthy volunteers who were studied to obtain the normal SSR. Volunteers were age-matched to cases, had no evidence of diabetes mellitus or neurologic disease on history and examination, and were not taking medications known to affect autonomic function during the study period. All study subjects gave informed consent, and the local Ethical Committee approved the study. Inclusion criteria for diabetic subjects were the presence of distal symmetric polyneuropathy according to the case definition criteria of the American Academy of Neurology,[18] which requires abnormal findings on nerve conduction studies (NCS) in a patient having at least 2 of the following: pain, tingling or numbness in the feet, distal muscle weakness or atrophy, reduced distal sensation, and decreased or absent ankle jerks. Exclusion criteria included stroke, carpal tunnel syndrome, and the presence of a peripheral nerve disorder not attributed to diabetes. Following a complete history and neurologic examination, data from each patient were recorded on a standard questionnaire, which classified patients as having either peripheral neuropathy only (PN) or peripheral neuropathy with autonomic neuropathy (PNAN). Autonomic neuropathy was defined as the presence of postural hypotension, abnormalities of sweating, gastrointestinal disturbance, urinary incontinence or impotence, occurring singly or in combination.

Nerve conduction studies. Using a Nicolet Biomedical Electromyography (EMG) system (Nicolet GMbH Kleinosthein, Germany), NCS were performed according to standard protocol.[19] Parameters measured were: motor conduction velocities (MCV) and compound muscle action potentials (CMAP) of the median, ulnar, tibial, and peroneal nerves evoked by stimulation at the wrist or ankle, distal motor latencies (DL) of median and ulnar nerves evoked by stimulation at the wrist, and sensory conduction velocity (SCV), and amplitude of sensory nerve action potential (SNAP) of median, ulnar, and sural nerves evoked by stimulation at the wrist or calfskin. Peripheral neuropathy was considered present when abnormal parameters were obtained in 2 or more nerves, one of which must be the sural nerve.

Measurement of SSR. The SSR testing was performed in a semi-darkened warm condition, with patients lying supine. Room temperature was in the range of 26-30°C, and hand and feet temperatures were maintained at 32-36°C. Using the Nicolet Biomedical EMG system, SSR was recorded from upper and lower limbs simultaneously, following a single electrical stimulation of the contra-lateral median nerve. Stimulations were repeated 4 times, at 2-4 minute intervals, to avoid habituation. Standard surface EMG disc electrodes were attached to the palms and the soles, with the recording electrodes at the center of the palms and soles, and the reference electrodes attached to the dorsal surfaces of the hands and feet. An electric stimulus of 10-30 mA intensity and 0.1 msec duration was applied, with band pass set at 0.5-2500 Hertz. The SSR responses were recorded as either present or absent. The SSR was considered absent if no response were recordable from at least one lower limb.

Statistical analysis. The SPSS for Windows version 11.5 was used for statistical analysis. Student's unpaired t test was used for comparison of continuous variables, while Fisher's exact test was used for comparison of nominal data. Spearman rank-order was used to test for correlations. *P*-values less than 0.05 were considered significant.

Results. The mean age of diabetic patients was 46.9±13 years, while that of healthy controls was

41.4±14.5 years, however, this difference was not statistically significant (p=0.13). There were 30 males and 20 females in the diabetic group, consisting of 41 patients with type I diabetes, and 9 patients with type II diabetes. Thirty-four patients had peripheral neuropathy, while 16 patients had peripheral neuropathy with autonomic neuropathy. Features of autonomic neuropathy included orthostatic hypotension documented in 5 patients, impotence in 7 patients, persistent diarrhea in 2 patients and abnormal sweating in 4 patients, with 2 patients having a combination of these features. Nineteen diabetic patients had hypertension, of whom 16 were on angiotensin converting enzyme (ACE) inhibitors, taken alone (11 patients), or in combination with a calcium channel blocker (3 patients) or a beta-blocker (2 patients). No patient was on a diuretic at the time of the study. The SSR was present in all healthy subjects, and in 32 of 50 diabetic patients (**Figure 1**).

