Journal of Neurological Sciences [Turkish] **32:(2)**# 44; 311-319, 2015
http://www.jns.dergisi.org/text.php3?id=884
Research Article

Effect of Alpha-Lipoic Acid on Small Fibre Neuropathy Findings in Patients With Type 2 Diabetes Mellitus

Mehmet YÜCEL[1], Serdar TAŞDEMİR[1], Ahmet ÇETİZ, Hakan AKGÜN[1], Abdullah TAŞLIPINAR[2], Çağdaş ERDOĞAN[3], Ümit H. ULAŞ[1], Zeki ODABAŞI[1] Yaşar KÜTÜKÇÜ[1]

[1]Gülhane Military Medical Academy, Department of Neurology Ankara Turkey [2]Gülhane Military Medical Academy, Department of Endocrinology Ankara Turkey [3]Pamukkale University, Department of Neurology Denizli Turkey

Summary

Objective: Cutaneous silent period (CSP) is an inhibitory spinal reflex and the afferent arm of this response involves A-delta nerve fibers. The aim of this study was to investigate CSP parameters in patients with type 2 diabetes mellitus (T2DM) and to examine the effects of alpha-lipoic acid (ALA) treatment on CSP. To the best of our knowledge, this investigation has not yet been carried out until date.
Methods: Seventeen patients with T2DM and 23 healthy volunteers were studied. CSP latency and duration in the upper and lower extremities of both the groups were examined. In T2DM patients, the variables were examined before and after ALA treatment.
Results: CSP latency in T2DM patients was longer than that in the controls. In the patient group, CSP latency in the upper and lower extremities and CSP Latency Differences (LD) shortened in the third month after treatment compared with the pre-treatment values.
Conclusions: The results suggest that ALA treatment may alleviate small-fiber neuropathy in T2DM patients and that CSP may be a useful supportive tool to evaluate ALA treatment effectiveness.

Key words: Cutaneous silent period, alpha-lipoic acid, small-fiber neuropathy, type 2 diabetes mellitus

Alfa- Lipoik Asit'in Tip 2 DM'li Hastalarda İnce Lif Nöropatisi Üzerine Etkisinin İncelenmesi

Özet

Amaç: Kutanöz Sessiz Periyot (KSP) bir inhibitör spinal reflekstir ve bu yanıtın afferent kolu A-delta sinir liflerini içerir. Bu çalışmanın amacı tip 2 diabetes mellituslu (T2DM) hastalarda KSP parametrelerini ve alfa-lipoik asit (ALA) tedavisinin KSP üzerine etkisini araştırmaktır. Şu andaki bilgimize göre şu ana kadar böyle bir çalışma yapılmamıştır.
Gereç ve Yöntem: 17 T2DM'li hasta ve 23 sağlıklı gönüllü çalışmaya alınmıştır. Her iki grupta KSP latansve durasyonları üst ve alt ekstremitelerde incelenmiştir. T2DM hastalarında değişkenler ALA tedavisinden önce ve sonra incelenmiştir.
Bulgular: KSP latansı T2DM hastalarında kontrol grubuna kıyasla uzundur. Hasta grubunda KSP latansı ve KSP Latans Farkları (LF) üst ve alt ekstremitelerde tedavinin 3.ayında tedavi öncesine göre azalmıştır.

Sonuçlar: Bulgular ALA tedavisinin T2DM hastalarında ince-lif nöropatisini hafiflettiğini ve KSP'ninALA tedavisinin etkinliğini göstermekte kullanışlı bir araç olabileceğini desteklemektedir.

