

Neuropathic Pain And Diabetes Mellitus; A Systematic Review

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Abstract

Background: Neuropathic pain is pain that is caused by a disease or lesion and affects the somatosensory system. Almost one-quarter of patients with diabetic neuropathy complain of neuropathic pain. It is necessary to study neuropathic pain among diabetic patients as it is often misdiagnosed and adversely affects the patients.

Aim: To assess the prevalence, risk factors, and characteristics of neuropathic pain among diabetic patients by reviewing studies conducted on this subject.

Methods: An exploration of scientific databases was performed to obtain related articles by using related terms. The definition of eligible studies included original, English, and full-text articles reporting neuropathic pain among diabetic patients and published after 2010.

Results: Eight studies met the inclusion criteria and were involved in the review with a total number of 9957 subjects, of them 9764 were diabetics and 193 were controls. The findings included risk factors, characterization, and impact of neuropathic pain on the patients.

Conclusion: Neuropathic pain is more common among diabetic patients, especially those with T2DM and those with diabetic peripheral neuropathy. The risk factors of neuropathic pain, included female gender, duration of diabetes, smoking, older age, certain ethnicity, poor glycemic control, and obesity. Neuropathic pain also adversely affects the quality of life of the patients, and it is more prevalent among lower extremities.

Keywords: Neuropathic pain, Nerve pain, DM, Prevalence, Risk factors.

Introduction:

Neuropathic pain (NP) is defined as a pain that is directly caused by disease or lesion and affects the somatosensory system [1, 2], including peripheral fibers such as A β , A δ , and C-fibers and central neurons which impacts 7-10% of the general population [3]. DM is associated with several chronic sequelae and almost one-half of diabetic patients develop polyneuropathy [4], which involves several symptoms such as itching, tingling, dysesthesia or abnormal sense of touch, muscle weakness,

numbness, and trouble with balance [5]. The increased incidence of DM, osteoarthritis, and rheumatoid arthritis is likely associated with an increased incidence of neuropathic pain [6].

Also, 25% of patients with diabetic neuropathy (DP) progress to neuropathic pain (NP) [5]. The symptoms of painful diabetic neuropathy (PDN) involve tingling, itching, dysesthesia, and muscle weakness in addition to feelings of burning, stabbing, electric shocks, pins and needles [7]. Painful diabetic peripheral neuropathy (PDPN) is a type of neuropathy where its main manifestation is pain [8, 9].

Neuropathic pain is often misdiagnosed as a result of varied manifestations of diseases which has implications on the treatment too [10]. However, it can be distinguished from other pain conditions as the pain generator starts with the disease of nonneural tissues [11]. It is necessary to study neuropathic pain among DM patients as it adversely affects the patient and results in poorer quality of life compared to diabetic patients without pain [12]. The increased incidence of neuropathic pain reduces the quality of life due to higher costs of the prescribed medicines morbidity from the pain, and visits to the healthcare professionals [6]. However, there was no previous systematic review that identified neuropathic pain among diabetic patients. So, this systematic review was performed to identify the prevalence, risk factors, characteristics, and impact of neuropathic pain among diabetic patients.

Method:

Searching process:

Adoption of the PRISMA statement [13] was guaranteed during writing this systematic review. Exploration of scientific databases was performed to obtain related articles, including searching through PubMed, Science Direct, Google Scholar, and Scopus. The search process was limited to the studies published after 2010 till now.

Various terms were used as keywords for the search process, including "Prevalence, Association, Neuropathic pain, Nerve pain, Neuralgia, Diabetes mellitus, Risk factors, Predictors, and Determinants." Such terms were used in different combinations to obtain all possible relevant studies.

Eligibility criteria:

After obtaining the articles, the first step involved the exclusion of duplicate articles to reduce the number of studies, followed by the exclusion of articles published in 2010 and before this year. Also, irrelevant articles were excluded. The raining studies were checked to include the original articles and exclude other types of articles. Then the language was checked to include English articles and exclude those written in other languages. Studies conducted on T1DM, T2DM, or both were eligible, and those involved neuropathic pain and diabetes in the titles. The articles that were available for abstracts only, those reported overlapped data, and incomplete data were excluded. An illustration of the search process and eligibility is declared in Figure 1.

