



# The effects of the physical procedures in patients with diabetic neuropathy

## Efekti fizikalne terapije kod bolesnika sa dijabetesnom neuropatijom

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### Abstract

**Background/Aim.** Neuropathy represents the most frequent complication in the patients with diabetes mellitus (DM). Symmetric distal sensorimotor polyneuropathy (DSP), which represents the most frequent type of diabetic neuropathy, is present in 30% of hospitalized diabetic patients. The aim of our study was to compare the effects of physical therapy (PT) and alpha-lipoic acid (ALA) supplementation on pain reduction and quality of life improvement in the DSP patients. **Methods.** The study was performed on 60 adult patients with DM type 2 and DSP. The patients were randomly divided into 2 groups: group A (n = 30) was treated by PT and group B (n = 30) was treated by ALA. The study lasted 6 months during which 3 diagnostic-therapeutic cycles were performed. To assess their pain before and after every of 3 cycles, we used visual analog scale (VAS). We also evaluated quality of life before the 1st and after the 3rd cycle with the European Quality of Life Ques-

tionnaire (EQ-5D-3L). To analyze results between groups we used mixed between-within subjects ANOVA and statistical significance was set on  $p < 0.05$ . **Results.** Pain intensity showed statistically significant influence of both PT and ALA ( $\lambda = 0.028$ ;  $p < 0.001$ ). A statistically significant difference between the effects of those two therapy modalities was observed ( $F = 4.78$ ;  $p < 0.05$ ): PT reduced pain to the greater extent than ALA. A statistically significant improvement was found in the domain of pain/discomfort both in the group A ( $\eta = 0.54$ ,  $p < 0.001$ ) and group B ( $\eta = 0.57$ ,  $p < 0.001$ ), as well as anxiety/depression (group A:  $\eta = 0.32$ ,  $p = 0.008$ ; group B:  $\eta = 0.22$ ,  $p < 0.019$ ) and EQ-VAS (both groups,  $p < 0.05$ ). **Conclusion.** Our research showed that physical therapy had a greater influence in pain reduction than alpha-lipoic acid in the patients with DSP.

**Key words:** diabetic neuropathies; physical therapy modalities; treatment outcome.

### Apstrakt

**Uvod/Cilj.** Neuropatija predstavlja najčešću komplikaciju kod bolesnika sa dijabetes melitusom (DM). Simetrična distalna senzomotorna polineuropatija (DSP) predstavlja najčešći tip dijabetesne neuropatije i zastupljena je kod 30% hospitalizovanih bolesnika sa dijabetesom. Cilj naše studije je bilo poređenje efekata primenjene fizikalne terapije (PT) i alfalipoične kiseline (ALA) na smanjenje bola i kvalitet života kod bolesnika sa DSP. **Metode.** U studiju je bilo uključeno 60 odraslih bolesnika sa DM tip II i DSP. Bolesnici su slučajnim izborom bili podeljeni u 2 grupe: Grupa A (n = 30) je bila tretirana PT, a grupa B (n = 30) primenom ALA. Tokom studije, koja je trajala šest meseci,

sprovedena su tri dijagnostičko-terapijska ciklusa. Za procenu bola pre i posle svakog od tri ciklusa korišćena je vizuelno analogna skala (VAS). Takođe, evaluiran je kvalitet života pomoću Evropskog upitnika o kvalitetu života (EQ-5D-3L). Za poređenje rezultata među grupama korišćena je kombinovana analiza varijanse, a značajnost razlike prihvaćena je na nivou  $p < 0,05$ . **Rezultati.** Intenzitet bola bio je statistički značajno smanjen kod obe grupe ispitanika primenom PT i ALA ( $\lambda = 0,028$ ;  $p < 0,001$ ). Utvrđena je statistički značajna razlika između dve vrste primenjenih terapija ( $F = 4,78$ ;  $p < 0,05$ ): PT je dovela do značajnije redukcije bola od ALA. Došlo je do statistički značajnog poboljšanja kvaliteta života u domenu bol/diskomfor u grupi A ( $\eta = 0,54$ ,  $p < 0,001$ ) i grupi B ( $\eta = 0,57$ ,  $p < 0,001$ ), kao i anksioznosti/depresije (grupa A:  $\eta = 0,32$ ,  $p = 0,008$ ; grupa B:  $\eta = 0,22$ ,  $p < 0,019$ ) i EQ-VAS (obe grupe,  $p < 0,05$ ).

u domenu anksioznost/depresivnost (grupa A:  $\eta = 0,32$ ,  $p = 0,008$ ; grupa B:  $\eta = 0,22$ ,  $p < 0,019$ ) i domenu EQ-VAS (obe grupe,  $p < 0,05$ ). **Zaključak.** Rezultati studije pokazuju da primena fizikalne terapije ima veći uticaj na smanjenje bola u poređenju sa primenom alfalipoične kiseline kod

bolesnika sa DSP.

