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Impact of pain severity on functioning domains, sleep, and cognition in painful diabetic peripheral polyneuropathy patients

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Abstract

Background: Several studies have observed that painful diabetic peripheral polyneuropathy (PDPN) had an impact on the level of functioning domains and quality of sleep as well as cognitive functions. This study is aimed to explore the relationship between severity of pain and level of functioning, sleep quality, and cognitive functions among these patients. We recruited 100 diabetics with a mean HbA1C% of 7.3±0.9, diagnosed with PDPN, and included in the study with a mean age of 51±12.8 years and disease duration of 10.2±7.4 years. The following assessment was done for each patient; clinical and neurophysiology assessment, routine laboratory assessment, measuring pain severity, and average pain severity interference scores using pain visual analog scale (VAS) and brief pain inventory (BPI) short form, respectively, sleep quality assessment using Pittsburgh Sleep Quality Index (PSQI) and Montreal cognitive function assessment (MOCA) scales.

Results: Moderate to severe pain was recorded in 71% of patients according to the VAS pain score. The severe pain group recorded the significant highest average pain severity and interference scores in BPI and domains compared to other less pain groups with average pain intensity scores of 7.5±0.6 vs 5.3±0.8 in the moderate and 3.3±0.4 in mild pain groups. Poor sleep quality and pattern were observed in these patients with a mean PSQI score of 6.8±3.1, and the severe pain group had a significant highest score of 9.4±2.3 compared to other less group scores of 7±2.3 and 3.7±1.8. Their mean MOCA score was low 24.2±2.2. Out of them 48/100 patients had mild cognitive impairment and recorded high frequency in the severe pain group (28/32) followed by the moderate pain (15/39) group. There is a significant correlation between the score of VAS and PSQI as well as MOCA.

Conclusions: Painful DPN patients had a poor level of functioning and sleep quality as well as cognitive impairment based on pain intensity.

Trial registration: This study was registered on a clinical trial with registration number NCT03275233 on 7 September 2017.

Keywords: Painful diabetic peripheral polyneuropathy (PDPN), Functioning domains, Sleep quality, Brief pain inventory short form, Pain visual analog scale, Cognitive function

Background

The International Diabetes Federation (IDF) reports have stated that more than 436 million people have diabetes [1, 2]. Distal symmetrical polyneuropathy (DPN) is the most prevalent diabetic neuropathy and is recorded in up to 50% of diabetics. According to the American Diabetes Association Position Statement, DPN is defined as "the

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presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes [3].

DPN is a major morbidity, causing non-traumatic amputations [4]. Patients with painful DPN (PDPN) reported in their complaints a stinging, burning, and keen sensation that increases at night with a loss of sensation or numbness of the involved area [5, 6].

The intensity of neuropathic pain is variable in PDPN. PDPN is observed in different clinical syndromes, and mixed large and small fiber neuropathy is the most common [7].

There are evidences suggesting the association between chronic pain and sleep [8]. However, other studies used different methods in analyzing these processes and findings, making comparisons difficult [9]. Moreover, sleep disturbances as a common squeal can affect cognitive function [10] that may explain cognitive function deterioration in these patients [11]. That could be explained by pain pathophysiology and different underlying neurobiological mechanisms [12]. So, PDPN had an impact on the quality of life of these patients and a broad financial burden [13].

This study is aimed to determine the impact of pain severity on functioning domains in patients' life with PDPN, sleep quality, and cognitive functions as well as the possible relationship between scores of VAS pain and used clinical rating scales.

Methods

This descriptive cross-sectional study was conducted over a 6-month duration elapsed from the 1st of September 2019 to the 29th of February 2020 in the neurology outpatients clinic at the Neuropsychiatry Department, in Assiut University Hospital. One hundred fifty recruited diabetic patients presenting with painful distal sensorimotor polyneuropathy were met the eligibility criteria for PDPN and included in the study.