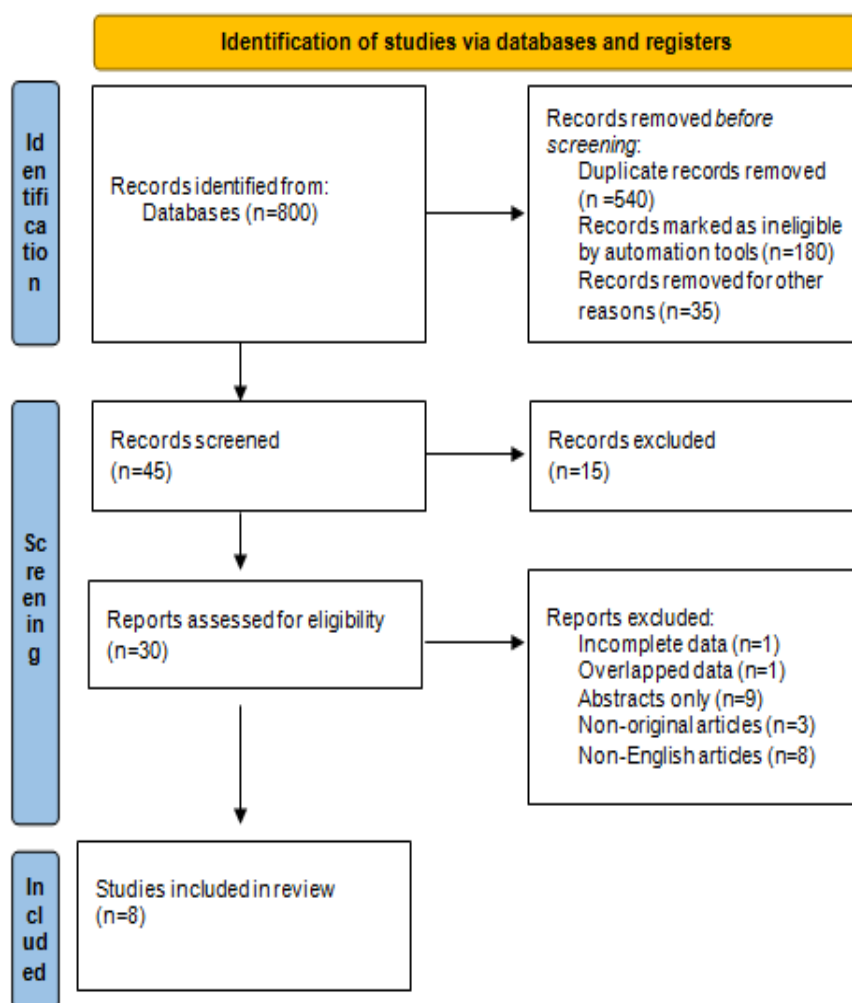


Fig1: Planning of Eligible Criteria

Data review and analysis:

Reviewing of abstracts of the included studies was performed to determine the data of interest, then the full articles were reviewed to extract such data. A pre-designed Excel sheet was used for the extracted data to revise the data. A pre-designed table was used to summarize the extracted and revised data.

Results:

A total of eight studies [14-21] met the inclusion criteria and were enrolled in this review (Table 1). The studies were published between 2014 and 2022. The designs of the studies were retrospective cross-sectional [14], cross-sectional [15, 20, 21], cross-sectional observational [16], and prospective cross-sectional observational [19], and weren't reported in two studies [17, 18]. There were four studies conducted on T2DM patients [15, 18, 20, 21], two studies were conducted on T1DM and T2DM [16, 19], one study didn't specify the type of diabetes and was conducted on DM patients with neuropathic pain to report the pain characteristics [17], and one study enrolled health subjects and patients with T2DM and T1DM to identify the prevalence of diabetes among patients with neuropathic pain [14].

The total number of subjects was 9957 individuals, of them 193 were controls [14] and the remaining 9764 individuals were diabetic patients.