**Ključne reči:**  
dijabetičke neuropatije; fizikalna terapija, metodi; tioktinska kiselina; lečenje, ishod.

## Introduction

Neuropathy represents the most frequent complication in the patients with diabetes mellitus (DM)<sup>1</sup>. Symmetric distal sensorimotor polyneuropathy (DSP), which represents the most frequent type of diabetic neuropathy, is present in 30% of hospitalized diabetic patients<sup>2</sup>. Prevalence of symmetrical DSP in the whole population of diabetics is 13%–68%<sup>3</sup>.

DSP is characterized by persistent or periodical pain localized mainly in feet, which is provoked even by light touch, gets worse during the night, but reduced during walking. This pain is very unpleasant and persistent, lasts for years, its intensity and frequency disturbs sleep and rest and reduces work energy and thus impairs the overall quality of life, contributing to a loss of autonomy and independence in performing many daily activities and the reduction of working capacity. Thus, the pain reduction and improvement of quality of life represent the challenge of modern medicine<sup>4</sup>.

Often, the primary objective of a therapy is to protect the lower extremities from damage caused by the loss of protective sensibility as well as the reduction of pain, which improves physical well-being and quality of life of DSP patients<sup>5</sup>. The DSP therapy is complex, directed towards both causal treatment (achievement and maintenance of an adequate level of glucoregulation, liporegulation and regulation of arterial blood pressure as well as pharmacological treatment) and symptomatic treatment. The symptomatic treatment includes antidepressants, anticonvulsants, opioids and local anesthetics as well as the physical therapy. The therapy directed towards the pathogenetic process involves aldose reductase inhibitors, alpha-lipoic acid (ALA), benfotiamine, protein kinase C inhibitors, gene therapy, gamma-linoleic acid, immunotherapy, and others<sup>6</sup>.

ALA is an endogenous antioxidant which gained a scientific support as the medicament of choice in diabetic neuropathy treatment<sup>7,8</sup>. It is particularly important to emphasize the necessity of timely implementation of the therapy before the occurrence of severe and irreversible changes of the nerves. The application of physical therapy (PT) in the treatment of patients with DSP is becoming increasingly important, especially as the analgesic therapy. The most frequently applied physical agents are transcutaneous electrical nerve stimulation, pulsed magnetic field therapy, stable galvanization, exercise therapy, etc. By reducing pain, the physical agents improve quality of life of patients.

Available scientific literature contains no research paper that compares the effects of combined PT vs ALA supplementation on the patient-centered treatment endpoints in diabetics with DSP. Thus, the aim of our research was to

compare the effects of PT and ALA supplementation on pain reduction and quality of life improvement in DSP patients.

## Methods

This clinical open prospective randomized intervention study was performed in the Center for Physical Medicine and Rehabilitation of the Clinical Centre Kragujevac. The study was conducted according to the principles of Helsinki Declaration and it was approved by the Independent Ethics Committee of Clinical Centre “Kragujevac”, Kragujevac, Serbia.

The study was performed on 60 adult patients with DM type 2 and DSP. The informed consent was obtained from the patients. The inclusion criteria were the following: 1) DSP presence for more than 2 months, diagnosed by the electromyoneurographic findings and the presence of symptoms and signs of DSP (pain, paresthesia, hyperesthesia to anesthesia, muscle weakness); 2) antidiabetic therapy constant for previous 6 months; 3) written informed signed consent of the patient. Exclusion criteria included: 1) a number of diseases and conditions [vitamin B12 deficiency, alcoholism, chronic renal insufficiency, thyroid dysfunction, immunodeficient diseases, systemic connective tissue disease, severe liver damage, cerebrovascular ischemia, cardiac decompensation, acute coronary syndrome within the previous 6 months, uncontrolled elevated blood pressure (systolic pressure >160 mmHg or diastolic pressure > 80 mmHg), subjection to chemotherapy in the past 10 years, and states after severe polytrauma]; 2) usage of drugs that can cause damage to the peripheral nerves (vincristine, cis-platinum, paclitaxel, streptomycin, isoniazid, ethionamide, dapsone, nitrofurantoin, metronidazole, misonidazole, emetine, chloroquine, amiodarone, carbamazepine, phenytoin, hydralazine, indomethacin), 3) the existence of any contraindication for the application of physical agents planned for the use in the study (pregnancy, fever, cancer, acute infectious disease, decompensation of the vital organs, presence of metals in the tissue, a disease or damage to the integrity of the skin at the site of electrode application). For the application of ALA, the exclusion criteria were hypersensitivity to the active substance of the drug, or any other ingredients.

