Original Article :

The Relationship Between Pain, Daily Function, and Sleep Quality in Diabetic Neuropathy.

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Abstract

Background and Aims:

Poor sleep quality affects insulin sensitivity and glucose metabolism. There were limited information about sleep quality in individuals with diabetic peripheral neuropathy. The Pittsburgh Sleep Quality Index was used in this study to measure sleep quality and determine how sleep quality and pain were related in patients with diabetic peripheral neuropathy.

Methods:

This is a secondary analysis of an aerobic exercise research study in patients with diabetic peripheral neuropathy. Participants performed the Pain Inventory and the Pittsburgh Sleep Quality Index at baseline to measure clinical pain and sleep quality, respectively. Pain Inventory consists of two components including The Pain Severity Index and the Pain Interference Index. The relationship between pain and sleep quality was evaluated using Pearson's correlations.

Results:

The study showed that 77.8% of the subjects had low sleep quality (i.e., Pittsburgh Sleep Quality Index scores > 5) (mean score of Pittsburgh Sleep Quality Index scores was 9.94±4.35). The mean scores of the Pain Interference Index and Pain Severity Index were 3.54±2.90 and 3.36±2.21, respectively. Both Pittsburgh Sleep Quality Index and Brief Pain Inventory-Pain severity index had positive relationship (r= 0.642, p = 0.004). In addition, there were positive relationship between Pittsburgh Sleep Quality Index and Brief Pain Inventory-Pain interference index (r= 0.591, p = 0.01).

Conclusions:

The majority of patient with diabetic peripheral neuropathy had low sleep quality. A higher pain intensity and more interference with daily activities were both strongly linked with poor sleep quality. The item of sleep discomfort in everyday activity was highly influenced in patients with diabetic peripheral neuropathy. Future studies are needed to determine if addressing poor sleep quality would impact perception of pain as well as diabetes management.

Keywords:

Pain, Sleep, Diabetes, Activity, Daily.

Introduction

Diabetic peripheral neuropathy (DPN) is a secondary development of diabetes, affecting 50 % to 68% of people with diabetes.[1] Lack of microvascular blood flow, poor glycemic control and irreversible nerve damage lead to DPN.[2-4] People with DPN usually experience a noticeable painful symptom called neuropathic pain (i.e., severe pain sensation when touched by bedclothes).[5,6] Neuropathic pain caused by somatosensory nervous system lesion[7], and manifested as feeling of burns, prickling pain, tingling, electric shock–like feelings, aching, tightness, or hypersensitivity to touch. Neuropathic pain affects 10-26% of people with DPN1,6, and 35% of people with diabetes.[7] Annually, DPN management costs have been reached 13.7 billion dollars in the United States.[8] Patients with P-DPN incur high intangible costs, which constitutes 9% of total health care costs.[8,9]

Previous studies showed people with chronic pain have poor sleep quality by using varied of sleep measures.[10-13] Sleep deficiency, daytime sleepiness, and awakening in middle of the night are positively correlated with pain severity.[14-16] Other causes of sleep disturbances include hyperesthesia and allodynia, which are neuropathic pain symptoms, that lead to severe pain sensation due to touches.[17,18] In fact, some studies showed a bidirectional influences between pain and sleep in which pain impact sleep, and poor sleep exacerbate pain.[24-26] Sleep questionnaires that are designed to measure different aspects of sleep quality, including difficulty in initiation, maintenance, respiratory problems, quantity, perceived adequacy and somnolence.[19-23] However, to our knowledge, no study has investigated the association between sleep quality and neuropathic pain severity in people with DPN using validated self-reported sleep measurement such as The Pittsburgh Sleep Quality Index (PSQI).

People with neuropathic pain often experience daily function limitations.[24] People with neuropathic pain may suffer from limitations in activities of daily livings (ADL) including general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life.[25,26] In children and adolescents, lower sleep quality may predict greater ADL limitations after controlling chronic pain.[27] In the case of P-DPN, worse health status, function, employment status and productivity, and frequent physician visits are significant in severe cases.[26] Changes in pain severity level will influence health status and function by at least one pain grade.[27] In addition, decreased pain was associated with greater function and ability to sleep.[28]

To our knowledge, no study has investigated the association between sleep quality, neuropathic pain, and ADL limitations in people with DPN.

