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Neuropathic pain as independent predictor of worse quality of life in patients with diabetic neuropathy

Neuropatski bol kao nezavisan prediktor lošijeg kvaliteta života kod bolesnika sa dijabetesnom neuropatijom

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Abstract

Background/Aim. The prevalence of diabetes mellitus in general population is constantly increasing. On the other hand, the number of diabetic patients with neuropathic pain is large. The aim of the study was to examine influence of neuropathic pain on quality of life (QoL) in patients with diabetic sensorimotor polyneuropathy (DSPN) who did not have any other diabetic complication or any other significant comorbidity. **Methods**. A total of 32 patients with DSPN and definitive neuropathic pain were compared with 32 patients with DSPN without neuropathic pain. The respondents were matched according to age, gender, and duration of illness. The following scales were used: the Pain Detect Questionnaire, Leeds Assessment of Neuropathic Symptoms and Signs, *Douleur Neuropathique* EN 4 *Questions*, Hamilton depression and anxiety rating scales, Neuropathy Impairment Score of the Lower Limb (NIS-LL), and the Short Form 36 Health Survey Questionnaire (SF-36). **Results.** Patients with neuropathic pain had significantly more severe DSPN measured with NIS-LL ($p < 0.01$). They were more likely to be engaged in physical work ($p < 0.05$), and had more symptoms of depression ($p < 0.05$) than patients without neuropathic pain. Patients with neuropathic pain had significantly lower QoL in both physical and mental domains ($p < 0.01$). Independent predictors of worse QoL in DSPN were presence of depression (beta=-0.58, $p < 0.01$) and presence of neuropathic pain (beta = -0.23, $p < 0.05$) - $R^2_{adjusted} = 0.48$. **Conclusion**. Independent predictors of QoL in patients with DSPN were presence of depression and neuropathic pain, which signifies importance of their early recognition and early treatment.

Key words:
anxiety; depression; diabetic neuropathies; neuralgia; quality of life; risk factors; surveys and questionnaires.

Apstrakt

Uvod/Cilj. Prevalenca šećerne bolesti u opštoj populaciji raste. Sa druge strane, veliki je broj obolelih od dijabetesa sa neuropatskim bolom. Cilj studije je bio da se ispita uticaj neuropatskog bola na kvalitet života kod bolesnika sa dijabetesnom senzorimotornom polineuropatijom (DSPN), koji nisu imali ni jednu drugu dijabetesnu komplikaciju niti bilo kakve druge komorbiditete od značaja. **Metode.** Ukupno 32 bolesnika sa DPN i definitivnim prusustvom neuropatskog bola su upoređivani sa 32 bolesnika sa DSPN bez neuropatskog bola. Ispitanici su bili upareni po polu, starosti i trajanju bolesti. Korišćene su sledeće skale: *Pain Detect Questionnaire, Leeds Assessment of Neuropathic Symptoms and Signs, Douleur Neuropatathique* EN 4 *Question*, Hamiltonova skala depresivnosti i anksioznosti, *Neuropathy Impairment Score of the Lower Limb* (NIS-LL) i *Short Form* 36 *Health Survey Questionnaire* (SF-36). **Rezultati.** Bolesnici sa neuropatskim bolom su imali znatno težu DSPN mereno pomoću NIS-LL ($p < 0,01$). Bolesnici sa neuropatskim bolom su se češće bavili fizičkim poslovima ($p < 0,05$) i češće su imali simptome i depresije ($p < 0,05$) u odnosu na bolesnike bez neuropatskog bola. Bolesnici sa neuropatskim bolom su imali značajno lošiji kvalitet života, kako u fizičkim, tako i u mentalnim domenima ($p < 0,01$). Nezavisni prediktori lošijeg kvaliteta života kod bolesnika sa DSPN su bili: prisustvo depresije (beta = -0,58, $p < 0,01$) i prisustvo neuropatskog bola (beta = -0,23, $p < 0,05$) – pilagođeno R2 = 0,4. **Zaključak.** Nezavisni prediktori lošijeg kvaliteta života kod bolesnika sa DSPN bili su prisustvo depresije i neuropatskog bola, što ukazuje na značaj njihovog ranog prepoznavanja i ranog lečenja.