Anahtar Kelimeler: Kutanöz sessiz periyot, alfa-lipoik asit, ince-lif nöropati, tip 2 diabetes mellitus

INTRODUCTION

Small-fiber neuropathy (SFN), the most important cause of burning perception in the feet especially in elderly people, is a type of neuropathy that occurs due to damage of the small unmyelinated peripheral nerve fibers typically caused by diabetes mellitus (DM).[27] Small fibers (A delta and C fibers) are the fibers initially affected in diabetic patients. Although routine electromyography examination in diabetic patients with neuropathic pain shows normal large fibers, the small fibers could be affected, thereby indicating SFN.(24) Recent trial studies have shown that the evaluation of cutaneous silent period (CSP) may be a useful tool for assessing small-fiber neural function.[4,16]

CSP is an inhibitory spinal reflex following strong electrical stimulation of a cutaneous nerve, and it suppresses the voluntary muscular contraction for a certain period.[4,8] The physiological mechanism underlying CSP is not clear; however, there are strong evidences indicating that the afferent arm of CSP is formed by somatic small fibers (A delta).[9,13,14,21,28] CSP pathologies may occur either due to the inexcitability of spinal motor neurons or due to the interruption of the descending corticomotoneuronal command.[6,15] The association of CSP measurement with SFN has been shown in diabetic patients with neuropathic complaints.[16] Moreover, some studies have shown that CSP changes can also be used for diagnosis and determining the efficacy of treatment in patients with restless legs syndrome (RLS).[17]

Alpha-lipoic acid (ALA), a natural dithiol compound, is known to be an essential cofactor for mitochondrial bioenergetic enzymes,[23] and pharmacological data show that it enables glycemic control[3] and prevents polyneuropathies associated with DM.[23] The effect of ALA on CSP parameters in patients with DM has not been previously investigated in the literature. The purpose of this study was to evaluate the CSP changes in patients with T2DM and the effects of ALA on CSP parameters.

MATERIAL AND METHODS

Study population

The study population consisted of T2DM patients and healthy volunteers. The study was approved by the local Ethical Board, and written informed consent was obtained from all participants. T2DM patients diagnosed during the last 10 years who had complaints and abnormal neurological examination findings (pain and temperature sensory dysfunction) suggesting somatic SFN with normal nerve conduction values were included in the present study. Patients who were taking oral anti-diabetic medications were also included.

Patients with any disorder other than diabetes causing central or peripheral nerve pathology such as cervical or lumbosacral pathology, peripheral blood circulation problems, rheumatologic disorders, or RLS were excluded. Patients with medical conditions associated with peripheral neuropathy, such as alcohol abuse, metabolic disorders, malignancy, or long-term drug use were also excluded. Additionally, patients with a reduction in deep tendon reflex, vibration, position or discriminative sensory dysfunction, those who had abnormal motor findings in neurologic examination, abnormal findings

in nerve conduction studies (NCS), those on medication for the treatment of neuropathic pain in the last 3 months, or those taking insulin were excluded from the study.

Seventeen patients (10 women and 7 men) fulfilling the above-mentioned inclusion and exclusion criteria and 23 healthy controls (14 women and 9 men) were included in the study. A detailed medical history was obtained, and systemic and neurologic examinations were performed. A pinprick test for assessing the discriminative senses and pain was performed.[19,25] A piece of cotton applied on the palmar and dorsal surfaces of all hands and feet was used to determine light touch sensation, and the presence of allodynia was assessed. Temperature sensation was evaluated by asking patients to differentiate warm from cold by using metal tubes adjusted to 10°C and 40°C,[2] respectively. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale was used to assess the symptoms and examination findings in terms of neuropathic pain.[32] The height and weight of all subjects were measured, and the body mass indexes (BMI) were calculated. ALA treatments were given at a dose of 600 mg/daily for 3 months.

Electrophysiological tests

Electrophysiological evaluations were performed using a 2 + 8 channel electromyogram (EMG) device (MEDELEC Synergy, USA) in the electrophysiology laboratory of the Gulhane Military Medical Academy (GMMA) Department of Neurology

Nerve conduction studies (NCS)

Sensory nerve action potential (SNAP) amplitudes and sensory conduction velocities were recorded in the bilateral sural and right median nerves. Distal motor latency (DML), compound muscle action potential (CMAP) amplitudes, motor conduction velocity, and F response latencies were recorded in the right peroneal and median nerves and the left tibial nerve. Data obtained in the NCS were assessed according to normal reference limits of the electrophysiology laboratory in GMMA, Department of Neurology.