Taken together, previous research studies provide empirical support for the relationship between sleep and pain severity.[43-49] Therefore, the purpose of this study was to investigate the relationships between sleep quality, neuropathic pain severity and ADL limitations in people with DPN. The results of this study will increase our understanding of sleep quality in people with DPN and neuropathic pain, since the poor sleep quality has a negative impact on glycemic control and diabetes care management. Eventually, the clinicians will understand the importance of assessing sleep quality in patients with diabetes to address any sleep disturbances at early stage to avoid future painful neuropathy.

Methods

This study is a secondary analysis of baseline data from a single-group trial that used an aerobic exercise intervention in people with DPN.[50] The study was approved by the Human Subjects Committee at University of Kansas Medical Center, and participants signed written consent form prior to study participation, between June 2012 and July 2013. Informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 declaration of helsinki as reflected in a priori approval by the institution's human research committee.

Sampling

Participants were recruited if they had been diagnosed with diabetes and had symptoms of neuropathy, indicated that they were sedentary, were between 40 to 70 years old, and did not have any other serious medical conditions. Recruited participants were excluded if they had serious cardiac pathology, open wounds on feet, walking disability, stroke history or impaired cognition and communication abilities. Details regarding the exact inclusion and exclusion criteria are provided in a previous manuscript.51 Clinical examination was obtained by a neurologist to confirm DPN via analysis of signs and symptoms, including nerve conduction studies and quantitative sensory testing.

Measures

This analysis reports on the results of the baseline assessment which occurred during a single session of testing.

Demographic and clinical characteristics

Demographic variables (age, gender, ethnicity, race, diabetes duration, neuropathy duration, educational level, marital status, and occupational status) were obtained

with a survey. Body mass index (BMI) was obtained using height and weight measurement. Diabetes and neuropathy duration were confirmed during the clinical examination. A disposable finger-stick blood testing kit (A1CNow, Bayer, Whippany, New Jersey) was used to measure Glycated hemoglobin A1C (HbA1c) which is an indicator of global glucose control over the last 3 months.

Neuropathy Assessment

Neuropathy was assessed using clinical measures: the Utah Early Neuropathy Scale (UENS) and the Michigan Neuropathy Screening Instrument (MNSI). The UENS is highly sensitive in detecting mild or early stages of neuropathy compared to other instruments.[52] For large fibers, neuropathy, MNSI is designed to detect moderate or severe stages of neuropathy and consists of a physical examination and a symptom questionnaire.53 The MNSI is a validated measure with high sensitivity of 65% and specificity of 83%.[53] The MNSI consists of two parts. The first part, Physical Examination, involves inspection of both feet, evaluation of the ankle reflexes and examination of the vibration sensation and fine touch. The second part, History Questionnaire, assesses signs and symptoms of neuropathy by asking about pain, numbness and temperature sensitivity in the feet.[53] The Neuropathy assessment was used to include only people with DPN in this study. A neurologist performed the assessment and made the final decision for enrollments the study.

Sleep quality

The PSQI is a validated 19-item questionnaire that yields a global sleep quality score over a month, ranging from 0 to 21. The PSQI components including sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction.[47] These items are separately scored from 0–3, with 3 representing the negative extreme, and summed to provide a global score. The cut-off score of PSQI was 5 scores for poor sleep quality indication (with 89.6% and 86.5% of sensitivity and specificity, respectively).[47] One item assesses trouble sleeping because of pain, which can be used to further clarify the reasons from poor sleep quality in people with neuropathic pain.[56,57]

Brief Pain Inventory Short Form for DPN (BPI-DPN)

