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Diabetes Mellitus Type Has Impact on Cutaneous Silent Period

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ABSTRACT

Introduction: Neurophysiological tests allow accurate assessment of the function of the peripheral nervous system. Detection of neurophysiological changes allows us to understand the neurological clinical symptoms and signs of patients with type 1 and type 2 diabetes and the possibility for their symptomatic treatment. **Aim:** Evaluate the effect of diabetes mellitus on the "cutaneous silent period" in detecting diabetic polyneuropathy. **Material and Methods:** The study included 150 subjects, 90 suffering from diabetes, divided into three groups of 30, depending on the disease duration, and a control group of 60 respondents not suffering from diabetes or other polyneuropathies. The control group are referred for EMG analysis on another basis (cervical radiculopathy, brachialgia, etc.). Group 1 consisted of 30 subjects with diabetes mellitus type 2 and duration of illness up to 5 years. Group 2 consisted of 30 subjects with type 2 diabetes mellitus 2 and illness duration from 5 to 10 years. Group 3 consisted of 30 patients with type 1 diabetes mellitus. The study groups consisted of patients referred for EMNG analysis to the EMG office of the Clinical Center of Sarajevo University, Neurology Clinic and the Neurophysiology Laboratory in Ljubljana, from July 1, 2011 to May 1, 2016. All patients were examined neurologically and electroneurographic analysis was performed. **Results:** A statistically significant difference was found in the incidence of pathologic CSP with respect to the study groups, $\chi 2 = 26.153$; p=0.001. Pathologic CSP was more common in group 1 and group 2 of subjects (56.17%) compared to group 3 and control subjects, where it occurred in 13.3% of the cases. **Conclusion:** The pathological cutaneous period of silence was more frequent in subjects of group 1 and group 2, that is, in subjects with DM type 2, compared to subjects with DM type 1.

Keywords: diabetes mellitus, polyneuropathy, neurophysiology, cutaneous silent period.

1. INTRODUCTION

Neuropathy is a common complication of diabetes mellitus and can cause dysfunction of thicker myelin fibers (Aα), thin myelin fibers (Aδ) and non-myelin fibers (C-fibers). In some patients with diabetic neuropathy, thinner fibers may be more severely affected than thicker fibers (1, 2). Thin fibers are more susceptible to damage, and their damage precedes damage to thick fibers in the development of diabetic neuropathy (3). Diabetics with neuropathy often complain of a burning sensation and tingling, especially in the distal parts of the extremities (4, 5). This presentation may underlie thin-fiber neuropathy. Thin-fiber neuropathy cannot be easily detected with standard electrophysiological tests, and the patient may exhibit normal strength, normal reflexes and electrophysiology. Therefore, standard clinical tests are not sensitive enough to detect initial changes on thin fibers, leaving initial sensory neuropathy undiagnosed. Despite its high frequency and clinical relevance, there are only a few methods for quantifying dysfunction of peripheral thin fibers. These include quantitative sensory testing (6), analysis of heart rate variability, assessment of motor-axon reflexes (7), or skin biopsy (8). However, the availability of these procedures in clinical practice is limited, and the sensitivity of these methods is questionable. Early detection of thin-fiber dysfunction would reduce severe neuromuscular complications and facilitate epidemiological monitoring of the incidence of neuropathy in diabetics. Clinical interest in the cutaneous silent period originate from its potential utility for evaluating segments and components of sensory nerves that are not well evaluated by standard electrophysiological methods (9). In addition, it provides information for understanding central nervous system disorders and their impact on motor and sensory function (10, 11). CSP is a potential electrophysiological method for the diagnosis of dysfunction of

peripheral thin fibers. During the cutaneous period of silence, temporary suppression of muscular contraction is achieved through postsynaptic inhibition of motor neurons or presynaptic inhibition of excitatory inputs of motor neurons reflecting voluntary contraction. Cutaneous afferent neurons are associated with various levels of the nervous system, so they have an effect on motor activity. During motor nerve stimulation, a mixture of excitatory and inhibitory effects is produced, which depends on the location and intensity of inputs, the specific muscles involved, and whether the task requires contraction or muscle relaxation. Electromyographic activity, one of the most powerful cutaneous reflexes, determines the cutaneous silent period, and it consists of a short break in the voluntary contraction after extensive stimulation of the cutaneous nerve and is useful for studying the circular flow of sensorimotor integration at the spinal and supraspinal levels (10). CSP is a transient suppression of the electrical activity of a muscle, during maximum effort, after vigorous stimulation of its nerves. The main hypothesis of electrical generation during the cutaneous silent period involves spindle afferents, cutaneous afferents, inhibitory spinal reflex systems, internuncial neurons, and descending active inhibitions from the motor cortex (12, 13). According to various reports, the cutaneous silent period is a combination of temporary cessation of muscle discharge of spindles, Golgi tendons, and cutaneous afferent nerve fibers (14). The cutaneous silent period is thought to arise from thin myelin high threshold cutaneous nerve fibers with slow conduction. The cutaneous silent period is an inhibitory spinal reflex, mediated by cutaneous Aδ afferent fibers (15,16). There are also studies to support the following theory. High intensity stimulations, usually 10 times the perceptual threshold, are required to evoke the cutaneous silence. Strong cutaneous nerve stimulation was then followed by a synchronized cutaneous silence period in several muscle groups. The characteristic distribution between the upper and lower extremities and cranial muscles depends on the site of stimulation (16).