Ključne reči:
anksioznost; depresija; dijabetesne neuropatije; neuralgija; kvalitet života; faktori rizika; ankete i upitnici.

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Introduction

Neuropathic pain (NP) is, as defined by the International Association for the Study of Pain (IASP), a pain that arises as a direct consequence of the lesion or disease of the somatosensory system [1]. According to the site of the lesion, it can be peripheral (lesions of peripheral nerve, nerve plexus, dorsal ganglion, nerve root) and central (lesion of the spinal cord or the brain) [2]. Peripheral NP is significantly more common and better studied than central NP, and its most common cause is diabetic polyneuropathy (DPN). The most common form of DPN is chronic, symmetrical, length-dependent sensorimotor polyneuropathy (DSPN), observed in 3%–50% of patients with diabetes mellitus (DM) [3]. Taking into account that the prevalence of DM in general population is above 8% and that it is constantly increasing, number of diabetic patients with NP is large [4]. In the United States prevalence of diabetes in 2014 was even 9.3% [5].

It has been shown that DPN reduces quality of life (QoL) [6, 7]. In addition, even patients with subclinical forms of DPN may have reduced QoL [8]. Numerous studies on QoL in patients with DPN were conducted, but they usually included patients who had other significant complications of DM or other associated comorbidities that could also strongly affect QoL [7, 9, 10]. Also, in many of these studies patients who did not have diagnosis of definite DPN were included. Assessment of NP in these studies has not been consistent, and some patients even used NP medication and antidepressant drugs.

The aim of this study was to assess the impact of NP on QoL in patients with confirmed diagnosis of DSPN and definitive diagnosis of NP, along with excluding all other significant complications of diabetes and other illnesses that could affect QoL, as well as excluding all patients that use or have used NP medication anytime in their life.

Methods

This research was approved by the Ethics Committee of the University Clinical Center of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina. Prior to the research, informed consent was obtained from all patients.

A total of 140 consecutive patients with suspected DPN as complication of DM type 2 were tested in the period from December 1, 2014 to December 1, 2015 at the Electromyography Laboratory, Neurology Clinic of the University Clinical Center of the Republic of Srpska. Among them, 58 patients had diagnosis of definitive NP according to criteria made by Haanpää et al. [11] and diagnosis of definitive DSPN in accordance to criteria proposed by Dyck et al [12]. Of these, 15 patients were excluded due to comorbidities, including history of stroke, and myocardial infarction, heart failure, renal failure, and limb amputation. Patients who abused alcohol, or use NP medication or psychiatric therapy were also excluded.

We used three questionnaires for the diagnosis of NP (the Pain Detect Questionnaire – PD-Q, the Leeds Assessment of Neuropathic Symptoms and Signs – LANSS and the *Douleur neuropathique* EN *4 Questions* – DN4). The questionnaires were filled in by patients in the presence of a neurologist who was available to them in case of difficulties in understanding certain questions. The PD-Q scale score ≥ 19 indicates a clear presence of NP [13]. Score ≥ 12 on the LANSS scale indicates the presence of NP [14], while score ≥ 4 indicates the presence of NP according to the DN4 [15]. The study focused on 32 patients who had a diagnosis of NP, according to all three questionnaires – definite NP.

The control group included 32 patients with diabetic neuropathy who did not have a clinical diagnosis of NP according to Haanpää et al.[11] and who had insignificant scores on all three applied diagnostic questionnaires for NP. Patients in the experimental and control groups were matched according to gender, age, and duration of the DPN.

In all 64 patients involved in the study, we excluded other causes of polyneuropathy (urea, creatinine, B12, thyroid hormones serum levels, immunological and virusological analyses, serum and urine protein electrophoresis with immunofixation, tumor markers etc.). General questionnaire was used to examine the demographic characteristics of patients, including sex, current age, level of education, occupation, employment and marital status. Clinical characteristics of the disease were also examined: age at the onset and duration of both DM and DPN, therapy for DM (oral, insulin or both), concomitant medication for any other disease, type of polyneuropathy according to the type of affected nerves (sensory, sensorimotor, motor), type of polyneuropathy according to the type of pathological impairment (axonal, axonal-demyelinating, demyelinating) and severity of polyneuropathy (Neuropathy Impairment Score of the Lower Limb – NIS-LL) [16]. The NIS-LL consists of three groups of tests: muscle strength, muscle reflexes and sensibility testing. Values range from 0, representing a normal finding, to 88 representing muscle paralysis, absence of muscle reflexes, and impairment of superficial and deep sensibility on the dorsal side of the thumb of the foot.