The BPI-DPN was developed to measure pain specifically due to diabetes rather than other causes.[58] There are three subscales in the BPI-DPN including the severity of pain (Severity scale), pain interfered ADL (Interference scale) and pain

aspects (location and medications). In this secondary analysis, we only used Severity scale and interference scale to focus on how pain may influence sleep. There are four items in the Severity scale including Worst Pain, Least Pain, Average Pain, and No Pain. Each question in the pain severity has a range of responses from 0 "No Pain" to 10 "Pain as bad as you can imagine". There are seven items related to pain interference ADL including General Activity, Mood, Walking Ability, Normal Work, Relations with Others, Sleep, Enjoyment of Life.[59] Each question in the pain interference ADL has a range of responses from 0 "does not interfere" to 10 "completely interferes". Each scale score (Pain Severity Index and Pain Interfered ADL Index) is the mean of the scale item responses.[60] A study suggested that the BPI-DPN is a reliable measure which showed sufficient construct validity, criterion validity, and internal consistency.[61] Thus, using BPI-DPN is excellent tool compared to the gold-standard procedures for BPI-DPN, such as skin biopsy and nerve conduction. For both the Severity and the Interference scales, the reliability as measured by Cronbach's alpha was high (94%).[61]

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics 24. Descriptive statistics were used to calculate the sample characteristics including mean with standard deviation, and percent of categorical variables. The sleep efficiency means the overall total sleep time divided by the total time in bed multiply by a hundred. The result of this calculation will give the percentage of the time in bed was spent asleep. To clarify the calculation, sleep efficiency was calculated using the following equation:

$$\left[\sum \frac{total\ sleep\ duration}{total\ time\ in\ bed} * 100\right].$$

The strength of association between sleep quality, pain severity and pain interference ADL was measured by Spearmen correlation coefficients. The level of statistical significance level of all analyses was set at $p < 0.05$.

Results

Demographic and clinical description of the sample

Eighteen subjects with DPN completed the baseline assessments for this secondary analysis. Demographic characteristics and clinical variables are presented in Table 1. A majority of participants (14 out of 18 or 77.8%) scored > 5 on PSQI indicating poor sleep quality. In addition, more than the half of participants had sleep duration below 7 hours. There was no significant difference between males and females (p=0.979) in the PSQI.

Table 1: Characteristics and clinical variables of the study population

Age (years)	59.34 ± 6.21
Female gender, n (%)	13 (72.2)
Diabetes Duration	14.94 ± 7.13
Neuropathy Duration	7.67 ± 4.13
Female of children bearing age, n (%)	
Yes	2 (11.1)
No	16 (88.9)
HbA1C	7.5 ± 1.88
Body Mass Index (kg/m^2)	35.93 ± 5.76
UENS	10.72 ± 5.78
MNSI physical examination	5.94 ± 2.31
MNSI Questionnaire	4.64 ± 2.71
Global PSQI	9.94 ± 4.34
Sleep Quality	1.33 ± 0.69
Sleep Latency	1.56 ± 1.2
Sleep Duration	1.58 ± 1.08
Sleep Efficiency	0.11 ± 0.32
Sleep Disturbances	1.61 ± 0.69
Use of Sleep Medication	1.39 ± 1.41
Daytime Dysfunction	1.16 ± 0.78
Sleep Duration (%)	6.0 ± 1.56
< 7 hours	12 (66.67)
7 – 8 hours	5 (27.78)
> 8 hours	1 (5.55)
Participants reported pain, n (%)	12 (66.67%)
BPI (Pain Severity total)	3.36±2.21
Pain in leg and feet (worst) within 24 hours	4.11 ± 2.78
Pain in leg and feet (least) within 24 hours	2.5 ± 2.40
Pain in legs and feet (Average)	3.16 ± 1.82
Pain in legs and feet (Right now)	2.55 ± 1.82
BPI (Pain interference ADL total)	3.54±2.90
General Activity	2.55 ± 2.61
Mood	3.00 ± 3.14
Walking Ability	3.05 ± 3.05
Normal Work	3.22 ± 3.37
Relations with other people	2.38 ± 3.07
Sleep	3.66 ± 2.97
Enjoyment of life	3.77 ± 3.05

Pain and Sleep Quality

In our sample, the mean Brief Pain Inventory (BPI) pain severity index was 3.36±2.21 and pain interference index was