The inclusion criteria were as follows: (a) Any type II diabetic patient, aged 18 years or more, was diagnosed as a diabetic distal symmetrical sensorimotor polyneuropathy or other subtypes of diabetic neuropathy associated with painful symptoms (i.e., burning, prickling, tingling, and/or shooting pain in the toes, feet, legs, and/or hands) of at least 3-month duration since the date of diagnosis of symptomatic (painful) diabetic neuropathy and (b) able to give consent for the participation in the study and providing personal medical and clinical data.

The exclusion criteria were as follows: (a) any patient with comorbid significant medical and neurological disorders or (b) patients with severe mental illness that may interfere with the study variables or (c) a patient with severe motor weakness was also excluded from the study.

All patients who participated in the study did not receive any specific medical treatment for pain either pain killer or anti-depressant. They are novel assessed for pain in this study.

We excluded fifty patients from the study who met the exclusion criteria as follows: twenty patients had serious unstable comorbid medical conditions (seventeen patients had uncontrolled hypertension, out of them five had renal insufficiency, and three patients had refractory heart failure), two patients had comorbid mood disorders, ten patients had previous stroke, one patient had a lumbar disc, four patients had chronic ischemia of the lower limbs, eight patients had uncontrolled diabetes and frequent diabetic coma, and five patients refused the participation in the study or do neurophysiology to confirm the diagnosis.

Ethics

This study had ethical approval from the Institutional Review Board (IRB) of the Faculty of Medicine, Assiut University, with an approval number (IRB17100291). This study was registered on a clinical trial with registration number NCT03275233, https:// clinical trials.gov/ct2/show/NCT03275233 in September 2017.

All eligible patients gave informed consent for participation in the study after the approval of the Ethical Committee of the Faculty of Medicine, Assiut University.

Study design

One hundred eligible patients were conducted with nerve conduction study to confirm the diagnosis of PDPN and underwent the following: (1) history case-taking, clinical and neurological assessment including the onset of DM and treatment; (2) cardiac assessment and ECG; (3) laboratory investigation, i.e., HbA1c%, serum urea, and creatinine; and (4) the following clinical rating scales.

Pain visual analog scale (VAS) [14]

It is a self-reported 10-cm visual analog scale (VAS) used for the pain intensity assessment by the subjects where "0" means no pain and "10" shows unbearable severe pain. VAS pain scores among these patients ranged from 3 to 8, so the pain severity is classified into mild (3), moderate (4–6), and severe ($\geq$7) pain suffers.

Brief pain inventory (short form) for measuring average pain intensity score and pain interference scores [15]

It is a self-reported nine-item scale measuring the average intensity of pain and the interference of pain on patient functioning domains. The mean of items 3–6 measures the pain severity score. BPI average pain intensity score was $\geq$3 among these patients. The mean of items 9A–9G measures the average pain interference

scores, i.e., the interference of the pain with the following aspects: general activity, mood, walking, normal work, relations with other people, sleep, and enjoyment of life). The BPI assessed the pain intensity score in the past 24 h and the severity of the pain right now. Outcomes for each item range from 0 (no) to 10 (bad). The BPI interference pain score with the patient's functioning in the past 24 h is ranged from 0 to10; 0=no interference and 10 =complete interference.

The Pittsburgh Sleep Quality Index (PSQI) [16] for the assessment of the sleep quality and pattern

It is a self-rated questionnaire, assessing the sleep quality and disturbances over a 1-month time interval. It is nineteen individual items and generates seven "component" scores, i.e., subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of the seven-component scores yields one global score. A total score of "5" or more is indicating poor sleep quality [16].

Montreal Cognitive Assessment (MOCA) [17]

MOCA is a 30-point test assessing the following domain; memory recall, visuospatial abilities, attention and concentration, language, abstraction, calculation, and orientation. MOCA score <26 is indicating cognitive impairment.

Statistical analysis

For the statistical analysis, SPSS-version 16 software was used. Data was expressed as the number and percentage or mean± standard deviation (SD). Chi-square test was used to compare proportions. One-way ANOVA was used for comparison between the three groups of the numeric data. Pearson's correlations were done between pain VAS score and demographics as well as clinical rating scales scores. Results were considered significant if P <0.05.