CSP evaluation

The procedure used for recording the CSP was modified from that previously reported.[6,11] Briefly, CSP measurements were carried out in the lower and upper extremities of subjects in the supine position. First, the sensory thresholds of the patients were measured. For this purpose, electrical stimuli of 0.2 ms duration and increasing in intensity from 0.6 mA were applied to the lateral part of the external malleolus in the lower extremity (sural nerve) and to the index finger in the upper extremity (median nerve). The value at which the patients began to feel the stimuli was designated as the sensory threshold. CSP measurements were performed in the right abductor pollicis brevis (APB) muscle for the upper extremity and the right tibialis anterior (TA) muscle for the lower extremity. In the upper extremity, electrical stimuli were applied to the second finger of the right hand by using a ring electrode at an intensity 15 times the sensory threshold. At this moment, the patient was instructed to perform an abduction movement with his/her right thumb, and recording was performed with the bar electrode from the right APB muscle when contracted voluntarily with 50% strength of the maximal muscle contraction (monitored by surface EMG). Similarly, for the right-lower extremity, recording was performed with the bar electrode from the right TA muscle after right sural nerve stimulation, and the TA muscle was contracted voluntarily with 50% strength of the maximal contraction (monitored by surface EMG). The CSP, appearing on the screen with the inhibition of muscle activity following the electrical stimulation, was recorded. CSP duration was determined by

measuring the time between the point of inhibition of muscle activity and the point where baseline muscle activity started to return (Figure 1). CSP was measured 10 times for each extremity. The minimum onset latency (Minimum of all these single values) and maximal (Maximum of all these single values) end latency of CSP were also measured, and the difference between them was recorded as CSP duration. The LD was calculated by subtracting the upper extremity CSP onset latency (the earliest) from the lower extremity onset latency (the earliest) of the examined patient.

CSP examinations were performed once in the control group and twice in the patient group before ALA treatment and at the third month of the treatment. Pre-treatment values of the patient group were compared with those of the control group. Additionally, post-treatment values of the patient group were compared with the pre-treatment values.

Statistical analyses

SPSS 15.0 for Windows (SPSS Inc.Chicago, IL) was used for statistical analyses. The differences between T2DM patients and the control group were evaluated using the Mann-Whitney U test. The differences between pre-treatment and post-treatment CSP values in T2DM patients were determined using the Wilcoxon Signed Ranks test. Data are shown as median (min-max), and p values less than 0.05 were considered to be statistically significant.

RESULTS

Demographic findings

No differences regarding age, gender, or BMI between the patients (n = 17) and the control group (n = 23; $p > 0.05$) were observed. The mean age of the patient group was 58 (47–71) years and that of the control group was 55 (51–62) years. The mean duration of the disease was 8.3 years, and the mean duration of the neuropathic complaints was 2.9 years. The pre-treatment LANSS scale 6 (3–19) was significantly different from the post-treatment LANSS scale 3 (0–6), respectively, $p < 0.001$) in the patient group.

The symptoms shown by the patients were usually nocturnal burning, numbness, dysesthesia, coldness, and pain. These symptoms were present only in the lower extremity in 60% of the patients and in both the lower and upper extremities in 40% of the patients. These symptoms (burning, numbness, dysesthesia, coldness, pain) were decreased in patients after treatment. All patients could use the drug. No side effects were observed.

Electrophysiological findings

The CSP latencies of the upper extremities were significantly different between the T2DM patients and the control group (79.50 (59.50–89.50) ms vs. 73.75 (56.00–81.25) ms, respectively, $p = 0.007$). The CSP duration of the upper extremities was not significantly different between the groups [37.25 (22.50–53.50) ms in T2DM patients vs. 40.00 (31.50–68.50) ms; $p = 0.234$]. However, the CSP latencies of the lower extremities were significantly different [112.75 (98.25–152.75) ms in the patient group (Figure 1) vs. 96.25 (80.00–113.00) ms in control group; $p < 0.001$]. Moreover, the CSP durations in the lower extremities were also significantly different between the groups [39.75 (20.25–66.50) ms in patient group vs. 51.00 (42.25–70.25) ms in the control group; $p = 0.008$]. The CSP LD between the lower and upper extremities was 36.25 (1.75–80.50) ms in the patient group and 15.75 (0.50–37.25) ms in the control group; this was statistically significant ($p < 0.001$) (Table 1).