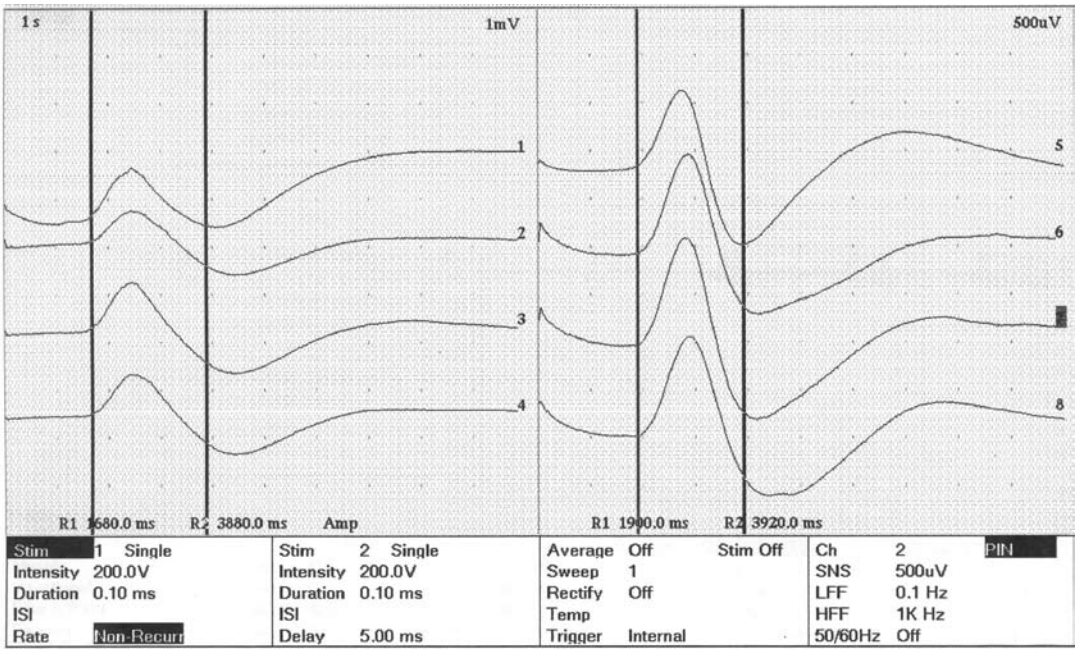

Figure 1 - Normal sympathetic skin responses obtained from **a**) the upper limbs, and **b**) lower limbs of a healthy 42-year-old male, following stimulation of the right median nerve at the wrist.

Table 1 - Clinical and laboratory findings in 50 diabetic patients grouped according to SSR response.

Clinical or laboratory variable	SSR present	SSR absent	*P*-value
Diabetic patients with PN	32	18	0.001
Diabetic patients with PNAN	2	14	0.001
Age, years (mean±SD)	44.7±12.7	47.8±15.6	0.39
Duration of diabetes, (years, mean±SD)	8.3±6.5	11.9±6.7	0.70
Patients on insulin (%)	31.3	27.8	1.0
Body mass index	28.32±7.64	24.76±5.27	0.24
HbA1C (%)	8.99±1.60	9.37±1.87	0.57
Ulnar nerve CMAP (μV, mean±SD)	5.39±2.21	3.92±1.6	0.09
Ulnar nerve MCV (m/sec, mean±SD)	52.42±8.36	43.14±7.18	0.008
Ulnar nerve SCV (m/sec, mean±SD)	51.25±7.62	43.27±19.58	0.09

SSR - sympathetic skin response, PN - peripheral neuropathy,
PNAN - peripheral neuropathy with autonomic neuropathy, SD - standard deviation,
HbA1C - glycosylated hemoglobin, CMAP - compound muscle action potential amplitude,
MCV - motor conduction velocity, SCV - sensory conduction velocity, m/sec - meters per second.