Result

Sociodemographic and clinical data

The mean age of the studied patients was 51±12.8 years old with a range of 22–74 years. In the studied sample, the male sex (55%) and rural residents (59%) were predominant. The majority of the studied cases (62%) were illiterate. Among these patients, the mean duration of DM was 10.2±7.4 years, and the mean HbA1c% was 7.3±0.9.

Based on the VAS pain score, 71% of patients had moderate to severe pain: the pain was recorded as follows: severe in 32 patients, moderate in 39 patients, and mild pain in the remaining (n=29) patients. The severe pain group was the oldest one compared to the mean age of other less pain groups [54.2±13.2 vs 52.5±11.7 vs 45.5±12.4 years], p>0.05. Illiteracy and low education were observed in high frequency among the severe pain group (29/32) compared to other less pain groups (23/32 & 10/29), p<0.05. Concerning glycemic control, a significant high mean HbA1c% was observed among the severe pain group compared to the mean HbA1c% of other less pain groups (8.3±0.5 vs 7.2±0.3 in moderate pain and 6.3±0.2 in the mild pain groups, p=0.0001). No observed significant difference was found in other demographic or clinical data between different pain groups (see Table 1).

Brief pain inventory (BPI) results were revealing that studied patients recorded an average pain severity score of 5.4 ± 1.8 and a high average interference pain score of 5.6±1.7. Also among studied patients, the average interference pain score to functioning domains was high, the general activity was 6.3±2.1, the mood was 5.6±2, the walking ability was 5.9±2.1, the normal walking was 5.8±2, the relation with other people was 3.8±1.7, sleep was 5.3±1.8, and the enjoyment of

Table 1 Demographic and clinical data of PDPN patients among different pain severity groups

Variable	Mild pain VAS=(3) *N*=29 Number (%)	Moderate pain VAS=(4–6) *N*=39 Number (%)	Severe pain VAS=(≥7) *N*=32 Number (%)	*P* value
Sex				
Male	15 (51.7%)	20 (51.3%)	20 (62.5%)	0.585
Female	14 (48.3%)	19 (48.7%)	12 (37.5%)	
Marital state				
Single	1 (3.4%)	1 (2.6%)	4 (12.5%)	0.170
Married	28 (96.6%)	38 (97.4%)	28 (87.5%)	
Education				
Educated	19 (65.5%)	16 (41.0%)	3 (9.4%)	0.0001
Non-educated	10 (34.5%)	23 (59.0%)	29 (90.6%)	
Smoking habit				
Smoker	5 (17.2%)	8 (20.5%)	10 (31.2%)	0.385
Non-smoker	24 (82.8%)	31 (79.5%)	22 (68.8%)	
Residence				
Rural	21 (72.4%)	20 (51.3%)	18 (56.2%)	0.200
Urban	8 (27.6%)	19 (48.7%)	14 (43.8%)	
Treatment				
Oral hypoglycemic	19 (65.5%)	22 (56.4%)	12 (37.5%)	0.078
Insulin	10 (34.5%)	17 (43.6%)	20 (62.5%)	
Duration of DM				
≤5years	13 (44.8%)	11 (28.2%)	6 (18.8%)	0.245
6–10years	8 (27.6%)	14 (35.9%)	15 (46.9%)	
›10years	8 (27.6%)	14 (35.9%)	11 (34.4%)	

life was 5.1±1. A significant high average pain severity score of 7.5±0.6 was recorded in the severe pain group compared to the average score in other less pain groups, 5.3±0.8 in moderate pain, 3.3±0.4 in mild pain, and p=0.0001. The same was recorded in the average pain interference score and average interference pain score for all functioning domains related to BPI, p=0.0001 for all (see Table 2).

On the assessment of the sleep quality and pattern in these patients using PSQI, we found that poor sleep quality and pattern were observed in them with a mean total PSQI score of 6.8±3.1, and the severe pain group had the significant highest PSQI score of 9.4±2.3 compared to other less pain groups [7±2.3 in moderate pain and 3.7±1.8 in mild pain], p=0.0001. The same was observed in all sleep component scores apart from C4 habitual sleep efficiency (see Table 3).