Effect of ALA treatment

The pre-treatment CSP latency of the upper extremity was 79.50 (59.50–89.50) ms in T2DM patients, while the post-treatment CSP latency was 74.75 (52.50–82.50) ms ($p = 0.008$). In contrast, the pre-

treatment CSP latencies of the lower extremity was 112.75 (98.25–152.75) ms, while the post-treatment CSP latencies was 104.75 (72.75–136.75) ms (Figure 2) (p = 0.020). The pre-treatment CSP durations were 37.25 (22.50–53.50) ms in the upper extremity and 39.75 (20.25–66.50) ms in the lower extremity, while the post-treatment CSP durations were 38.00 (26.50–54.20) ms in the upper extremity and 43 (20.00–74.00) ms in the lower extremity (p = 0.868, p = 0.118, respectively, Table 2). Although no significant change was observed in the CSP durations after the treatment, a significant difference was observed between the pre-treatment CSP LD in the upper and lower extremities and post-treatment CSP LD [36.25 (1.75–80.50) ms vs. 27.25 (0.25–68.75) ms; p = 0.003].

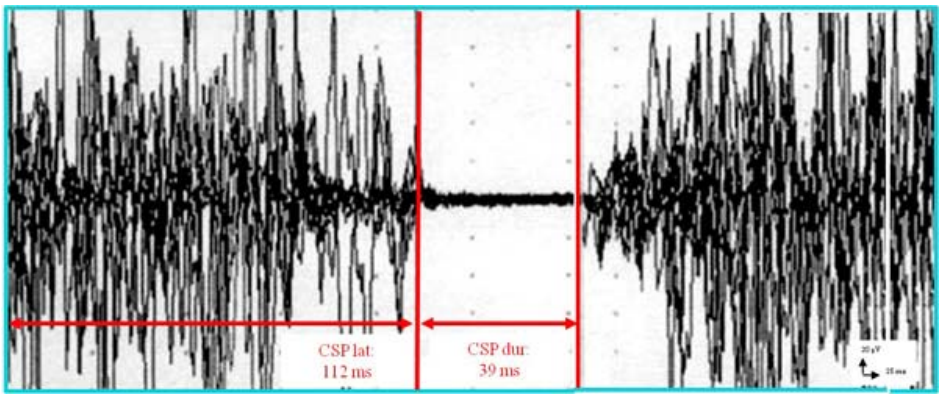

Figure 1: *Cutaneous silent period investigation of the lower extremity in a patient with DM before treatment.*

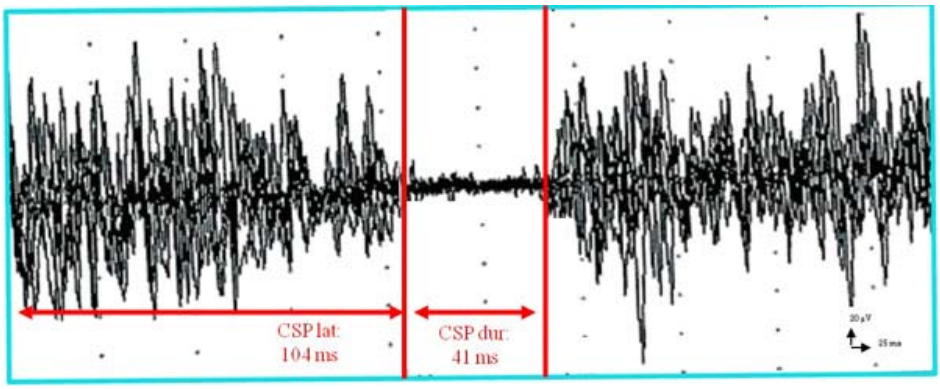

Figure 2: *Cutaneous silent period investigation of the lower extremity in a patient with DM after treatment.*

Table 1: Comparison of pre-treatment **Cutaneous silent period** values of patients with control group