By using the Microsoft Excel Rand between function, the patients were randomly divided into 2 groups: 1) group A (n = 30), DM DSP patients who were treated by PT, and 2) group B (n = 30), DM DSP patients who were treated by ALA.

The study lasted 6 months, during which 3 diagnostic-therapeutic cycles were performed. Each diagnostic-therapeutic cycle lasted 14 days (2 weeks), while pause between them lasted 6–7 weeks.

Combined PT included: 1) transcutaneous electrical nerve stimulation (TENS), 2) pulsed electromagnetic field therapy (PEMF), 3) stable galvanization (SG) and 4) exercise. TENS was applied once daily for 30 minutes, using TENS-2 (Electronic Design Medical, Serbia) apparatus on both legs, longitudinally (frequency: 85 Hz, impulse duration: 4 ms). PEMF was applied once daily for 30 minutes, on Magomil-2 apparatus (Electronic Design Medical, Serbia), along both lower legs and feet, over the antenna (frequency: 10 Hz, intensity: 40 mT). SG was applied once daily for 20 minutes, on Galvan Plus apparatus (Electronic Design Medical, Serbia), using standard rectangular electrodes placed longitudinally descendently along both legs (intensity 0.1–0.5 mA/cm<sup>2</sup>, according to the subjective experience of patients). Exercise was applied once daily for 30 minutes, according to individually adapted program (active-assisted and active exercises for strengthening muscles of legs and improvement of range of motion in all joints of legs).

The ALA supplementation (Thiogamma<sup>®</sup>, Wörwag Pharma, Germany) was performed according to the manufacturer's instructions (indications, dosing, precautions, etc.) and standard clinical practice. From 2nd to 15th day of hospitalization, the patients were treated with the intravenous application of preparation of alpha-lipoic acid (600 mg in 500 ml 0.9% NaCl). Upon completion of hospitalization, and throughout the entire study period, those participants continued to regularly take ALA orally in dose of 600 mg (one tablet per day, in the morning, before breakfast).

At admission to hospital (before every diagnostic-therapeutic cycle) as well as after every diagnostic-therapeutic cycle, the patients were asked to assess their pain level by using 100 mm visual analog scale (VAS score). To assess their quality of life, the patients were asked to fulfill the European Quality of Life Questionnaire (EQ-5D-3L) before the 1st diagnostic-therapeutic cycle, and after the 3rd (the last) diagnostic-therapeutic cycle. EQ-5D-3L is a general standardized indicator of quality of life that assesses 5 domains. These 5 domains provide an assessment within 3 levels ranging from 1 (best quality of life) to 3 (worst quality of life): 1) mobility, 2) self-care, 3) perform in regular daily activities, 4) pain/discomfort and 5) anxiety/depression. EQ-5D also includes the 20 cm vertical visual analog scale (EQ-VAS), so called the assessment scale, where the respondent assesses the quality of their own overall health status scores of 0 (worst) to 100 (best)<sup>9,10</sup>.

The statistical analysis was performed in the SPSS 20.0. The continuous variables are presented as mean ± standard deviation (SD), while the categorical variables are presented as proportions, i.e., percentage of an individual category. The normality of data distribution of all examined continuous variables was examined using the Shapiro-Wilk test. For comparison of mean values of continuous variables within the tested groups at the beginning and the end of the study *t*-test (for related samples with normal distribution) and Wilcoxon's matched pairs test (for the outcomes that do not fol-

low a normal distribution) were used. In order to compare the mean values of continuous variables between the groups, the independent *t*-test or Mann-Whitney *U* test was used, depending on whether the distribution was, or was not normal. The Chi-square ( $\chi^2$ ) test was used to determine the significance of differences in frequencies of certain categories in the categorical variables, and the Fisher's test when the frequency of some categories was small. Testing the efficacy of two therapeutic modalities to reduce pain in two groups included performance of the combined analysis of variance (mixed between-within subjects ANOVA). The results were considered statistically significant when probability of the null hypothesis was lower than 5% ( $p < 0.05$ ).