On cognitive function assessment of these patients using the MOCA scale, we found that their mean MOCA score was low 24.2±2.2. Out of them, 48/100 patients had mild cognitive impairment with the recorded high frequency of severe pain (28/32) followed by the moderate pain (15/39) group and the least frequency in the mild group 3/29, p=0.0001.

There was a significant correlation was found between VAS pain score and age (r=0.283, p=0.004) as well as serum HbA1c% (r=0.909, p=0.0001) using Pearson correlation. A significant positive correlation was observed between the VAS pain score and average interference pain score as well as the average interference pain score to all functioning domain scores related to (9A–9G items) BPI (r=0.988, 0.952, 0.903, 0.892, 0.912, 0.884, 0.797, 0.883, and 0.864, respectively, to these (9A–9G items) domains, p=0.0001 for all). Also there is a significant correlation between VAS pain score and PSQI score (r=0.771, p=0.0001) and MOCA score (r= −0624; p=0.0001).

Discussion

The present study is conducted on 100 PDPN patients to determine the impact of the pain severity on PDPN patients' functioning domains, sleep quality and cognitive functions, and the relationship between VAS pain score and clinical rating scale scores on the one hand and

Table 2 Mean value ± SD of average pain severity, interference pain scores, and functioning domain scores in BPI among different pain severity groups

Average score ±SD	Mild pain VAS= (3) *N*=29	Moderate pain VAS=(4–6) *N*=39	Severe pain VAS=(≥7) *N*=32	ANOVA *F*	*P* value
Pain severity	3.33±0.35	5.29±0.76	7.53±0.60	357.825	0.0001
Pain interference	3.60±0.41	5.38±0.81	7.61±0.67	268.763	0.0001
General activity	4.03±1.14	6.08±0.90	8.69±0.82	182.348	0.0001
Mood	3.55±0.63	5.23±0.90	7.91±1.32	148.878	0.0001
Walking ability	3.76±0.68	5.59±0.90	8.25±1.16	167.522	0.0001
Normal walk	3.59±0.73	5.56±0.99	8.00±1.16	153.298	0.0001
Relation with other people	1.79±1.04	4.10±0.94	5.23±0.92	101.774	0.0001
Sleep	3.41±0.62	5.26±1.17	7.16±1.05	111.673	0.0001
Enjoyment of life	3.14±0.52	5.18±1.09	6.88±1.23	102.411	0.0001

Table 3 Mean value score± SD of total PSQI and component scale among different pain severity groups

Components scale score of Total PSQI	Mild pain VAS=(3) *N*=29	Moderate pain VAS=(4–6) *N*=39	Severe pain VAS=(≥7) *N*=32	ANOVA F	*P* value
Total PSQI	3.66±1.77	7.03±2.34	9.41±2.35	52.314	0.0001
C1 sleep quality	0.41±0.50	1.03±0.42	1.56±0.50	44.494	0.0001
C2 sleep latency	0.72±0.70	1.49±0.94	2.16±0.72	23.738	0.0001
C3 sleep duration	0.52±0.50	1.10±0.78	1.50±0.84	13.595	0.0001
C4 habitual sleep efficiency	0.55±0.50	0.79±0.83	1.03±0.78	3.233	0.44
C5 sleep disturbance	0.59±0.50	0.97±0.42	1.12±0.49	10.555	0.0001
C6 use of sleep medication	0.31±0.47	0.95±0.79	1.16±0.51	14.917	0.0001
C7 daytime dysfunction	0.55±0.57	0.67±0.57	0.88±0.49	2.746	0.0001

demographics of PDPN patients and their clinical data on the other hand.

More than two thirds of the studied patients were suffering from moderate to severe pain based on the VAS pain score, and the severe pain group was the oldest group. Moreover, age had a significant positive association with the VAS pain score ($p<0.01$). Our data are consistent with many studies that reported age as a risk factor for pain among PDPN patients [18–23], while few studies have shown no association [24].