2. AIM

Evaluate the effect of diabetes mellitus on the cutaneous silent period in detecting diabetic polyneuropathy.

3. MATERIAL AND METHODS

The study included 150 subjects, 90 suffering from diabetes, divided into three groups of 30, depending on the disease duration, and a control group of 60 respondents not suffering from diabetes or other polyneuropathies. The control group consisted of 60 subjects not suffering from diabetes mellitus or some other polyneuropathies and who are referred for EMG analysis on another basis (cervical radiculopathy, brachialgia, etc.). Group 1 consisted of 30 subjects with diabetes mellitus type 2 with up to 5 years duration of illness. Group 2 consisted of 30 subjects with type 2 diabetes mellitus 2 and duration of illness from 5 to 10 years. Group 3 consisted of 30 subjects with type 1 diabetes mellitus. The groups studied consisted of patients referred for EMNG analysis to the EMG laboratory of the Clinical Center of Sarajevo University, Neurological Clinic and the Neurophysiological Laboratory in Ljubljana, from July 1, 2011 to May 5, 2016. The study is of a prospective, experimental-laboratory, clinical and applied character. The three groups included subjects of both sexes suffering from diabetes mellitus. The control group included the following subjects: healthy volunteers, subjects of both sexes, over 18 years of age, with negative anamnestic data in terms of the existence of any metabolic disease, or other types of polyneuropathies, normal cognitive parameters, psychologically healthy persons capable of adequately completing the forms foreseen for this study. All subjects were analyzed for the neurophysiological parameter of the peripheral nerves, or the angular period of silence. The computer neurophysiological system of MedelecSinergy, USA, was used. Standard electrodes from Viasys were used as electrodes, namely the large bipolar stimulator (W/O 256644) and the registration electrodes (09497). The apparatus for EMNG analysis in Ljubljana is identical to that at the Clinical Center of Sarajevo University, Neurological Clinic–Medelec Synergy. The examination is done without anesthesia and is not painful if there is cooperation with the patient. It lasts from 30 to 45 minutes and can be more or less uncomfortable. The test is performed on technologically highly computerized apparatus, in this research the Sinergy EMNG machine, where the conductivity of peripheral nerves, motor and / or sensory, is usually first examined.

4. RESULTS

Figure 1 shows the average values of the first latency of the cutaneous period. The mean values of L1 in the subjects of group 1 were 101.93±2.47 ms and were 10.76% higher than the values determined in the control group of subjects (92.36±1.21). This difference was statistically significant (p<0.001). In group 2 subjects, the values of the first latency of the cutaneous silent period were 100.93±2.40 and were 9.7% higher than the values determined in the control group. Also, this difference was statistically significant (p<0.002). However, the values of the first latency of the cutaneous silence period in group 3 did not differ significantly from the values determined in

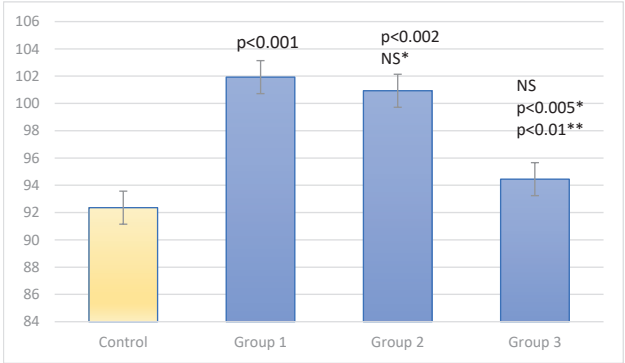

Figure 1. Values of the first latency (L1) of cutaneous silent period in patients with diabetes mellitus. he average values of the first latency (L1) of the cutaneous period of silence (X ± SEM) in the control group and the subjects with diabetes mellitus are presented. p–significance, NS–not significant, *–in relation to Group 1, **–in relation to Group 2