3.54±2.9. The highest scores were indicated on the specific items regarding how pain affected sleep and enjoyment of life (mean 3.66 ± 2.97 and 3.77 ± 3.05, respectively). There was a significant stronge positive correlation between PSQI and BPI-Pain severity index (r= 0.652, p = 0.003) as represented in figure 1 and between PSQI and BPI-Pain interference index (r= 0.591, p = 0.01) (figure 2), as presented in Table 1. All items of pain severity were significantly related to PSQI, as can be seen in Table 2. The pain interference items that were significantly related to PSQI were mood, relations with other people, and enjoyment of life. No other significant correlations were found between PSQI, BMI, A1C, diabetes duration, neuropathy duration UENS, MNSI Physical Examination or MNSI Questionnaire.

Table 2: Correlation of PSQI with BPI of two components, BMI, HbA1C, and Diabetes and Neuropathy Duration

Variables	PSQI	P VALUE
PSQI	1	
Pain Severity total	.652**	.003
Pain in leg and feet (worst) within 24 hours	.618**	.006
Pain in leg and feet (least) within 24 hours	.503*	.033
Pain in legs and feet (Average)	.588*	.010
Pain in legs and feet (Right now)	.658**	.003
Pain interference ADL total	.591**	.010
General Activity	.443	.066
Mood	.590**	.010
Walking Ability	.310	.210
Normal Work	.399	.101
Relations with other people	.610**	.007
Seep	.600**	.008
Enjoinment life	.716**	.001
BMI	-0.362	0.14
HbA1C	0.108	0.944
Diabetes Duration	-0.179	.477
Neuropathy Duration	-0.064	0.8
Sleep Duration	-0.607**	0.008
UENS	0.154	0.543
MNSI Physical Examination	0.393	0.107
MNSI Questionnaire	-0.068	0.789

Discussion

This study provides evidence for the association between pain and sleep quality using validated outcome measures in people with neuropathic pain, and the results are consistent with previous studies that examined the association between