The prevalence of neuropathic pain among DM patients ranged between 5.4% [18], and 43.3% [15]. The prevalence of pain among T2DM ranged between 10%[18], and 43.3% [15], whereas the

prevalence of pain among T1DM was reported in one study among 20% and it was lower compared to its prevalence among T2DM (40.6%) in the same study [16].

Pain was significantly higher among females (<0.05), older age ($P=0.05$) [20], and time of diabetes ($P=0.03$) [21]. However, no association was found between pain prevalence and gender, controlled glycemia, depressive symptoms, or adherence to treatment [21], whereas, the risk of pain was reduced with higher physical activity (aOR 1.4) [15].

Various risk factors for neuropathic pain were reported and they included increased duration of diabetes (aOR 1.9-3.3) and the odd ratio is increased with increasing the duration of diabetes, obesity (aOR 1.8), poor glycemic control (aOR 1.3), female gender (aOR 1.3) [15], (OR 3.9) [16], hyperlipidemia (aOR 1.5) [15], anemia (OR 2.7) [16], smoking (OR 1.52) [18], Indian ethnicity (OR 5.4) [19], peripheral neuropathy (OR 3.4) [19], patients with DPN (OR 4.5), and the severity of DPN ($r=0.73$, $P<0.001$) [16].

The studies focused on the prevalence of neuropathic pain among DM patients, but only one study in this review assessed the prevalence of DM among patients with neuropathic pain. The prevalence of diabetes among neuropathic pain patients was higher compared to those without neuropathic pain, with T2DM being more affected by neuropathic pain compared to T1DM patients ($P=0.01$). However, there was no significant variation between the prevalence of diabetes types among patients with neuropathic pain and subjects without neuropathic pain. Gender and age weren't predictors for DM among patients with pain [14].

The impact of neuropathic pain on patients includes the association between pain and lower quality of life, poor sleep, symptoms of anxiety and depression ($P<0.001$), [18]. It was also reported that the mean score of pain was mild based on the VAS scale [17], but another study reported higher average pain score intensity [19]. Regarding mental health, neuropathic pain has a lower impact on mental health compared to DPN [18], and it was found that pain affected the daily living activities among 64% of the patients [17].

One study reported the characteristics of neuropathic pain and regarding the location, the major pain locations were lower extremity (60%), and upper and lower extremity (24%). The positions increasing the pain included standing (20%), supine (14%), and walking (12%). Pain frequency was commonly every day (80%), more than 3 times weekly (6%) and 2-3 times per week (6%). Duration of pain was predominantly 1-12 months (48%), and 1-5 years (36%) [17].

Table 1: Summary of the extracted data

Author and Publication year	Study design	Characteristics	Results and main findings
Lavaee et al 2022 [14]	Retrospective cross-sectional	-Patients with and without DM 1&2 -N=386 subjects -Groups: *TN=193 *Control=193	*The prevalence of DM among the TN group was 11.4% (10.34% T2DM, 1.03% T1DM) and 9.8% among controls (9.3% T2DM, 0.5% T1DM (P=0.6). *The OR for DM in TN patients was 1.18, but didn't display a significant risk for diabetic patients to be affected by TN. -The prevalence of type 2 DM in TN cases was significantly higher than type 1 (P=0.01). *There was no difference between the prevalence of T1D (P=0.71) or T2DM (P=0.69) between TN group and healthy controls. *No significant association was found between DM and TN in males or females (OR 1.76, 95% CI: 0.79- 3.92). *According to age, the prevalence of DM in TN (P=0.08) and the controls (P=0.1) did not have a significant difference.
Ponirakis et al 2022 [15]	Cross-sectional	-T2DM -N=3021	*The prevalence of pain was 43.3%, of whom 54.3% were undiagnosed. *The aOR for pain was higher with increasing diabetes duration (aOR 1.9-3.3), obesity (aOR 1.8, P<0.0001), poor glycemic control (aOR 1.3, P<0.01), female gender (aOR 1.3, P<0.05) and hyperlipidemia (aOR 1.5, P=0.001), and reduced with greater physical activity (aOR 1.4, P<0.0001).
Chukwubuzo et al 2022 [16]	Cross-sectional observational	-T1DM& T2DM -N=422	*There 27.7% had neuropathic pain. *Among 61.8% of patients with DPN, the prevalence of neuropathic pain was 40.2% (OR 4.5, P<0.001) and it was 7.5% among non-DPN patients. *Painful DPN occurred in 20.0% of T1DM and 40.6% of T2DM. *The prevalence of pain increased as the severity of DPN increased (r=0.73, P<0.001). *The female gender (OR 3.9, P=0.001) and anemia (OR 2.7, P=0.01) significantly predicted PDPN among diabetics, whereas age, diabetes duration, smoking, and alcohol habits, didn't affect pain.
Guntel et al 2021 [17]	-----	-DM with neuropathic pain -N=50	*The mean score of VAS was 6.86±2.79. *The major location of pain was lower extremity (60%), and upper and lower extremity (24%). *Positions that aggravated the pain, included standing (20%), supine (14%), and walking (12%). *The major frequency of the pain was every day (80%), more than 3 times weekly (6%) and 2-3 times per week (6%).

