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ORIGINAL RESEARCH REPORT

Frequency of neuropathic pain in type 2 diabetes mellitus at the Lagos University Teaching Hospital: A questionnaire-based outpatient survey

Oluwadamilola O. Ojo, Ifedayo A. Odeniyi[1], Sandra O. Iwuala[1], Olajumoke O. Oshinaike[2], Njideka U. Okubadejo, Olufemi A. Fasanmade[1]

Department of Medicine, Neurology Unit, [1]Department of Medicine, Endocrinology and Metabolism Unit, College of Medicine, University of Lagos, [2]Department of Medicine, Neurology Unit, College of Medicine, Lagos State University, Lagos, Nigeria

ABSTRACT

Background: Neuropathic pain (NP) is one of the most common complications of type 2 diabetes mellitus (DM). The frequency of NP in population living with type 2 DM is unclear. **Objective:** To determine the frequency of NP symptoms in patients with type 2 DM. **Materials and Methods:** This cross-sectional study recruited 250 type 2 DM patients attending the outpatient diabetes clinic of the Lagos University Teaching Hospital (LUTH) over a period of 4 weeks. Demographic data and data regarding current DM treatment, prior diagnosis of NP, and current treatment of NP were obtained using a structured questionnaire. Glycaemic status of the patients was assessed measuring fasting blood glucose and glycosylated hemoglobin level. Presence of NP was documented using the painDETECT questionnaire (PDQ). **Results:** NP was present in 54 out of the 250 type 2 DM patients studied giving a frequency of 21.6%. Out of 54 patients 36 (66.7%) were females and 18 (33.3%) were males giving a male: female ratio of 1:2 ($P < 0.05$). The mean age of type 2 DM patients with NP was significantly higher than the mean age of type 2 DM patients without NP (62.4 ± 10.9 years vs 58.9 ± 11.7 years; $P = 0.05$). Glycaemic status and disease duration did not differ among DM patients with or without NP. Only 10 out of 54 (18.5%) patients were treatment naïve at the time of study; however, out of the 44 patients receiving treatment only 9 (20.5%) were on appropriate treatment compared to international guidelines on treatment of diabetic NP. **Conclusion:** NP was present in 21.6% of type 2 DM patients attending the LUTH.

Key words: Lagos University Teaching Hospital, neuropathic pain, treatment, type 2 diabetes mellitus

Address for correspondence:
Dr. Oluwadamilola O. Ojo, Department of Medicine, Neurology Unit, College of Medicine, University of Lagos, PMB 120003, Idi Araba, Lagos, Nigeria.
E-mail: drlaraoyatoye@yahoo.com

INTRODUCTION

Neuropathic pain (NP) is defined as pain resulting from damage to the peripheral or central somatosensory system.[1,2] It is associated with considerable disability including functional impairment and psychosocial dysfunction.[3] The causes of NP include painful diabetic neuropathy (PDN), postherpetic neuralgia, painful nondiabetic small fiber neuropathy, entrapment neuropathies, and radiculopathies. The most common cause of peripheral neuropathy worldwide, Nigeria inclusive, is diabetes mellitus (DM) and PDN is the most common neurologic complication of type 2 diabetes.[4] Overall, approximately 10% of patients with diabetes experience persistent pain from distal symmetric polyneuropathy (DSP)[5] and approximately 20% of them experience pain that is severe enough to result in significant amount of impairment in motor functioning and quality of life.[6]

PDN is the presence or occurrence of NP in patients with DM. Though there is considerable evidence regarding the

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pathophysiologic mechanisms causing nerve damage in DM, they do not distinguish between painless and painful DM neuropathy. The following mechanisms have been proposed to result in altered pain transmission leading to PDN[7]: Spinal rewiring (sprouting of A-fibers),[8,9] peripheral sensitization leading to central spinal sensitization,[10,11] ectopic electrical impulses,[12] metabolic changes such as rapid changes/fluctuation in blood glucose,[13,14] and sorbitol accumulation in the nerves from activation of the polyol pathway.[15]

Clinical features of DSP comprise both "positive" and "negative" symptoms and may be asymptomatic. Positive symptoms include abnormal excessive sensations such as burning, pricking, or tingling, and these positive symptoms result in NP. The negative symptoms such as numbness or sensory loss are sometimes severe enough to lead to painless injuries.