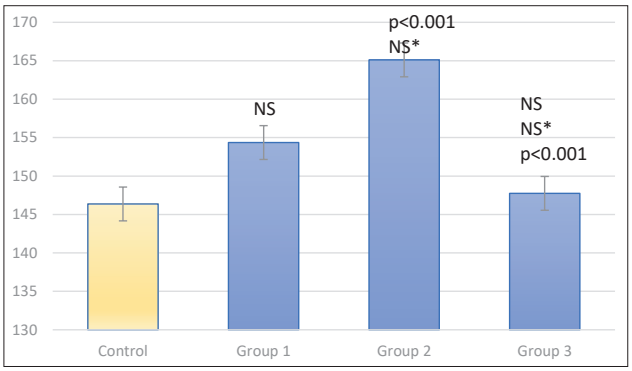

Figure 2. Values of second latency (L2) of cutaneous silent period in patients with diabetes mellitus. Average latency (L2) values of cutaneous silent period (X±SEM) in the control and diabetic subjects were presented. p–significance, NS–not significant, *–in relation to Group 1, **–in relation to Group 2

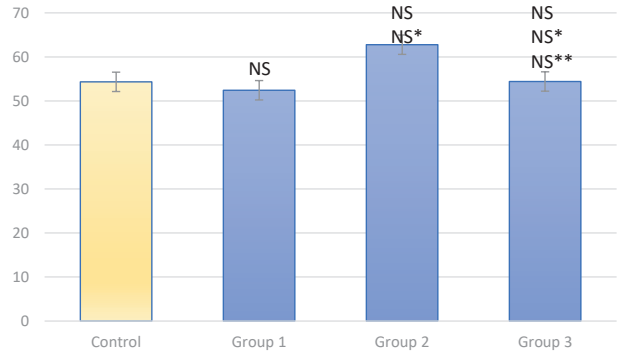

Figure 3. Differences in mean values of second and first latency of cutaneous silent period in patients with diabetes mellitus. The differences between the mean values of the second and first latencies of the cutaneous silent period (X±SEM) in the control group and the subjects with diabetes mellitus were presented. p–significance, NS–not significant, *–in relation to Group 1, **–in relation to Group 2

the control group. No statistically significant difference was found between group 1 and group 2 in the mean values of the first latency of the cutaneous silent period. However, statistically significant lower first latency was observed in group 3 subjects compared to group1 and group 2 subjects ($p<0.005$; $p<0.01$).

Figure 2 shows the average values of the second latency of the cutaneous silent period. The mean L2 values in the subjects of group 1 were 154.36±4.09 ms and were 5.5% higher than the control group (146.37±2.2). This difference was not significant. In group 2 subjects, the mean values of the second latency of the cutaneous silent period were 165.11±4.05 ms and were 12.8% higher than the values determined in the control group of subjects. This difference was statistically significant ($p<0.001$). The average values of the second latency of the cutaneous silent period in the group 3 subjects were 147.75±2.29 ms and were not statistically significant compared to the values determined in the control group of subjects. There was no statistically significant difference between group 1 and group 2 as well as between group 1 and group 3 in the average values of the second latency of the cutaneous silent period. However, a statistically lower average value of the second latency of the cutaneous silence period in group 3 was found compared to the values determined in group 2.

Figure 3 shows the differences in the average values of the second and first latencies of the cutaneous silent period. The average values of the difference between the second and the first latency in the group 1 subjects was 52.42±3.85 ms, and in the group 2 subjects it was 62.77±4.47 ms (6.3-128). In group 3 it was 54.41±1.95 ms, and in the control group subjects it was 54.33±1.98 ms. No statistically significant difference was found in the mean values of the difference between L2 and L1 KPT between the tested groups with diabetes mellitus and the control group of subjects, as well as between individually between each group of subjects with diabetes mellitus.

GROUPS	CSP			
	Physiological		Pathological	
	N	%	N	%
Control	52	86.7	8	13.3
Group 1	13	43.3	17	56.7
Group 2	13	43.3	17	56.7
Group 3	26	86.7	4	13,3
Total	104	69.3	46	30.7

Table 1. Frequency of pathologic findings of cutaneous silent period (CSP) in subjects with diabetes mellitus. Numerical and percentage incidence of physiological and pathological findings of cutaneous silent period in the control and diabetic subjects were presented.

Using the chi-square test in Table 1, a statistically significant difference in the incidence of pathologic CSP was found with respect to the study groups, $\chi 2=26.153$; $p=0.001$. Pathologic CSP was more common in group 1 and group 2 subjects (56.17%) compared to group 3 and control subjects, where it occurred in 13.3% of the subjects. No correlation was found between CSP and biochemical parameters in subjects with diabetes in all three study groups.