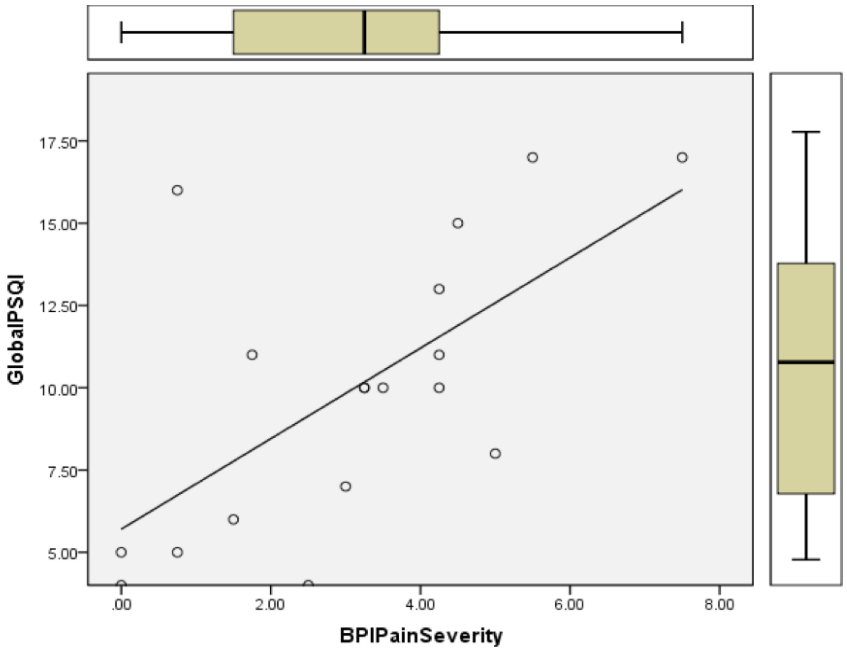


Figure 1: Association between pain severity ADL and poor sleep quality

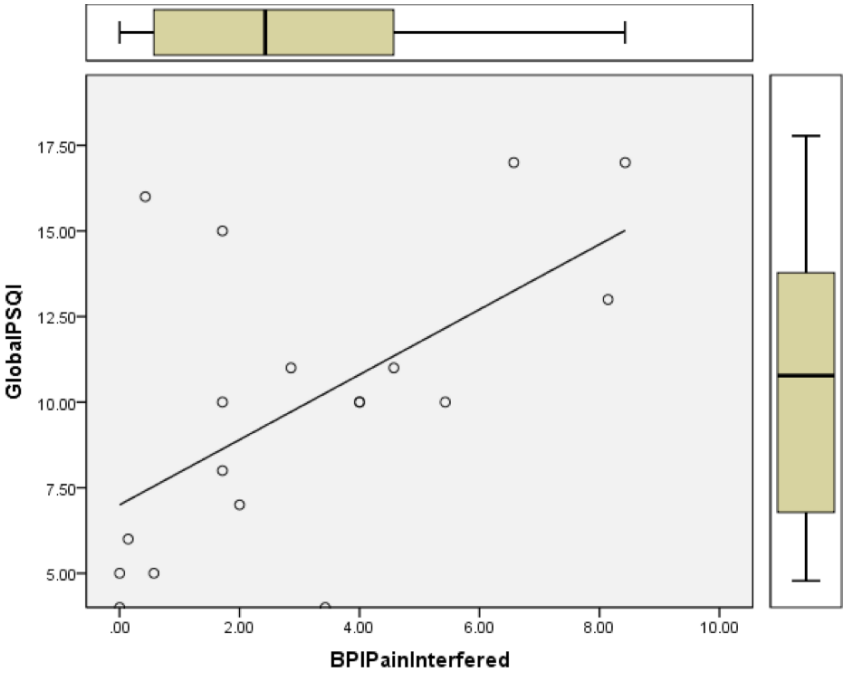


Figure 2: Association between pain interference ADL and poor sleep quality

sleep disturbances and pain in people with DPN.[62.63] The results demonstrated significant positive correlations between sleep quality, pain severity and pain interfering with ADL. Other factors such as diabetes duration, BMI and neuropathy severity were not correlated with sleep quality or pain. The current study improves understanding regarding the prevalence of poor sleep quality and the magnitude of the association between sleep quality and pain in people with neuropathic pain.

The most common outcome measure for sleep in the previous studies was Medical Outcome Study (MOS)-Sleep scale.[43] However, the PSQI has the advantage of including a specific item that measures whether someone uses medications for sleep, and the PSQI has a cutoff score that differentiates between poor sleepers and good sleepers. Consistent with our findings, previous evidence drawn from BPI and MOS-Sleep scale reports has showed that pain severity was associated with greater interference in functional abilities including sleep.[43] Another study suggested that the sleep item in the BPI is a key domain for pain interference ADL among people with neuropathic pain. Gore et al. reported that 77% of their patients with diabetes did not have optimal sleep, and they have more sleep problems than general U.S. population.

Pain and sleep may have a bidirectional relationship such that pain may affect sleep and poor sleep may exacerbate pain.[64-66] Previously, a drug trial also found that changes in pain that interfered with sleep were strongly correlated with changes in pain severity.[64] Previous evidence on healthy people has shown that sleep disruption or deprivation results in more pain due to increased release of pro-inflammatory cytokines as well as decreased pain tolerance. In our study, however, we did not find association between sleep quality and HbA1c or DPN severity. One study found that people with DPN may have poor sleep quality due to the exacerbation of pain during sleep due to allodynia and hyperesthesia.[18]

Previous evidence in a healthy population has shown that sleep disruption or deprivation results in more pain due to the increased release of pro-inflammatory cytokines as well as decreased pain tolerance.[75] The concept of synaptic efficiency for sleep theory may explain the interaction between poor sleep quality in people with DPN. Sleep involves in oscillations of neurons excitation or inhibition which results in synaptic balance during wake/sleep sets.[73] On the other hand, peripheral neuropathy imbalances between central excitatory and inhibitory signaling leads to a series of changes in long term from the periphery to the brain.[73,74] Sleep deprivation has a negative impact on sleep quality, which are associated with oxidative stress that plays a critical role in developing peripheral neuropathy.[75-77]