Diabetic pain syndromes can be classified according to its duration.[16] Those that occur for less than 6 months are classified as acute. These include a self-limiting syndrome such as insulin neuritis syndrome that occurs often at the beginning of therapy for diabetes. Pain syndromes continuing longer than 6 months are classified as chronic.[16] The pain may be ongoing, spontaneous, or hyperalgesic (increased response to a painful stimulus). NP in DM is usually severe and sometimes intractable.

The diagnostic evaluation of NP in DM (just like NP from any other etiology) requires a concise clinical history, physical examination, and confirmatory investigations. Clinical features suggestive of NP are presence of positive phenomenon described above in the presence of sensory loss. The most common confirmatory tests are nerve conduction studies (NCSs), and the most common feature found is reduction in the sensory nerve action potential amplitudes of lower extremities. Other tests such as skin biopsy with measurement of intraepidermal nerve fiber density can be used in patients with suspected small fiber neuropathy with normal NCSs.

Surveys have shown that nearly 25–39% of diabetes patients with NP are either undiagnosed, and therefore, untreated or poorly treated with minimal control of pain.[17-19] The associated discomfort continues to interfere considerably with sleep, daily functioning, and other aspects of quality of life.[18]

Several studies have reported the prevalence of NP in patients with type 2 DM. However, reports vary as the methodology and case definition differ from study-to-study. Historically, the prevalence of PDN ranges 10–20% of the diabetic population and 40–50% of the diabetic patients with peripheral neuropathy.[3,20-22]

In a review of the epidemiology of PDN, the prevalence was estimated as 15% in the diabetic population.[23] There are several reports in our environment on peripheral neuropathy in patients with DM; however, studies addressing NP are usually sparse hence the need for this study.

Our aim was to determine the frequency of NP symptoms in type 2 DM patients from an outpatient perspective and also to determine the proportion of these that are on treatment.

MATERIALS AND METHODS

Approval of the study protocol was obtained from the Health Research and Ethics Committee of the Lagos University Teaching Hospital (LUTH). The study was cross-sectional and descriptive in nature and conducted at the outpatients diabetes clinic of the LUTH. All consecutively attending persons with type 2 DM over a 4-week period were recruited after obtaining informed consent from them.

The study instrument incorporated the PainDETECT questionnaire (PDQ) along with demographic data, and questions regarding current DM treatment, prior diagnosis of NP, and current treatment of NP where relevant. Glycaemic status was assessed using fasting plasma glucose and glycosylated hemoglobin level. The PDQ is a simple screening tool designed to detect NP symptomatology in patients with pain. The total score on the pain questionnaire is graded as follows: 0–12 (negative: NP component is unlikely), 13–18 (unclear: result is ambiguous; however, an NP component may be present), and 19–38 (positive: an NP component is likely).

The instrument was interviewer administered, with additional information obtained from case records at the time of the interview. All information was based on historical data.

NP was defined as pain arising as direct consequence of a lesion or disease affecting the somatosensory system for the purpose of the study. Pain restricted to the joints was classified as somatic/nociceptive pain (probable osteoarthritis).

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS-Inc., Chicago, US).

RESULTS

A total of 250 type 2 DM patients were recruited for the study from the diabetic clinic of the LUTH. The study subjects comprised 96 males and 154 females. The demographic parameters (age, sex ratio) and DM-related characteristics (mean duration of diabetes, body mass index, mean indices of glycaemic control) are shown in Table 1. Out of all the subjects, 58.6% had long-duration diabetes (defined as diagnosis of DM >5 years).