A nerve conduction study (NCS) was performed in all patients by the same examiner on the Oxford Synergy device. Temperature of the tested limbs was above 31ºC. NCS were conducted using superficial stimulation and registration electrodes. Motor conduction velocity (MCV) (median, ulnar, peroneal and tibial nerves) and sensory conduction velocity (SCV) (median, ulnar and sural nerves) were examined. Also, we tested the amplitudes of the compound muscle action potentials (CMAP) and minimum F-wave latency for previously mentioned motor nerves and amplitude of the sensory nerve action potentials (SNAP).

21-item Hamilton Depression Rating Scale (Ham-D) was used to assess depression, where score > 8 indicates the presence of depression [17]. Hamilton Anxiety Rating Scale (Ham-A) was used to estimate anxiety, where score > 18 indicates the presence of anxiety [18]. As a measure of health-related QoL, each patient filled in the Serbian version of the Short Form 36 Health Survey Questionnaire (SF-36) [19] which is a generic measure that combines eight general health concepts: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT),

social functioning (SF), role emotional (RE), and mental health (MH). Beside the total SF-36 score, physical composite score (PCS) and mental composite score (MCS) are two main scores to summarize these eight scales. All scores were interpreted with a 0–100 scale, where higher numbers represent better QoL.

Statistical data processing was performed in SPSS version 17.0 (SPSS Inc., Chicago, Illinois, USA). All examined variables were first analyzed using the Kolmogorov-Smirnov test to determine whether they were distributed by normal distribution. For the comparison of nominal and ordinal variables, the χ^2 test or Fisher test were used. Difference between two continuous nonparametric variables was investigated using the Mann-Whitney *U*-test, while Student's *t*-test was used for continuous parametric variables. All variables that differed between patients with and without NP were included in the multiple linear regression analysis (stepwise method) as independent variables, while the SF-36 score was considered dependent variable. Level of statistical significance was 0.05 for statistically significant difference and 0.01 for statistically highly significant difference.

Results

Sociodemographic and clinical characteristics of our cohort of patients are shown in Table 1. Patients with NP had significantly more severe form of DSPN measured with the NIS-LL scores ($p < 0.01$), and were more likely to be engaged in physical work than patients without NP ($p < 0.05$). Other parameters did not significantly differ.

Results of psychological status assessment are shown in Table 2. Patients with NP had a significantly higher score on depression scale and a higher percentage of depression compared to the patients without NP.

Results of QoL assessment are shown in Table 3. All SF-36 domains were significantly worse in patients with NP, except for RE. Patients with NP also had significantly lower PCS, MCS, and total SF-36 scores.

In multiple linear regression analysis (stepwise method), we included all variables that differed between patients with and without NP (presence of NP, NIS-LL total score, occupation and results on Ham-D) (Table 4). Presence of NP and presence of depression appeared as independent predictors of poor QoL in DSPN.

Table 1

Sociodemographic and clinical characteristics of DSPN patients with and without neuropathic pain (NP)

Characteristics	Patients with NP (n = 32)	Patients without NP (n = 32)
Gender (% of men)	50.0	50.0
Age (years, mean ± SD)	60.0 ± 6.7	59.2 ± 8.6
Education (%)		
lower	25.0	6.2
medium	62.5	71.9
high	12.5	21.9
Occupation (%)*		
physical job	65.6	31.2
intellectual work	34.4	68.8
Employment (%)		
employed	43.8	53.1
unemployed	56.2	46.9
Marital status (%)		
lives with a partner	87.5	87.5
lives alone	12.5	12.5
Age at onset of DSPN (years, mean ± SD)	51.5 ± 7.9	51.3 ± 8.0
Disease duration (years, mean ± SD)	8.4 ± 2.6	7.9 ± 1.8
Diabetes therapy (%)		
oral	21.9	37.5
insulin	56.2	53.1
both	21.9	9.4
Type of polyneuropathy (%)		
sensory	43.8	43.8
sensorimotor	56.2	56.2
Type of polyneuropathy (%)		
axonal	56.2	50.0
axonal-demyelinating	43.8	50.0
NIS-LL motor score (mean ± SD)*	1.3 ± 1.8	0.2 ± 0.7
NIS-LL sensory score (mean ± SD)**	6.6 ± 1.2	2.8 ± 1.0
NIS-LL reflex score (mean ± SD)**	4.4 ± 2.1	1.8 ± 0.8
NIS-LL total score (mean ± SD)**	12.4 ± 3.5	4.7 ± 1.6