Gylfadottir et al 2020 [18]	-----	-T2DM -N=5514	<p>*The major durations of the pain were 1-12 months (48%), and 1-5 years (36%).</p> <p>*The Pain affected the daily living activities among 64%</p> <p>*The prevalence of pain was 10%.</p> <p>*Smoking displayed an association with pain (OR 1.52).</p> <p>*Pain was independently and additively associated with lower quality of life, poorer sleep, and symptoms of depression and anxiety (P<0.001).</p> <p>*Neuropathic pain has a lower impact on mental health compared to DPN itself.</p>
Goh et al 2017 [19]	Prospective cross-sectional observational	-T1DM & T2DM -N=242	<p>*There was 5.4% of the patients have neuropathic pain symptoms and this was independently associated with peripheral neuropathy (OR 3.4), and Indian ethnicity (OR 5.4).</p> <p>*Patients with neuropathic pain had higher average pain intensity scores.</p>
Oluwadamilola et al 2016 [20]	Cross-sectional	-T2DM -N=250	<p>*Neuropathic pain was present in 21.6% T2DM.</p> <p>*Among patients with pain, 66.7% were females and 33.3% were males (P < 0.05). *The mean age of patients with neuropathic pain was significantly higher than those without neuropathic pain (P = 0.05).</p> <p>*Glycemic status (P=0.7), fasting blood glucose (P=0.7), and disease duration (P=0.08) did not vary among patients with or without neuropathic pain.</p>
Cortez et al 2014 [21]	Cross-sectional	-T2DM -N=72	<p>* The prevalence of neuropathic pain was 16.7% and this was associated with the time of T2DM (P=0.031), but no gender (P=0.3), controlled glycemia (P=0.6), depressive symptoms (P=0.6), or adhesion to treatment (P=0.1).</p>

DM; Diabetes mellitus, TN; Terminal neuralgia, T2DM; Type 2 diabetes mellitus, T1DM; Type 1 diabetes mellitus, OR; Odd ratio, DPN; Diabetic peripheral neuropathy, PDPN; Painful diabetic peripheral neuropathy, VAS; Visual analogue scale

Discussion:

This review was conducted to identify neuropathic pain among patients with DM as there was no previous systematic review focused on this subject, but there is a great focus on neuropathic pain in diabetic neuropathy, even though neuropathic pain affects 25% of diabetic neuropathy patients [5]. In our review, we found that the prevalence of neuropathic pain ranged between 5.4% and 43.3% and it was significantly higher among patients with diabetic peripheral neuropathy as this condition increased the risk of neuropathic pain by more than fourfold (OR 4.5).

It was revealed that the pain prevalence among diabetic patients ranges between 10% to 20% and it was higher among diabetics with diabetic neuropathy ranging between 40% and 50% [22]. Our review reported higher prevalence rates of neuropathic pain among diabetic patients that reached a maximum rate of 43.3%, but the findings revealed a prevalence of 40.2% among patients with diabetic peripheral neuropathy similar to the previous report [22]. Additionally, diabetic peripheral neuropathy (DPN) increased the risk of pain by 4.5-fold (OR 4.5). Furthermore, the severity of DPN was positively and significantly associated with neuropathic pain ($r=0.73$) [16].