All study subjects were on treatment for DM. Out of these subjects, 65.6% were on a combination of sulfonylureas and biguanides; 9.6% were on biguanides only; 8.8% were on insulin only; 4.8% were on a combination of sulfonylureas, biguanides, and thiazolidinediones; 4% were on insulin and biguanides; 2.8% were on sulfonylurea only. Insulin with sulfonylureas was used by 0.8% of the study subjects.

Frequency and characteristics of NP symptoms

Out of 250 study subjects, 99 (39.6%) experienced pain as per the PDQ. The distribution of the different types of pain is shown in Figure 1.

Out of the 99 patients, 54 who reported pain were likely to have NP making the frequency of PDN in our type 2 DM patients 21.6%. Out of all the subjects, 36 (66.7%) were females and 18 (33.3%) were males giving a male: female ratio of 1:2 (χ^2 = 11.9, P < 0.05).

Pattern of NP using the PDQ

Of the 54 type 2 DM patients with NP symptomatology, 17 (31.5%) experienced pain attacks with pain in between, while 9 (16.7%) experienced pain attacks without pain in between. Fourteen (25.9%) patients with DM had persistent pain with pain attacks, while 13 (24.1%) experienced persistent pain with slight fluctuations. Only 8 (14.8%) experienced radiating pain.

Clinical characteristics of DM with NP

The mean age of our patients with type 2 DM with NP was 62.4 ± 10.9 years, which was significantly higher than the mean age of the patients with DM without NP [58.9 ± 11.7 years (P = 0.05)].

There was no statistically significant difference in disease duration between DM patients with and without NP (P > 0.05, Table 2). Though there was a trend of increasing disease duration in the DM patients with NP, other clinical characteristics such as glycaemic status did not differ between the two groups as shown in Table 2.

Treatment pattern in PDN

Out of 54 type 2 DM patients 44 (81.5%) with NP were on treatment at the time of the study, while 10 (18.5%) were treatment naïve. However, out of the 44 patients on treatment, only 9 (20.5%) were on evidence-based treatment (4 on pregabalin, 1 on gabapentin, and 3 on amitriptyline), and the remaining 35 (79.5%) were on inappropriate treatment (28 on carbamazepine, 1 on acetaminophen, 3 on vitamin B, and 3 on nonsteroidal anti-inflammatory drugs) (χ^2 = 82.1, P = 0.000).

DISCUSSION

The frequency of NP in type 2 DM patients attending the LUTH was 21.6% that is higher than the worldwide prevalence estimate of 15%.[23]

Table 1: The demographic and treatment-related characteristics of the study population

Parameters	Mean
Age±SD (years)	59.7±11.6
Male: female	1:1.6
BMI*±SD (kg/m²)	27.5±4.7
FPG±SD (mg/dL)	140.9±63.2
HbA1c¶±SD	7.9±2.5
Mean duration of DM±SD (months)	106.2±89.4

*BMI=Body mass index, §FPG=Fasting plasma glucose, ¶HbA1c=Glycosylated hemoglobin

Table 2: Clinical characteristics of DM cohort with and without neuropathic pain

	Neuropathic pain		*F*	*P*
	Yes	No		
Age (years)	62.4±10.9	58.9±11.7	3.73	0.05
DM duration (months)	121.1±91.7	97.3±87.7	3.05	0.08
HbA1c (%)	8.06±2.26	7.88±2.43	0.14	0.71
FPG (mg/dL)	138.1±59.7	141.7±64.3	0.13	0.71

DM=Diabetes mellitus, HbA1c=HbA1c=Glycosylated hemoglobin, FPG=Fasting plasma glucose