CSP	Patients with DM (n = 17) (ms)	Control (n = 23) (ms)	p*
UE Latency	79.50 (59.50–89.50)	73.75 (56.00–81.25)	0.007
UE Duration	37.25 (22.50–53.50)	40.00 (31.50–68.50)	0.234
LE Latency	112.75 (98.25–152.75)	96.25 (80.00–113.00)	<0.001
LE Duration	39.75 (20.25–66.50)	51.00 (42.25–70.25)	0.008
Latency Difference	36.25 (1.75–80.50)	15.75 (0.50–37.25)	<0.001

*Mann-Whitney *U* test, UE: Upper extremity, LE: Lower extremity. Data are presented in milliseconds (ms) as median (min-max).

Table 2: Comparison of pre-treatment and post-treatment **Cutaneous silent period** values in patients

CSP	Patients with DM (n = 17)		p*
	Pre-treatment (ms)	Post-treatment (ms)	
UE Latency	79.50 (59.50–89.50)	74.75 (52.50–82.50)	0.008
UE Duration	37.25 (22.50–53.50)	38.00 (26.50–54.20)	0.868
LE Latency	112.75 (98.25–152.75)	104.75 (72.75–136.75)	0.020
LE Duration	39.75 (20.25–66.50)	43 (20.00–74.00)	0.118
Latency Difference	36.25 (1.75–80.50)	27.25 (0.25–68.75)	0.003
LANNS	6 (3–19)	3 (0–6)	<0.001

*Wilcoxon Test, UE: Upper extremity, LE: Lower extremity. Data are presented in milliseconds (ms) as median (min-max).

DISCUSSION

In this study, we showed that the pre-treatment CSP latencies measured in the upper and lower extremities of patients with T2DM were longer than those of the control group, and the pre-treatment CSP durations in the lower extremities of the patients were shorter than those of the controls. The pre-treatment LD between the upper and lower extremities was significantly longer in patients with T2DM than in the control group. Importantly, a marked improvement in the results was observed after ALA treatment.

Peripheral neuropathies generally affect small fibers, and the most common cause of SFN is DM.[27] Pain, burning, tingling, or numbness often occurs in the distal parts of the extremities due to damage or loss of small somatic nerve fibers. Allodynia, hyperalgesia, decrease in touch and temperature senses may also be observed upon examination. Previous studies have shown that the small fibers are affected much more in pre-diabetic or glucose intolerant individuals—which is indicative of SFN—but in diabetic patients, small fibers are initially affected followed by involvement of the large fibers leading to polyneuropathy.[26]

Since NCS are only effective for the assessment of large fibers, routine NCS are not used for SFN diagnosis. The definitive diagnosis of SFN is made by skin biopsy since a reduced density is observed in intra-epidermal small myelinated and unmyelinated cutaneous nerve fiber axons. This examination is an invasive procedure and can only be performed in a very limited number of laboratories.[29] Alternatively, autonomic tests assessing sudomotor function can also provide information regarding small fibers, and they are used for SFN diagnosis.[12]

Besides skin biopsy and autonomic tests, the utility of CSP examination in SFN diagnosis has also been demonstrated.[11,16,31] A study performed by Koytak et al., indicated that CSP examination is significantly more useful than autonomic tests for SFN diagnosis. This study showed a significant prolongation of CSP latencies and a significant reduction in CSP durations in the lower extremities of patients with T2DM compared to those of the control group. Moreover, when CSP examination was compared with sympathetic skin response (SSR) examination, CSP examination displayed a higher sensitivity and specificity for SFN diagnosis.[12] In another study performed by Önal et al., CSP latency was shown to support the diagnosis in diabetic patients with suspected somatic SFN. Our findings are in agreement with this study, and in particular, we have shown that the LD between the lower and upper extremities during CSP examination could be used to