It was found that almost 25-39% of diabetic patients with neuropathic pain are either undiagnosed or poorly treated with minimal pain control [23-25]. One study of our analysis reported a higher rate of undiagnosed patients with pain as 54.3% of them were undiagnosed [15]. T1DM and T2DM are the most common types of diabetes [16]; however, the study of neuropathic pain was more common among T2DM patients. Also, the prevalence of neuropathic pain was highly prevalent among T2DM compared to those with T1DM [16]. Another study in our analysis revealed that T2DM is significantly more prone to develop neuropathic pain compared to T1DM ($P=0.01$) [14].

It was proposed that pain related to diabetic neuropathy is related to worsening glucose tolerance, longer duration of diabetes, older age, and smoking [26, 27]. One study in our analysis reported no association between pain prevalence and gender or glycemia [21]. However, the association between pain and older age [20] and time of diabetes [21] was reported. Additionally, other studies reported that the increased duration of diabetes increased the risk of pain by 1.9-3.3 fold based on the duration of diabetes, where those with a duration of diabetes of ten years or fewer had an increased risk by 1.9fold, whereas patients with diabetes for more than 20 years had an increased risk of 3.3fold [15]. Additionally, poor glycemic control increased the risk of pain by 1.3fold [15], and smoking increased the risk by 1.52fold [18].

It was also reported that painful neuropathic symptoms were more prevalent among females, T2DM, and people of South Asian ethnicity [28]. Similarly, we found that pain was more prevalent among females [20], and female gender increased the risk of pain by 1.3 and 3.9 folds [15, 16]. One study in our analysis revealed that Indian ethnicity was a predictor for pain with an increased risk of 5.4fold [19]. This may indicate that some ethnicities are at increased risk of developing neuropathic pain compared to others and this in turn leads us to propose that genetic factors may be incorporated into the development of neuropathic pain among diabetic patients with certain ethnicities.

It was stated that patients with PDN experience increased distress and poorer quality of life in comparison to those without pain, diabetic patients, and the general population [12]. Additionally, reduced employability and productivity at work are associated with neuropathic pain among patients with DN [29]. This indicates that neuropathic pain results in poorer outcomes and negatively affects the life of the patients and this can be supported by the finding of one study that revealed that DPN with no painful manifestation had no impact on mental health [12]. In the present review, neuropathic pain adversely affected the patients and it was significantly associated with poor sleep, reduced quality of life, and symptoms of anxiety and depression [18], and pain affected the daily living activity among a significant proportion of patients [17]. However, regarding mental health, the impact of neuropathic pain was lower compared to DPN, but a previous study revealed that DPN with no painful manifestation had no impact on mental health [12] which reflects that pain has the impact on mental health and this was in contrast to our findings. However, it was reported that neuropathic pain is one of the strongest predictors of reduced quality of life among patients with T2DM [30]. The painful symptoms are

commonly severe and lead to reduced quality of life, anxiety, depression, and sleep disorder [31], and such findings were in agreement with ours.

One study in our analysis reported the characterization of neuropathic pain among diabetic patients, but there was no focus in the literature regarding the characterization of the pain. However, we could identify the major location of pain, the major positions increasing pain, as well as the frequency and duration of pain [17].

Conclusion:

Neuropathic pain is more common among diabetic patients, especially those with T2DM and those with diabetic peripheral neuropathy. The risk factors of neuropathic pain, included female gender, duration of diabetes, smoking, older age, certain ethnicity, poor glycemic control, and obesity. Neuropathic pain also adversely affects the quality of life of the patients, including its association with poor sleep, anxiety, and depression symptoms as well as daily living activities. Lower extremities are the major location of neuropathic pain. However, stronger evidence is required for the determination of risk factors, and further studies are required to report the characterization of neuropathic pain among diabetic patients.

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