***$p < 0.05$; **$p < 0.01$.**

SD – standard deviation; DSPN – diabetic sensorimotor polyneuropathy; NIS-LL –Neuropathy Impairment Score of the Lower Limb.

Table 2

Anxiety and depression in DSPN patients with and without neuropathic pain (NP)

Score	Patients with NP (n = 32)	Patients without NP (n = 32)	Test (*p*)
HamD (mean ± SD)	8.5 ± 5.1	4.9 ± 3.4	*U* (0.01)
% of patients with depression	37.5	15.6	χ^2 (0.04)
HamA (mean ± SD)	11.4 ± 7.8	7.1 ± 5.8	*U* (0.08)
% of patients with anxiety	28.1	12.5	χ^2 (0.12)

DSPN –diabetc sensorimotor polyneuropathy; SD – standard deviation; HamD – Hamilton Depression Rating Scale; HamA – Hamilton Anxiety Rating Scale.

Table 3

Quality of life in DSPN patients with and without neuropathic pain (NP)

SF-36 domain	SF-36 score		
	patients with NP (n = 32)	patients without NP (n = 32)	Test (*p*)
PF	83.0 ± 12.3	91.9 ± 6.1	*t* (0.00)
RP	29.7 ± 37.8	70.3 ± 40.4	*U* (0.00)
BP	45.1 ± 13.2	64.6 ± 10.4	*t* (0.00)
GH	29.3 ± 9.1	39.8 ± 10.2	*t* (0.00)
VT	49.1 ± 18.8	68.0 ± 17.5	*U* (0.00)
SF	54.7 ± 6.7	71.9 ± 14.9	*t* (0.00)
RE	65.6 ± 48.3	71.8 ± 43.3	*U* (0.60)
MH	56.1 ± 21.4	76.0 ± 17.7	*U* (0.00)
PCS	47.2 ± 15.6	66.9 ± 14.3	*t* (0.00)
MCS	51.0 ± 18.8	65.5 ± 18.8	*U* (0.00)
Total SF36	51.6 ± 17.5	69.3 ± 17.3	*t* (0.00)

SF-36 – Short Form 36 Health Survey Questionnaire; **DSPN – diabetic sensorimotor polyneuropathy; PF – physical functioning; RP – role physical; BP – bodily pain; GH – general health; VT – vitality; SF – social functioning; RE – role emotional; MH – mental health; PCS – physical composite score; MCS – mental composite score.**

Table 4

Predictors of total SF-36 score in patients with DSPN (a multiple linear regression analysis – stepwise method)

Included variables	Beta	*p*
Neuropathic pain	-0.23	0.02
HamD	-0.58	0.00
	$R^2_{adjusted}$ = 0.48	

SF-36 – Short Form 36 Health Survey Questionnaire; HamD – Hamilton Depression Rating Scale (excluded variables: NIS-LL total score, occupation); DSPN – diabetic sensorimotor polyneuropathy.

Discussion

The results of our research showed reduced QoL in patients with DSPN, especially in those with NP. This means that treatment of NP might significantly improve QoL of these patients, particularly because there is no effective causative therapy for polyneuropathy. In our group of patients with NP compared to those without NP, much lower PCS, MCS and total SF-36 scores were observed. Furthermore, the study showed that all QoL domains (except RE) were significantly worse in patients with NP. We demonstrated that NP was an independent predictor of poorer QoL in patients with diabetic neuropathy.