support early detection of SFN in diabetic patients.[16] Similar to these findings, Yaman et al. have reported prolonged CSP latency in 35 patients with diabetic neuropathy compared to controls, and they found that CSP duration was shortened in addition to a prolonged CSP latency in diabetic patients with small fiber involvement. The authors have demonstrated that prolongation of CSP latency occurs not only due to small fiber involvement but also due to large fiber pathology. They concluded that although CSP was not superior to routine electrodiagnostic studies in the diagnosis of diabetic neuropathy, it could be a useful method for the early detection of distal sensory diabetic neuropathy.[31] In accordance with these findings, Kim et al. reported that routine NCS in patients with DM whose large fibers were affected showed a significant correlation with CSP findings. Because the NCS findings represent large diameter neural fiber function, the authors concluded that the significant correlation between NCS and CSP suggests that CSP may be affected by large diameter fiber function as well as small-diameter fiber function or that the small-fiber function was also damaged by the same pathologic mechanisms that caused the large-fiber damage.[11]

Some studies have shown that CSP latencies may be used to support the diagnosis of SFN in T2DM patients,[11] whereas some have reported that both CSP latencies and duration maybe used to support the diagnosis.[12,16] In our study, CSP examination performed in patients whose routine nerve conduction findings were within normal limits and who had clinically diagnosed SFN revealed that CSP onset latencies were prolonged in the lower and upper extremities, while CSP duration was shortened in the lower extremity. Again, onset LD between the lower and upper extremities were found to be significantly prolonged compared to those of the control individuals. Our results show that CSP onset latencies in the lower and upper extremities and especially the LD between the lower and upper extremities may support SFN diagnosis. Prolongation of CSP latencies in patients with T2DM with suspected SFN who had normal routine NCS suggested that involvement of small fibers can occur earlier by a mechanism similar to that affecting the large fibers. Significantly reduced CSP durations in the lower extremities could be explained by increased complaints with the lower extremities.

The aim of SFN treatment should be correction of the underlying cause and elimination of the neuropathic pain symptoms, since this type of treatment should prevent or slow down the progression of SFN. ALA, a natural dithiol compound and a very important micronutrient with various pharmacological and antioxidant properties, has long been known as an essential cofactor for mitochondrial bioenergetic enzymes[23] ALA, whose biosynthesis decreases with age in humans,[18] is also known to provide glycemic control, and it prevents polyneuropathies associated with DM.[23] Additionally, it reduces the toxicities occurring with heavy metal intoxication. As an antioxidant, ALA has direct effects on free radicals, causes chelation of transition metal ions, increases cytosolic glutathione and vitamin C levels, and prevents toxicities due to their loss. These various actions show that ALA exerts its effect through a number of physiological and pharmacological mechanisms. ALA treatment has even been shown to contribute to prevention of pulmonary edema re-expansion by reducing oxidative stress.[5] In a study performed by Singh et al., ALA treatment in patients with DM was useful for glycemic control, decreasing oxidative stress, and reducing neuropathic complaints.[23] Another study showed that ALA had marked benefits in prevention of diabetic polyneuropathy development.[22] Studies have also shown

that ALA prevents the damage caused by ischemia by indirectly regulating the level of cellular glutathione.[10,30] Moreover, many clinical studies have shown that ALA decreases the symptoms in patients with diabetic polyneuropathy,[1,20,33] and Heinisch et al. showed that intravenous ALA treatment decreased the risk of vascular events by increasing endothelium-dependent vasodilatation in patients with T2DM.[7]

In our study, the favorable effects of ALA on the neuropathic complaints of DM patients were shown both clinically with LANSS scoring and in electrophysiological findings with CSP examination. This study shows for the first time that the clinical impact of ALA is supported by a laboratory finding via CSP parameters. Shortening of prolonged CSP latencies in patients with T2DM by ALA suggests that it can be useful for the treatment of SFN symptoms.

The results of our study provide important and new insights into the diagnosis and treatment of SFN in T2DM patients. However, the study does have a few limitations. First, a limited number of cases were studied. Additionally, although it can be demonstrated quantitatively with the other tests used, the presence of SFN in our study was determined solely on the basis of patient complaints. Performing the placebo-controlled double-blind trials as well as comparative studies with other drugs used in the treatment of neuropathic pain should provide valuable and more definitive results. Finally we didn't measure arm and leg length.