Previous research has demonstrated that reduced pain tolerance may result from shortened or disturbed sleep.[28-34] Furthermore, some studies showed a reciprocal influence between pain and sleep in which pain disturbs sleep, and poor sleep increases pain.[35-37]Although there is less evidence

about the mechanisms of how pain effect sleep quality, several studies suggests the contribution of poor sleep quality in increasing the pain severity. Sleep deprivation reduces serotonin levels, which leads to increased pain sensitivity.[38] In animal studies, rats showed higher pain sensitivity after deprived of asleep.39,40 Additionally, other studies investigated the pain sensitivity, which was higher after a short time of sleep deprivation.[41,42]

Increases in sleep disturbances due to pain may eventually then lead to a vicious cycle of sleep deprivation. Sleep deprivation contributes in lower energy and ability of patients functioning during daily activities.[67] The current study found a strong correlation between poor sleep quality and pain interfering with ADL.[68] Further, the most frequent daily activities disrupted by pain were sleep and the enjoyment of life. These findings are consistent with a burden of illness survey study that demonstrated increasing pain severity from mild to severe corresponded with increasing sleep problems.[69] Despite the high prevalence of sleep impairments in the population with neuropathic pain, there is an association between greater interference in functional abilities including sleep for people with neuropathic pain compared to the general population, and the BPI sleep item being a key domain for pain interference ADL among people with neuropathic pain.[70,71] Although the findings from the results were largely consistent with these studies, these studies had limitations such as the differences in age across groups as well as not measuring BMI, and both limitations may have affected their results.

Several studies have already established a relationship between sleep deprivation and low glycemic control in people with diabetes and people with DPN.[72] Indeed, sleep directly influences glucose metabolism and insulin sensitivity.[79,80] Thus, poor sleep quality has a potential negative impact on the progression of diabetes[78], and it may contribute in DPN development for long term. Although the evidence of sleep problems has showed a negative impact on diabetes care, there are no recommendations were provided in Diabetes Care Guidelines to optimize the sleep quality in people with diabetes and DPN. Therefore, it is imperative to include sleep assessments into evaluation sequelae for patients with diabetes and DPN to assure the optimum diabetic care.

Our study has few limitations mainly due to the nature of this secondary analysis. We obtained our reported results from a small sample size, and we did not exclude participants with diagnosed sleep disorders such as obstructive sleep apnea, insomnia or restless leg syndrome.

Furthermore, sleep was assessed using a subjective instrument rather than the gold standard of sleep lab called Polysomnography, which relays on perceived self-judgment. Nevertheless, our results strongly indicate the need for future studies assessing sleep large sample of people with DPN using objective measurements. Subjective measurements of sleep quality may indicate other undiagnosed sleep disorders in which using a sleep lab instrument instead of relying on subjective questionnaires might help clinical disclaim making for simple sleep hygiene or advanced therapy. We were not able to gather information about the medication adherence for pain or sleep adjustments. Future research is needed to control for pain or sleep medication to better understanding about the complex relationships between sleep and pain in people with DPN. In addition, longitudinal studies would be the optimal method to establish causality between sleep disturbances and diabetes progression or vice versa.

In conclusion, the results demonstrated a significant correlation between sleep quality and pain in people with DPN. Therefore, studies examining the bidirectional relationship between sleep and pain are highly recommended. In addition, as sleep modulates glucose metabolism, insulin sensitivity, and pain transmission, future studies are needed to determine if addressing poor sleep quality would impact perception of pain as well as diabetes management. Future studies should be conducted to find the changes in global score of PSQI or objective sleep measurements after applying an interventional experiment among people with DPN. This study supports the use of PSQI to assess the sleep quality in people with painful neuropathy. Clinicians may use PSQI as recommended survey for patients with DPN. In addition, healthcare professions should assess sleep quality in patients with DPN or diabetes to address any sleep disturbances which is an important aspect of care for patients with painful neuropathy.

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Conflict of interest

The authors declare that they have no conflict of interest.

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