## Results

Basic characteristics of patients are presented in Table 1. Groups were similar according to the gender ( $p = 0.598$ ), diabetes mellitus genetic heritage ( $p = 1.000$ ), active smoking ( $p = 0.347$ ), profession ( $p = 0.837$ ), age ( $p = 0.090$ ), body mass index ( $p = 0.773$ ), disease duration ( $p = 0.090$ ) and laboratory parameters – levels of glycosylated hemoglobin ( $p = 0.403$ ), urea ( $p = 0.679$ ) and creatinine ( $p = 0.524$ ).

At the admission, no statistically significant difference between groups was found either in VAS score ( $p = 0.635$ ) or domains of the EQ-5D-3L score (mobility:  $p = 1.000$ ; self care  $p = 1.000$ ; usual daily activities  $p = 0.945$ ; pain/discomfort  $p = 0.962$ ; anxiety/depression = 1.000; EQ-VAS  $p = 0.136$ ).

The pain intensity, assessed using the VAS scale, before and after every 14-day therapy cycle (PT application, or ALA supplementation) is presented in Table 2. By using combined analysis of variance, a statistically significant influence both of PT and ALA was observed ( $\lambda = 0.028$ ;  $p < 0.001$ ). A statistically significant difference between the effects of those two therapy modalities was observed ( $F = 4.78$ ;  $p < 0.05$ ).

Also, the pain was found significantly reduced in the A group (PT therapy) after the 2nd therapy cycle ( $p = 0.032$ ), as well as before ( $p = 0.029$ ) and after ( $p = 0.001$ ) the 3rd therapy cycle (Table 2).

Quality of life, assessed by EQ-5D-3L questionnaire, is presented in Table 3. There was no statistically significant difference in EQ-5D-3L domains between the groups, neither at the beginning, nor at the end of the study (Table 3). At the end of the study, results in the domains related to mobility, self-care and regular daily activities were not significantly different ( $p > 0.05$ ) compared to the results at the beginning of the study in either group. A statistically significant improvement was found in the domain of pain/discomfort both in the group A ( $\eta = 0.54$ ,  $p < 0.001$ ) and group B ( $\eta = 0.57$ ,  $p < 0.001$ ) and anxiety/depression domain (A group:  $\eta = 0.32$ ,  $p = 0.008$ ; B group:  $\eta = 0.22$ ,  $p < 0.019$ ). EQ-VAS was also significantly improved (groups A and B:  $p < 0.05$ ).

Table 1

## Characteristics of patients with diabetic polyneuropathy (DPN)

Characteristics	Group A (n = 30)	Group B (n = 30)	p value
Sex, n (%)			
male	11 (36.67)	13 (43.33)	0.598 <sup>†</sup>
female	19 (63.33)	17 (56.67)	
Heredity for DM, n (%)			
yes	13 (43.33)	13 (43.33)	≈ 1.000 <sup>†</sup>
no	17 (56.67)	17 (56.67)	
Active smoking, n (%)			
yes	8 (26.67)	5 (16.67)	0.347 <sup>†</sup>
no	22 (73.33)	25 (83.33)	
Profession, n (%)			
pension	23 (76.76)	22 (73.33)	0.837 <sup>†</sup>
employed	6 (20)	6 (20)	
unemployed	1 (3.33)	2 (6.67)	
Age (years), mean ± SD	63.17 ± 7.68	62.77 ± 8.35	p = 0.09 <sup>‡</sup>
Body mass index (kg/m <sup>2</sup> ), mean ± SD	27.2 ± 4.56	27.2 ± 3.93	0.773*
Duration of diabetes (years), mean ± SD	12.22 ± 7.58	11.70 ± 5.75	p = 0.09 <sup>‡</sup>
HbA1c (%), mean ± SD	7.80 ± 1.87	7.30 ± 1.21	0.403*
Urea (mmol/L), mean ± SD	6.51 ± 2.94	6.01 ± 2.08	0.679*
Creatinine (μmol/L), mean ± SD	81.1 ± 22.19	76.33 ± 17.67	0.524*
VAS, mean ± SD	7.67 ± 1.06	7.60 ± 0.89	0.635*
EQ-5D / VAS, mean ± SD	36.57 ± 7.73	39.03 ± 7.24	0.136*