In summary, evaluation of CSP may be a useful supportive tool to assess small-fiber neural function and can be used to show the efficacy of ALA treatment. Early diagnosis of T2DM patients with SFN symptoms by CSP examination and their treatment are very important for preventing the progression of SFN to polyneuropathy, which affects both the large and the small fibers. We have no direct evidence that for the CSP test parameters is enough for the diagnose of SFN yet. Further investigations are warranted in this respect.

Correspondence to:
Mehmet Yucel
E-mail: drmehmetyucel@yahoo.com.tr

Received by: 26 August 2014
Revised by: 14 April 2015
Accepted: 14 May 2015

The Online Journal of Neurological Sciences (Turkish) 1984-2015
This e-journal is run by Ege University Faculty of Medicine,
Dept. of Neurological Surgery, Bornova, Izmir-35100TR
as part of the Ege Neurological Surgery World Wide Web service.
Comments and feedback:
E-mail: editor@jns.dergisi.org
URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
Abbr: J. Neurol. Sci.[Turk]
ISSNe 1302-1664

REFERENCES

1. *Ametov AS, Barinov A, Dyck PJ, Hermann R, Kozlova N, Litchy WJ, et al. The sensory symptoms of diabetic polyneuropathy are improved with alpha-lipoic acid: the SYDNEY trial. Diabetes Care 2003;26:770–6.*
2. *Campbell WW, DeJong RN, Haerer AF. Dejong's the neurologic examination [Celebisoy N, trans.]. Istanbul: Gunes Tip Kitabevleri; 2005.*
3. *Evans JL, Heymann CJ, Goldfine ID, Gavin LAl. Pharmacokinetics, tolerability, and fructosamine-lowering effect of a novel, controlled-release formulation of alpha-lipoic acid. Endocr Pract 2002;8:29–35.*
4. *Floeter MK. Cutaneous silent periods. Muscle Nerve 2003;28:391–401.*
5. *Gumus S, Yucel O, Gamsizkan M, Eken A, Deniz O, Tozkoparan E, et al. The role of oxidative stress and*

effect of alpha-lipoic acid in reexpansion pulmonary edema – an experimental study. Arch Med Sci 2010; 6, 6: 848-853.