Of 16 patients with autonomic neuropathy, the SSR was absent in 14, and present in 2. Conversely, 4 of 34 patients without autonomic neuropathy also had absent SSR. Using Fishers' exact test, a strong association was observed between absence of the SSR, and the presence of autonomic neuropathy ($p<0.001$). While diabetic patients with autonomic neuropathy had longer duration of diabetes (12.4±7 years) compared to those without it (8.2±6.2 years, $p=0.04$), the difference in duration of diabetes between those with SSR absent, (11.9±6.7 years) or present (8.3±6.5 years) was not statistically significant ($p=0.07$). There was also no correlation between the SSR and patients' age. Taking clinical features of autonomic neuropathy as the reference standard, absence of the SSR as an indicator of autonomic neuropathy had a sensitivity of 87.5%, a specificity of 88.2%, a positive predictive value of 77.8%, and a negative predictive value of 93.7%. Ulnar nerve MCV was significantly slowed among diabetic patients with absent SSR compared to those in whom the SSR was present ($p=0.008$), although no difference was observed between the 2 groups in respect of the ulnar nerve SCV or CMAP, body mass index, insulin therapy, fasting plasma glucose, or HbA1C levels (**Table 1**).

Discussion. Absence of the SSR in 87.5% of our patients with autonomic neuropathy was consistent with observations made in other studies. In a study of diabetic patients with peripheral neuropathy, Soliven et al[7] found the SSR absent in 90% of those with autonomic neuropathy, and in 66% of the overall cohort. Similarly, Niakan and Harati[11] reported absence of the SSR in 83% of 72 diabetics with peripheral neuropathy, half of whom had autonomic dysfunction in the form of postural hypotension and an abnormal Valsalva test. In the present study, the SSR was also absent in 4/34 (11.8%) patients who had no evidence of autonomic neuropathy. There are 2 possible explanations for these findings. A few studies have shown that over half of diabetic patients with no autonomic symptoms, exhibit abnormalities on neurophysiologic tests of autonomic function,[20,21] suggesting that absence of the SSR may be an indicator of subclinical autonomic neuropathy. However, a second explanation was suggested by Uncini et al,[10] who proposed that peripheral neuropathy is sufficient to abolish the SSR, in the absence of autonomic neuropathy. The authors reported cases of demyelinating neuropathy in which the SSR was absent on electrical stimulation and was obtainable by deep breathing, suggesting an interruption of afferent pathways that were by-passed when SSR was elicited by methods other than electrical stimulation of nerves. Their conclusion that lesions to autonomic efferents as well as sensory afferents could each abolish the SSR independently may well explain the findings in 4 of our patients who had absent SSR in the absence of autonomic neuropathy. However, current evidence suggests that all 4 probably had subclinical autonomic neuropathy as the SSR has shown consistent correlations with other tests of autonomic function such as orthostatic hypotension,[11] R-R interval variation,[7,12] sweat volume,[22] skin blood flow,[3] and bladder function.[4]

What constitutes an abnormal SSR still remains a matter of debate. While some studies have reported the SSR only as absent or present,[9,11] others analyzed the SSR waveform,[23] amplitude, and latency.[24,25] However, analysis of the SSR can be confounded by the wide variability of its waveform within the normal population,[15,23] and while some investigators consider reductions in SSR amplitude of greater significance than delays in SSR latency,[25,26] others maintain views to the contrary.[27]

Major limitations of our study include its small sample size, and the exclusion of other tests of autonomic function such as R-R interval variation with breathing, a sensitive marker of impaired parasympathetic activity. However, we do not believe that these shortcomings will significantly affect our results, since the main aim of the present study was to evaluate the utility of the SSR as a measure of impaired autonomic function.

In conclusion, we have shown the SSR to be a reliable test of autonomic function in diabetic patients with peripheral neuropathy. We advocate for the inclusion of this simple test in the evaluation of diabetic patients with suspected autonomic neuropathy. Further studies are needed, however, both to clarify the role of SSR testing in asymptomatic diabetics, and to determine the utility of SSR amplitude and latency in the assessment of autonomic function.

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