Group A – patients treated by physical therapy; Group B – patients treated by alpha-lipoic acid; VAS – visual analog scale; EQ-5D – European Quality of Life Questionnaire; HbA1c – glycated hemoglobin; DM – diabetes mellitus; SD – standard deviation; \* – Mann-Whitney test; <sup>†</sup> –  $\chi^2$ ; <sup>‡</sup> – *t*-test.

Table 2

## Pain estimation in patients with diabetic polyneuropathy by Visual analog scale (VAS)

Parameter	Group A (n = 30) mean ± SD	Group B (n = 30) mean ± SD	p value <sup>†</sup>	p value <sup>‡</sup>
VAS scale I series				
before treatment	7.67 ± 1.06	7.60 ± 0.89	0.635	< 0.05*
after treatment	3.03 ± 1.73	3.73 ± 1.78	0.073	
VAS scale II series				
before treatment	6.43 ± 1.22	6.90 ± 1.00	0.131	< 0.05*
after treatment	2.60 ± 1.50	3.20 ± 1.40	0.032*	
VAS scale III series				
before treatment	5.33 ± 1.32	5.98 ± 1.24	0.029*	< 0.05*
after treatment	1.67 ± 0.84	2.63 ± 0.89	0.001*	

Group A – patients treated by physical therapy; Group B – patients treated by alpha-lipoic acid; \* – statistically significant; <sup>†</sup> – Mann-Whitney test; <sup>‡</sup> – mixed between-within subjects ANOVA test.

Table 3

## Proportion of levels 1, 2 and 3 by EQ-5D dimension and type of therapy in patients with diabetic polyneuropathy

EQ-5D DIMENSION		Group A (n = 30), n (%)	Group B (n = 30), n (%)	TOTAL (n = 60), n (%)	p value (between groups)
Mobility	Treatment				
L1	before therapy	28 (93.3)	29 (96.7)	57 (95.5)	Before: p ≈ 1.000 <sup>§</sup>
	after therapy	28 (93.3)	29 (96.7)	57 (95.5)	
L2	before therapy	2 (6.7)	1 (3.3)	3 (5.0)	After: p ≈ 1.000 <sup>§</sup>
	after therapy	2 (6.7)	1 (3.3)	3 (5.0)	
L3	before therapy	0 (0.0)	0 (0.0)	0 (0.0)	
	after therapy	0 (0.0)	0 (0.0)	0 (0.0)	
p value (within group) <sup>††</sup>		p ≈ 1.000	p ≈ 1.000		

Table 3 (continued)