6. *Han JK, Oh K, Kim BJ, Koh SB, Kim JY, Park KW, et al. Cutaneous silent period in patients with restless legs syndrome. Clin Neurophysiol 2007:11; 1705–1710.*
7. *Heinisch BB, Francesconi M, Mittermayer F, Schaller G, Gouya G, Wolzt M, et al. Alpha-lipoic acid improves vascular endothelial function in patients with type 2 diabetes: a placebo-controlled randomized trial. Eur J Clin Invest. 2010;40(2):148-54*
8. *Higgins DC, Lieberman JS. The muscle silent period: variability in normal man. Electroencephalogr Clin Neurophysiol 1968b;24:176–82.*
9. *Inghilleri M, Berardelli A, Cruccu G, Manfredi M, Priori A, Rothwell JC. Inhibition of hand muscle motoneurones by peripheral nerve stimulation in the relaxed human subject. Antidromic versus orthodromic input. Electroencephalogr Clin Neurophysiol. 1995 Feb;97(1):63-8.*
10. *Kilic F, Handelman GJ, Traber K, Tsang K, Packer L, Trevithick JR. Modelling cortical cataractogenesis XX. In vitro effect of alpha-lipoic acid on glutathione concentrations in lens in model diabetic cataractogenesis. Biochem Mol Biol Int 1998;46:585–95.*
11. *Kim BJ, Kim NH, Kim SG, Roh H, Park HR, Park MH, et al. Utility of the cutaneous silent period in patients with diabetes mellitus. J Neurol Sci. 2010 Jun 15;293(1-2):1-5.*
12. *Koytak PK, Isak B, Borucu D, Uluc K, Tanridag T, Us O. Assessment of symptomatic diabetic patients with normal nerve conduction studies: utility of cutaneous silent periods and autonomic tests. Muscle Nerve. 2011;43(3):317-23.*
13. *Kranz H, Adorjani C, Baumgartner G. The effect of nociceptive cutaneous stimuli in human motoneurons. Brain 1973;96:571–90.*
14. *Leis AA, Ross MA, Emori T, Matsue Y, Saito T. The silent period produced by electrical stimulation of mixed peripheral nerves. Muscle Nerve 1991;14:1202–8.*
15. *Leis AA, Stětkárová I, Berić A, Stokić DS. Spinal motor neuron excitability during the cutaneous silent period. Muscle Nerve. 1995 Dec;18(12):1464-70.*
16. *Onal MR, Ulas UH, Oz O, Bek VS, Yucel M, Taslipinar A, et al. Cutaneous silent period changes in Type 2 diabetes mellitus patients with small fiber neuropathy. Clin Neurophysiol. 2010;121(5):714-8.*
17. *Oz O, Erdoğan C, Yücel M, Akgün H, Kütükçü Y, Gökçil Z, et al. Effect of pramipexole on cutaneous-silent-period parameters in patients with restless legs syndrome. Clin Neurophysiol. 2011 Jul 12. [Epub ahead of print]*
18. *Packer L, Witt EH, Tritschler HJ. alpha-Lipoic acid as a biological antioxidant. Free Radic Biol Med 1995;19:227–250.*
19. *Perkins BA, Olaleye D, Zinman B, Bril V. Simple screening tests for peripheral neuropathy in the diabetes clinic. Diabetes Care 2001;24:250–6.*
20. *Reljanovic M, Reichel G, Rett K, Lobisch M, Schuette K, Moller W, et al. Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). Alpha Lipoic Acid in Diabetic Neuropathy. Free Radic Res 1999;31:171–9.*
21. *Serrao M, Parisi L, Pierelli F, Rossi P. Cutaneous afferents mediating the cutaneous silent period in the upper limbs: evidences for a role of low-threshold sensory fibres. Clin Neurophysiol 2001;112:2007–14.*
22. *Shay KP, Moreau RF, Smith EJ, Smith AR, Hagen TM. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. Biochim Biophys Acta. 2009;1790(10):1149-60.*
23. *Singh U, Jialal I. Alpha-lipoic acid supplementation and diabetes.Nutr Rev. 2008 Nov;66(11):646-57.*
24. *Singleton JR, Smith AG, Bromberg MB. Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. Diabetes Care 2001;24:1448–53.*
25. *Smieja M, Hunt DL, Edelman D, Etchells E, Cornuz J, Simel DL. Clinical examination for the detection of protective sensation in the feet of diabetic patients. International Cooperative Group for Clinical Examination Research. J Gen Intern Med 1999;14:418–24.*
26. *Sumner CJ, Sheth S, Griffin JW, Cornblath DR, Polydefkis M. The spectrum of neuropathy in diabetes and impaired glucose tolerance. Neurology 2003; 60:108–111.*
27. *Tavee J, Zhou L. Small fiber neuropathy: A burning problem. Cleve Clin J Med. 2009 ;76(5):297-305.*
28. *Uncini A, Kujirai T, Gluck B, Pullman S. Silent period induced by cutaneous stimulation. Electroencephalogr Clin Neurophysiol. 1991 Oct;81(5):344-52.*
29. *Walk D. Role of skin biopsy in the diagnosis of peripheral neuropathic pain. Curr Pain Headache Rep 2009;13(3):191–6.*
30. *Wolz P, Krieglstein J. Neuroprotective effects of alpha-lipoic acid and its enantiomers demonstrated in rodent models of focal cerebral ischemia. Neuropharmacology 1996;35:369–75.*
31. *Yaman M, Uludüz D, Yüksel S, Pay G, Kiziltan ME. The cutaneous silent period in diabetes mellitus. Neurosci Lett. 2007; 4:419(3):258-62.*
32. *Yücel A, Senocak M, Kocasoy Orhan E, Cimen A, Ertas M. Results of the Leeds assessment of neuropathic symptoms and signs pain scale in Turkey: a validation study. J Pain 2004;5:427–32.*
33. *Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schutte K, Kerum G, Malessa R. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7- month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. Diabetes Care 1999;22:1296–301.*