Concerning sex predisposition, males are higher in frequency (55%) than females (45%) without a significant difference or association among studied PDPN patients. These data are consistent with the reported data of men who had been at higher risk than women for PDPN development in diabetes [25], while the observed female preponderance was found in another study [26]. In this study, no sex predisposition for PDPN severity was observed ($p>0.05$). The present observation was supported by others who reported no sex difference [27]. However, other studies were retrospectively observed that men had early onset of diabetic neuropathy that may be attributed to their exposure to more hazardous than women in lifestyle [28, 29].

Concerning other demographic data in our study among PDPN patients, we found that 94% were married, only 38% were educated, and 61% were not working, which indicate a low socioeconomic state. Moreover, 59% were rural residents. These data are matched with the observed protective effect of marriage, high educational level, and family income, as it is consistent with the studies' results that the link between better health care and self-care knowledge and practice with higher educational and family income levels [30, 31]. Moreover, the marriage may buffer against stress and thereby reduce the activation of the neuroendocrine system [32]. In our study, no relationship was found between PDPN and smoking ($p>0.05$). However, cigarette smoking was found to be associated with an increased risk of PDPN in other studies [33, 34]. These different data in this study could be attributed to patients with vascular complications or other causes attributed to DPN that were excluded, whereas different studies' findings could be attributed to the criteria of the selected patients and study designs as well as the used tools in different studies.

In this study, the majority of severe pain (81.2%) in PDPN patients suffered from DM of about 6 years or more. Moreover, a positive association was found between PDPN pain score and DM duration ($p>0.05$). However, others reported that DM duration is a risk factor for the development of PDPN [35–38].

Based on HbA1c%, the studied PDPN patients had poor glycemic control and showed a significant correlation between HbA1c% and VAS pain score ($p<0.0001$). In another study, it was observed that glycemic control over time was significantly worse in those with PDPN compared with no PDPN [39]. Moreover, good glycemic control could potentially delay PDPN development and progression as well as other microvascular complications in different DM types, T1D and T2D [40, 41]. Inflammation and dysfunction of the endoneural, perineurial, and epineural blood vessels are leading to axonal atrophy, degeneration, and impaired axonal transport as well as contributing to functional and structural abnormalities in PDPN [42]. Thus, good glycemic control in these patients could go a long way in preventing or delaying the development of PDPN; however, others observed a lack of association between PDPN and HbA1c% [35, 43].

Based on the VAS pain score, we found that 29 patients had mild pain, 39 patients had moderate pain, and 32 patients had severe pain. Among these pain severity groups, BPI data is revealing that these studied patients assuming average pain severity scores of ≥ 4 are indicative of considerable daily suffering [44, 45] and experienced substantial pain (see Table 2). Our results about the average pain experience severity score among these patients have been found to be higher than others [46–48]. It may be related to the low socioeconomic state and educational level of our patients with PDPN. Moreover, according to the average interference pain score in functioning domains of BPI, chronic pain restricts a patient's performance in daily activities of functioning domains, causing a negative impact on their functioning domains including the general activity, mood, walking ability, normal walk, relation with other people, sleep, and enjoyment of life as the average interference pain score for all patients was >4 (5.6 ± 1.7) and the average interference pain scores in different domains were >3 in the studied patients ranged from 3.8 ± 1.7 in an average interference pain score in relation with other people's domain to 6.3 ± 2.1 in the interference pain score to the general activity domain, as the majority of domains recorded the interference pain score of > 4 (see the "Results" section). Furthermore, patients in this study experienced a significantly high substantial average PDPN pain-related interference score (≥ 4) in functioning domains of patients' life in the severe pain group compared to the moderate and mild pain groups (see Table 2). Moreover, their reported scores were higher than the reported pain functional interference scores of other studies [47, 49]. However, our results of high average BPI score are consistent with the results of BPI of another study [50]. Moreover in our study, there is a strong significant positive correlation between the VAS pain score and average pain severity score and the pain interference score in all these functioning domains in BPI ($p<0.0001$).