Aslam et al. [9] found similar results regarding individual SF-36 domains, PCS and MCS while examining 25 patients with painful DSPN and 25 patients without NP. In another study, authors found lower PCS and MCS scores on 12-Item Short Form Survey (SF-12) in patients with NP compared to those without it [7]. One recent study conducted in Croatia has shown worse scores on all SF-36 domains in 80 patients with painful DSPN compared to 80 patients with DSPN and no pain [10]. However, these authors included patients with significant comorbidities and those who used NP drugs that altogether may have influence patients' QoL and results of the study.

Patients with DSPN from both groups (with and without NP) had the best scores in PF domain. Similar findings were obtained by Wasserman and Trifonova [20], as well as in our work from 2014 [21]. Such a good result for PF in our patients is due to the fact that DSPN is predominantly sensory

polyneuropathy in which motor fibers are long preserved and that patients with significant comorbidities were excluded. On the other hand, different results were obtained in other studies that found PF to be among the worst scores [9, 10, 22]. It is of note that patients with significant comorbidities were included in these studies which certainly may affect the results.

The worst results on the SF-36 were obtained for GH in both investigated groups of patients, which is a score where patients directly estimate and anticipate their health and diseases. These findings correspond to the results in most of the studies published so far, in which it was found that this item was among the most commonly and severely affected on the SF-36 scale [9, 10, 20, 21]. RP was a subdomain with very low scores in patients with NP, and very high in patients without NP. Similar results were found in other studies which suggest significant influence of NP on patients' working ability and other daily activities scale [9, 10, 20, 21]. It should also be mentioned that patients with NP in our study more frequently performed physical than intellectual job. So, it is possible that NP has impact on their working ability and *vice versa*.

Patients with NP in our study had more severe form of neuropathy since they probably have more nerve fibers affected. Similarly, multiple sclerosis patients who were more affected had a greater physical disruption of myelin and axons in their central nervous systems so they were more likely to suffer from NP [23]. Ruts et al. [24] reported similar findings in Guillain-Barré syndrome and noticed that the prevalence of pain was significantly higher in the severely affected patients.

Patients with DSPN and NP had a significantly higher score on the depression scale and a higher percentage of depressed patients compared to the patients without NP. Moreover, depression was an independent and the most significant predictor of QoL in our patients with DSPN. In the group of patients with NP, the percentage of depressed (38%) and anxious patients (28%) corresponds to the results in other studies [9, 20, 25, 26]. Aslam et al. [9] used the Hospital Anxiety and Depression Scale (HADS) in their study to assess the presence of depression and anxiety and obtained worse scores, as well as a higher percentage of depressed and anxious patients in the group of patients with painful DSPN compared to the patients without NP, although the results were statistically significant only for anxiety. Gore et al. [25] obtained a significant association between painful DSPN and depression/anxiety in the study on 255 patients with painful DSPN.

Linear regression analysis showed that the presence of depression and NP were predictors of worse QoL in patients with DSPN and that the obtained model explained almost 50% of the total SF-36 score variance. It is of note that there are another factors not included in our analysis that could explain remaining 50% of the variance. Previous studies showed that the most important predictors of QoL in diabetic patients with or without neuropathy are associated with disease itself rather than with sociodemographic factors [27, 28], while the presence of macrovascular complications is the most important predictor, as was noted in one review article [29]. In a prospective study of 53 patients with DSPN in DM type 2, Lyracos et al. [27] found that QoL was significantly reduced compared to the general population, and the most important predictors of QoL were: symptoms and signs of DPN measured by the Michigan Neuropathy Screening Instrument, HgbA1C level, reduction of activity, mental fatigue, depression, neuropathy treatment and the presence of cardiovascular diseases. Papadoupolos et al. [28] found that significant predictors of QoL were female sex, complications of DM, other associated diseases not related to DM and duration of DM

Main limitation of our study is a relatively small sample size. The strength is in the fact that the research involved patients who had a confirmed DSPN diagnosis and a definitive diagnosis of NP, and that control group of patients with DSPN without NP was also included. In addition, we included only the patients with no other significant complications of DM or comorbidites that could affect QoL.

Conclusion

We found significantly lower QoL in both physical and mental domains in patients with DSPN and NP compared to patients with DSPN without NP. Independent predictors of QoL in patients with DSPN were presence of depression and NP, which signifies importance of early recognition and early treatment of these symptoms.

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