EQ-5D DIMENSION		Group A (n = 30), n (%)	Group B (n = 30), n (%)	TOTAL (n = 60), n (%)	p value (between groups)	
Self- car	Treatment					
L1	before therapy	27 (90)	26 (86.7)	53 (88.3)	Before: $p \approx 1.000^{\S}$	
	after therapy	27 (90)	26 (86.7)	53 (88.3)		
L2	before therapy	3 (10)	4 (13.3)	7 (11.7)		After: $p \approx 1.000^{\S}$
	after therapy	3 (10)	4 (13.3)	7 (11.7)		
L3	before therapy	0 (0.0)	0 (0.0)	0 (0.0)		
	after therapy	0 (0.0)	0 (0.0)	0 (0.0)		
<i>p</i> value (within group) <sup>††</sup>		$p \approx 1.000$	$p \approx 1.000$			
Regular daily activities	Treatment					
L1	before therapy	24 (80.0)	23 (76.7)	47 (78.3)	Before: 0.945 <sup>\S</sup>	
	after therapy	25 (83.3)	24 (80.0)	49 (81.7)		
L2	before therapy	5 (16.7)	6 (20.0)	11 (18.3)		After: 0.936 <sup>\S</sup>
	after therapy	4 (13.3)	5 (16.7)	9 (15.0)		
L3	before therapy	1 (3.3)	1 (3.3)	2 (3.3)		
	after therapy	1 (3.3)	1 (3.3)	2 (3.3)		
<i>p</i> value (within group) <sup>††</sup>		0.317	0.317			
Pain/Discomfort	Treatment					
L1	before therapy	1 (3.3)	1 (3.3)	2 (3.3)	Before: 0.962 <sup>\S</sup>	
	after therapy	10 (33.3)	10 (33.3)	20 (33.3)		
L2	before therapy	20 (66.7)	19 (63.3)	39 (65.0)		After: $p \approx 1.000^{\S}$
	after therapy	19 (63.3)	19 (63.3)	38 (63.3)		
L3	before therapy	9 (30.0)	10 (33.3)	19 (31.7)		
	after therapy	1 (3.3)	1 (3.3)	2 (3.3)		
<i>p</i> value (within group) <sup>††</sup>		< 0.001*	< 0.001*			
Anxiety/Depression	Treatment					
L1	before therapy	6 (20.0)	6 (20.0)	12 (20.0)	Before: $p \approx 1.000^{\S}$	
	after therapy	14 (46.7)	12 (40.0)	26 (43.3)		
L2	before therapy	14 (46.7)	14 (46.7)	28 (46.7)		After: 0.870 <sup>\S</sup>
	after therapy	15 (50.0)	17 (56.7)	32 (53.3)		
L3	before therapy	10 (33.3)	10 (33.3)	20 (33.3)		
	after therapy	1 (3.3)	1 (3.3)	2 (3.3)		
<i>p</i> value (within group) <sup>††</sup>		0.008*	0.019*			
EQ-VAS	Treatment					
	before therapy	36.57 ± 7.73	39.03 ± 7.24		0.136 ± 0.230 <sup>†</sup>	
	after therapy	75.63 ± 10.11	72.53 ± 9.70			
<i>p</i> value (within group) <sup>††</sup>		$p < 0.05^*$	$p < 0.05^*$			

Group A – patients treated by physical therapy; Group B – patients treated by alpha-lipoic acid; L – level; EQ – MD dimension – European Quality of Life Questionnaire; EQ-VAS – European Quality of Life – Visual Analog Scale; \* – statistically significant; † – Mann-Whitney test; § – Fisher's exact test; †† – Willcoxon signed rank test.

## Discussion

Research on quality of life and pain reduction in the patients with diabetes mellitus are very popular around the world, which is understandable if one takes into account the participation of diabetes mellitus in the structure of morbidity and mortality and the fact that the timely implementation of appropriate medicamentous and physical therapy achieves not only the prevention of many complications but also significantly improves the quality of life. Studies show that the

patients with diabetes and complications have poor quality of life and determinants with the strongest influence are ischemic heart disease, stroke and neuropathy<sup>11</sup>.

The usage of the pharmacological preparations in the therapy of DM patients with DSP has been widely studied, while there are not many studies on the effects of physical therapy on quality of life of those patients. The efficiency of the TENS therapy in pain reduction in these patients was confirmed in many studies<sup>12-15</sup> as well as the efficiency of PEMF<sup>16,17</sup>, SG<sup>18,19</sup> and exercise<sup>20,21</sup>, which is in accordance with our research.

SG exhibits its analgesic effects by inducing hyperemia in the skin and deeper tissues through which it passes. The pain reduction may also be explained by the gate control mechanism, since SG acts on the sensory endings in the skin and suppresses pain in the rear horns of the spinal cord as well as by the release of endogenous opioids<sup>22</sup>. A study by Armstrong et al.<sup>18</sup> showed a statistically significant pain reduction after 4 weeks of SG treatment.

Analgesic effect of TENS therapy is achieved by secretion of endogenous opioids (endorphins, enkephalins) in the central nervous system<sup>23,24</sup> which inhibit the transmission of pain impulses by closing the door (gate control) for the painful impulses transmitted by C fibers<sup>25</sup>. The TENS therapy showed to be efficient in reducing pain in the patients with DSP in a number of studies. Thus, its use is recommended in treatment of diabetic neuropathy<sup>26-28</sup>. Furthermore, a study by Jin et al.<sup>29</sup> showed that a 4-week TENS therapy induced a statistically significant pain reduction. Our results correlate with previously mentioned study: although the pain was reduced in both groups after 6 months, it was reduced to the greater extent in the patients treated with PT. The difference in pain intensity between the A and B groups in our research was observed after the 2nd therapy cycle and remained until the end of the study.