5. DISCUSSION

By analyzing the latency of the cutaneous silent period in this study, we came to the following data. The mean L1 values in the group 1 subjects were 101.93±2.47 and were 10.76% higher than the values determined in the control group (92.36±1.21). This difference was statistically significant ($p<0.001$). In Group 2 subjects, the values of the first latency of the cutaneous silent period were 100.93±2.40 and were 9.7% higher than the values determined in the control group. Also, this difference was statistically significant ($p<0.002$). However, the values of the first latency of the cutaneous silent period in group 3 did not differ significantly from the values determined in the control group. No statistically significant difference was found between group 1 and group 2 in the mean values of the first latency of the cutaneous silent period. However, statistically significant lower first latency was observed in group 3 subjects compared to group1 and group 2 subjects ($p<0.005$; $p <0.01$). The mean L2 KPT values in the subjects of group 1 were 154.36±4.09 and were 5.5% higher than the control group (146.37±2.2). This difference was not significant. In group 2 subjects, the mean values of the second latency of the cuta-

neous silent period were 165.11±4.05 and were 12.8% higher than the values determined in the control group of subjects. This difference was statistically significant (p<0.001). The average values of the second latency of the cutaneous silent period in the group 3 subjects was 147.75±2.29 and were not statistically significant compared to the values determined in the control group of subjects. There was no statistically significant difference between group 1 and group 2 as well as between group 1 and group 3 in the average values of the second latency of the cutaneous silent period. However, a statistically lower average value of the second latency of the cutaneous silent period in group 3 was found compared to the values determined in group 2.

Kim et al. (17) performed a study to evaluate whether the cutaneous silent period was metrically useful for detection thin-fiber neuropathies in diabetics. The cutaneous silent period was measured on the abductor pollicis brevis muscle in 30 healthy subjects and 110 diabetics, which were divided into three subgroups (subjects with neuropathies of thick fibers, thin fibers and asymptomatic patients. The relationship between the cutaneous silent period and clinical characteristics between groups was analyzed. the group of patients had a significant delay of the cutaneous silent period relative to the control group, which was correlated with the results of this study. The authors conclude that delays in the cutaneous silent period can be a useful tool in assessing damage to thin neural fibers in diabetics.

Onal et al. (18) conducted a study aimed at assessing changes in the cutaneous silent period in patients with type 2 diabetes mellitus. The study included 43 subjects with type 2 diabetes mellitus and 41 healthy subjects as a control group. They investigated the duration of CSP latency as well as the difference between the upper and lower extremities. CSP delay was longer at the lower extremities (122.1+/-15.5 vs. 96.4+/ 6.4 ms; p<0.001). CSP duration was shorter (29.5+/-8.9 vs. 43.1+/-5.0 ms; p<0.001), and the delay difference was longer (48.1+/-12.6 vs. 22.7+/-3.7; p<0.001) in subjects diagnosed with diabetes mellitus than in control subjects. The difference was more significant in patients with neuropathic pain present. Evaluation and upper extremity CSP revealed a significant difference. Which is correlated with the results of the conducted study. In conclusion, the authors state that evaluation of CSP, together with nerve conduction studies, has been proven useful and that the latency difference performance and length of CSP may be valuable parameters in the electrophysiological evaluation of diabetics with thin-fiber neuropathies.

Pinar et al. (19) conducted a study to verify the parameters of the cutaneous silent period (latency and duration) in symptomatic diabetics, with clinically defined thin-fiber neuropathy and normal nerve conduction. The study included 31 diabetics and 30 healthy control subjects. The results indicate that the parameters of the cutaneous silent period did not differ statistically between the studied groups, while in the lower extremities patients with diabetes had an extended latency of the cutaneous silent period (p=0.018) and a shortened duration of the cutaneous silent period (p<0.001). The upper latency limit of the cutaneous silent period was 115.9 ms and the lower 31.5 ms. According to these values, 4 (12.9%) of the subjects had an abnormal delay of the cutaneous silent period and 10 (32.3%) of them had an abnormal duration of the cutaneous period. The sensitivity of the cutaneous silence method in this study was 32.6% and the specificity was 96.7%.

6. CONCLUSION

The cutaneous silent period (CSP) is a sensitive method for the early detection of diabetic polyneuropathy, with the measurement of other neurophysiological parameters. CSP was directly related to the duration of diabetes and pathological findings were more common in DM type 2 subjects compared to DM type 1 and control subjects. No correlation was found between CSP and biochemical parameters in subjects with diabetes in all three study groups.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms.
- **Author's contribution:** Both authors gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. Each author had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflicts of interest:** There are no conflicts of interest
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