Concerning the sleep quality and pattern that were measured by Pittsburgh sleep quality index PSQI, it was observed that cases with a sleep disturbance and poor sleep quality, whose scores are ≥5 in PSQI [51]. These studied patients recorded a high mean score of PSQI (6.8±3.1), indicating that PDPN patients had a significant poor sleep quality among different pain severity groups in PDPN patients. Moreover, the highest recorded score was 9.4±2.3 among the severe pain group compared to other less pain groups, $p<0.0001$(see Table 3). The prevalence rate of sleep disturbances in these PDPN patients was 86%. It is consistent with various researches on chronic pain found that sleep disturbance rate range between 50 and 80% [52, 53]. Our recorded prevalence rate is similar to the Iranian prevalence rate (85.5%). Moreover, Gore et al.'s screening study reported that the subjects with PDPN have greater sleep problems compared with the general US population using the medical outcome of the study sleep problem (MOS sleep scale), as their mean overall sleep index score was 47.1 PDPN versus 25.8 population norm score [48]. Also, others using the MOS sleep scale found that patients with PDPN had a substantially higher overall score of 48.5, ranged from mild to severe sleep problems, which indicate worse sleep outcomes [54]. Furthermore, in our study, there is a significant positive correlation between the VAS pain sore and PSQI score regarding all components of the PSQI questionnaire ($p<0.0001$).

Nearly half of the total PDPN patients had a mild cognitive impairment (MOCA score<26), and the highest frequency was recorded among the severe pain group compared to other less pain groups, $p<0.0001$. The same was found in other studies [11, 55, 56]. However, this deterioration in cognitive function may be attributed to central microangiopathy in DM associated with poor glycemic control among PDPN patients. These patients have been investigated in many studies and showed thalamic neuronal dysfunction and perfusion abnormalities in MRI studies and somatosensory afferent pathway dysfunctions in evoked potential studies [57–59]. So, these data are suggesting a connection between cognitive dysfunction and PDPN in diabetics, as some similarities in the pathogenic mechanisms of both cognitive dysfunction and PDPN development were observed regarding common predisposing risk factors for both such as chronic hyperglycemia and HAlb1c% levels [60]. This cognitive deterioration in diabetics has been established by others [61]. Moreover, in this study, we found that there is a significant negative correlation between VAS pain score and MOCA score ($p<0.0001$). This association was found by others [11, 56]. Thus, diabetes and chronic pain may explain and consider cognitive dysfunction as observed complications in PDNP patients [56].

Conclusions

In summary, PDPN patients have significant impairment of functioning domains as well as sleep disturbance associated with longer sleep latency duration and cognitive impairment. These findings are based on pain severity among these patients and glycemic control.

Study limitations

Important limitations of this study are the relative small sample size and lack of follow-up of these patients after the management of neuropathic pain using the same rating scales for measuring outcomes on their quality of functioning level in life domains, sleep pattern, and cognitive functions.

Abbreviations

PDPN: Painful diabetic peripheral polyneuropathy; VAS: Visual analog scale; BPI: Brief pain inventory; PSQI: Pittsburgh Sleep Quality Index; MOCA: Montreal cognitive function assessment scale; DPN: Distal symmetrical polyneuropathy; ECG: Electrocardiogram; DM: Diabetes mellitus; IDP: The International Diabetes Federation; T1D and T2D: Type I DM and type II DM; MOS sleep scale: Medical outcome study for sleep scale.

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Authors' contributions

NA, RG, and AF recruited the participants, analyzed and interpreted the data, and were the contributors to writing the manuscript. NA, RG, and AF revised the data interpretation, read, and approved the final manuscript. AF helped in the data entry and analyzed and generated the result sheets. The authors have read and approved the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

The protocol and study design were approved by the local ethical committee in the Faculty of Medicine, Assiut University, Egypt (IRB17100291). An informed signed consent was obtained from all participants.

Consent for publication

All the participants' consent for publication was obtained.

Competing interests

The authors declare that they have no competing interests.

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