PEMF has analgesic, neurostimulating, trophic and vasoactive effects<sup>30</sup>. By the mechanisms of depolarization, hyperpolarization and repolarization, it may modulate neuropathic pain and nerve impulses<sup>31</sup>. In contrast to our study, a study by Weintraub et al.<sup>32</sup> showed no statistically significant pain reduction in the DSP patients after the PEMF treatment, but it did show neurodegenerative effect of PEMF. On the other side, a study by Graak et al.<sup>31</sup> did show a statistically significant reduction of pain in the DSP patients after the PEMF administration for 12 weeks, which correlated with our results.

Exercise positively affects pathological factors associated with neuropathy by increasing microvascular vasodilatation, reduction of oxidative stress and increase of neurotrophic factors, but insufficient number of studies explores the effects of exercise on signs and symptoms of DSP. One study showed a statistically significant reduction of pain and improvement of the neurological symptoms in the patients with DSP after 10 weeks of exercise treatment<sup>33</sup>, which coincided with the results of our study.

Some studies showed that ALA reduces neuronal sensitivity to pain by selective inhibition of neuronal calcium channels of the T-type<sup>34,35</sup>. Also, ALA has a clear metabolic effect, improves the microcirculation and has an anti-inflammatory effect. All the above mentioned effects act synergistically in a complex chain of pathophysiological events in the course of the disease<sup>36,37</sup>.

The psychological status of patients with DSP is in correlation with pain, subsequent problems with mobility as well as limitations in an independent functioning<sup>10,11</sup>. The results of our study showed that the use of PT and the patients' involvement in the rehabilitation program as well as the use of ALA, had a positive effect on improvement of quality of life of diabetics with DSP, which is manifested by the increase in degrees of quality of life measured by EQ-5D.

A study by Bertolloto and Massone<sup>38</sup> showed a statistically significant reduction in pain (measured by VAS scale) in the DM DSP patients after the ALA administration. Pain was also significantly reduced in a study by Patel et al.<sup>39</sup>, in which ALA was applied for 6 months.

Investigation of depression and quality of life is an important part of this study because the literature data indicated that the rate of depression in the population of DM patients is 2–3 times higher than usual. Symptoms of depression occur in about 30% of DM patients and major depression in 10% of DM patients<sup>40</sup>, which significantly contributed to the development of type 2 diabetes and may accelerate the development of complications caused by the disease<sup>41</sup>. Numerous studies showed that diabetes significantly affects quality of life of patients. The scores on scales of quality of life were becoming lower due to the simultaneous action of underlying disease and other (somatic or psychological) diseases as its resulting complications or as comorbidity.

Many studies indicated lower quality of life and more symptoms of depression in the patients with DM type 2 in comparison with those without DM<sup>42-44</sup>. One study, that explored quality of life by using EQ-5D, showed a significant decline in quality of life of DM patients, with a higher decrease results in a subgroup of patients with DM and complications. The study showed a clear influence of DM type 2 and its complications on reduction of quality of life<sup>45</sup>.

By investigating the effect of low frequency magnetic fields on quality of life (measured by the EQ-5D questionnaire) and pain in the DM patients with DSP, Wrobel et al.<sup>46</sup> showed a statistically significant reduction in pain and improved quality of life of patients. Our results correlate with the results of that study, except that in our study, in addition to the magnetic therapy, the electrotherapy (TENS and SG) and exercise were applied. Also, another study<sup>47</sup> demonstrated the effect of exercise on improvement of quality of life.

In this research, we demonstrated the synergistic effect of the applied physical procedures on pain reduction and improvement of quality of life of DM patients with DSP. The application of combined physical procedures showed more pronounced effect in the reduction of pain, but did not give such good results in the improvement of quality of life. This may be a consequence of the application of the generic test for estimating the quality of life or some other factors, such as too short investigation protocol. Because of the numerous comorbidities, the adverse effects and lack of effective pharmacological preparations, application of physical methods in the treatment of these patients should be more prevalent in everyday clinical practice.

## Conclusion

Our research showed that both physical therapy and alpha-lipoic acid supplementation have a significant influence on pain reduction and quality of life in the diabetic patients with distal sensorimotor polyneuropathy, but physical therapy has a greater influence on pain reduction.

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Received on April 29, 2017.

Revised on October 17, 2017.

Accepted on October 24, 2017.

Online First November, 2017.