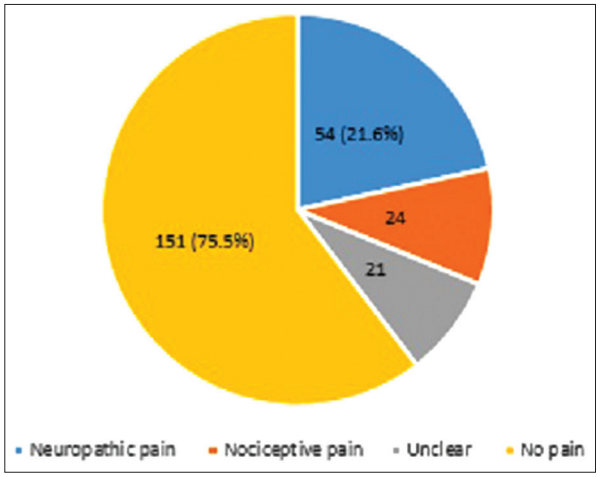

Figure 1: Distribution of pain syndromes using the PainDETECT questionnaire

A previous study in Jos, Nigeria, estimated the frequency of diabetic sensorimotor neuropathy to be 40.4%[24] A previous study by Okubadejo *et al*.[25] at this same facility estimated the prevalence of symptomatic somatic neuropathy to be 47.6%.[25] However, these studies did not distinguish between painful and painless DM neuropathy.

The frequency of PDN obtained in this study is also higher than what was obtained in Turkey where Erbas *et al*.[26] obtained a prevalence of 14% in their population of people with DM. Though the Turkey study also involved patients attending diabetes outpatient clinics of university hospitals, the study population consisted of both type 1 and type 2 DM patients unlike the current study. Their study instrument was the Leeds Assessment of Neuropathic Signs and Symptoms (LANSS) scale that included both symptoms

and signs as opposed to the present study that used the PDQ that focused mainly on symptoms.

Bouhassira *et al*.[27] in a multicenter study involving 1,194 type 1 and type 2 diabetics obtained a prevalence of 18% in their subcohort of type 2 DM. They evaluated diabetics already screened for peripheral neuropathy with a Neuropen for NP using the Douleur Neuropathique 4 (DN4) questionnaire.

The prevalence rate in the present study is, however, much lower than figures obtained from a university clinic in Saudi Arabia where prevalence rate of painful diabetic peripheral neuropathy was 65.3%.[28] Their prevalence rate is much higher than the global prevalence estimates. They used the DN4 to screen for NP but found that prevalence was higher in type 1 than type 2 diabetics. The authors postulated poor glycaemic control to be responsible for the higher than expected prevalence; however, they did not assess their populations' glycaemic status.

Our DM patients with NP were significantly older than those without NP. This is similar to findings in Turkey and Saudi Arabia and agrees with the literature.[17,29] Also NP in our DM cohort occurred more in females which is in agreement with findings from Saudi Arabia[28] and Turkey.[26] In contrast to those two studies, our study did not reveal a relationship between diabetic NP and duration of disease. DM patients with PDN historically have longer disease duration than those without PDN. Also though DM NP correlates with poor glycaemic status in the literature, this was not corroborated by our findings. There was no difference in glycaemic profile [fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c)] between DM patients with NP and those without NP. This is in keeping with earlier work done at the same center on symptomatic somatic neuropathy in type 2 DM.[25]

Only 20.5% ($N = 9$) of our type 2 DM patients experiencing NP received first line agents for treatment according to international guidelines.[30,31] The first line agents for treatment of diabetic NP are pregabalin, duloxetine, nortriptyline, gabapentin, venlafaxine, and tramadol. This low frequency could be attributed to high cost of these first line agents in our environment and nonavailability. Also the side effect profile of the tricyclic antidepressant amitriptyline could contribute to its underutilization as nortriptyline is not readily available in our environment. More than half of our patients were on carbamazepine that is not in line with international guidelines for the management of diabetic NP.[30,31] The high use of carbamazepine could be attributed to its availability, its cost (cheaper than the other first line agents such as pregabalin and gabapentin), and the fact that it has a better side effect profile than amitriptyline. Other agents used for treatment in this study that are not in compliance with international guidelines on treatment of NP in type 2 DM patients are acetaminophen, nonsteroidal anti-inflammatory drugs, and vitamin B.

In conclusion, the frequency of diabetic NP in type 2 DM patients attending our health-care facility is higher than the worldwide prevalence. Also management of these patients needs to conform to international best practice to improve symptomatology and patients' quality of life.

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Conflicts of interest

There are no conflicts of interest.

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