Original Article

Prevalence And Associations Of Neuropathic Pain Among Subjects With Diabetes Mellitus In The Enugu Diabetic Peripheral Neuropathy (Edipen) Study

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Abstract

The present study examined the prevalence and associations of neuropathic pain among subjects with diabetes mellitus. Four hundred and twenty two (422) type 1 and type 2 diabetic patients between18 and 70 years were drawn for study from medical outpatient unit of Enugu State University Teaching Hospital, Parklane-Enugu, with mean Age of *M* = 57.06; *SD* = 10.01). Diabetic Peripheral Neuropathy Questionnaire (Feldman and Stevens, 1994) was used in collecting data for the study, while data were analyzed using Hayes regression-based PROCESS macro for SPSS. Results showed that: there was a significant association between having positive pain and presence of DPN. Prevalence of painful symptoms increased progressively as the severity of DPN increased. The gender (female) and anemia significantly predicted PDPN among diabetic patients, while age, diabetes duration, smoking, and alcohol habits, do not trigger nor influence PDPN. Therefore, medical practitioners who manage these diabetic patients should look out for positive pain among diabetic patients with diabetic peripheral neuropathy; they (medical practitioners) and patients should as well expect increased painful symptoms as severity of diabetic peripheral neuropathy increases, and age, diabetes duration, smoking, and alcohol habits, do not trigger painful diabetic peripheral neuropathy among diabetic patients rather being a woman and having illnesses like anemia can trigger it.

Keywords: diabetes mellitus, neuropathic pain, peripheral neuropathy, type 1 diabetes, type 2 diabetes.

INTRODUCTION

One significant health concern for many countries is Diabetes Mellitus (DM). DM is an increasing problem in sub-Saharan Africa, especially Nigeria, with type 2 DM being the most common. Diabetes Mellitus commonly referred to as Diabetes; is a metabolic disease that causes high blood sugar. The insulin hormone regulates blood sugar by moving sugar (glucose) gotten from food into cells to be stored or used for energy. Subjects with diabetes either do not produce enough insulin or cannot use the insulin produced effectively (WHO, 2014). As such, when the glucose becomes too much in the blood or body, a lot of problems can arise which eventually may lead to death. Type 1 and type 2 diabetes are the common types of diabetes mellitus. The type 1 results from failure of the pancreas to produce enough insulin due to loss of beta cells which is caused by an autoimmune response (Norman and Henry, 2015) while Type 2 diabetes begins with insulin resistance, a condition in which the cells fails to respond or use the insulin properly (WHO, 2013). Gestational diabetes is also another type of diabetes that affects mostly females during pregnancy. Some women have very high levels of glucose in their blood, and their bodies are unable to produce enough insulin to transport all of the glucose into their cells, resulting in progressively rising levels of glucose (WHO, 2013).

Diabetic patients present symptoms ranging from unintended weight loss, increased urination, and increased thirst to increased hunger (Cooke and Plotnick, 2008). Others present symptoms such as blurred vision, headache, fatigue, slow healing of cuts, and itchy skin. Vision change or loss caused by prolonged high blood glucose can lead to absorption of glucose in the lens of the eye, thereby leading to blindness or changes in vision. Among these symptoms, a common and significant one is neuropathy of which 90% of patients are affected. Neuropathy is the damage or dysfunction of one

or more nerves that typically results in numbness, tingling**,** muscle weakness, and pain in the affected area. Neuropathy may be peripheral or central, thus it indicates a problem within the peripheral or central nervous system and is present in subjects suffering from diabetes mellitus.
Diabetic neuropathyis heterogenous in their clinical presentation, risk factors and pathophysiology, is not a single entity; it encompasses not only a wide spectrum of clinical manifestations but also different levels of neurological involvement. The prevalence rate of diabetic neuropathy has been reported to range from 8% to 63% in type1 diabetes and from 13% to 51% in type2 diabetes (America Diabetes Association, 2020). These neuropathic syndromes fall under two broad subgroups; typical and atypical diabetic neuropathies. Typical DPN is by far the most prevalent form of neuropathy in diabetes and characteristically affects both sensory and motor nerves in a peripheral distribution (Dyck et al., 1993). However, the relative impact on small and large sensory fibers and motor fibers varies among individuals. Atypical DPNs are different in several important features, i.e. onset, course, manifestations, associations, and perhaps putative mechanisms (Boulton et al., 2005; Thomas, 2003). Onset of symptoms may be acute, sub-acute, or chronic, but the course is usually monophasic or fluctuating over time.

The several types of diabetic neuropathy occur depending on the nerve type affected (sensory vs. motor vs. autonomic), site of nerve injury (focal vs. multi-focal vs. generalized), and disease time course (acute vs. chronic) (Albers & Pop-Busui, 2014; Pop-Busui et al., 2017). These diabetic neuropathic syndromes include the peripheral neuropathy also called diabetic nerve pain or distal polyneuropathy that mostly affects the feet and hands, proximal neuropathy (also known as amyotrophy), autonomic neuropathy (which controls involuntary functions in the body and is responsible for symptoms of indigestion and frequent urination) and focal neuropathy (American Diabetes Association, 2017). The most prevalent of these neuropathic syndromes fall under the typical DPN subgroup which is the chronic diabetic peripheral sensorimotor neuropathy (DPN), affecting up to 50% of people with diabetes (Pop-Busui et al., 2014).
The Toronto Diabetic Neuropathy Expert Group defined DPN as "a symmetrical, length dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure (DM) and cardiovascular risk covariates (Tesfaye et al., 2010). In cross-sectional and longitudinal epidemiological surveys of population-based cohorts of patients with diabetes mellitus, total hyperglycaemia has been shown to be an important risk covariate (Tesfaye et al., 2016).

Diabetic peripheral neuropathy (DPN) is "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes (Ziegler et al, 2018). It is a microvascular complication of DM that increases the potential for morbidity and disability due to ulceration and amputation (Genuth et al., 2003). The prevalence of painful neuropathy in Type 2 diabetes is more than twice that seen in Type 1 diabetes. DPN leads to degenerative and atrophic changes throughout the peripheral and central nervous system (Sloan et al., 2018; Tesfaye et al., 2016). The peripheral end terminals of nociceptors, intra-epidermal nerve fibers, are depleted in a distal symmetrical manner in DPN (Sloan et al., 2018). More proximally, peripheral nerve changes have been welldescribed and include; demyelination of myelinated nerve. Furthermore, autopsy and more recent advanced imaging studies have found spinal cord and cerebral atrophy associated with DPN (Selvarajah et al., 2014). However, the exact causal links between hyperglycemia and clinical DPN is uncertain.

The current understanding is that hyperglycemia, as well as vascular risk factors, activate detrimental pathways ultimately leading to downstream injury to the microvessel endothelium, nerve support cells, and nerve axons (Yang et al., 2020). Unfortunately, DPN is often diagnosed late when irreversible nerve injury has occurred and its first presentation may be with a diabetic foot ulcer. DPN is associated with increased mortality and leads to morbidity, principally as a result of its two major clinical consequences, diabetic foot ulceration, and neuropathic pain (Dietrich et al., 2017). Lower-limb complications of diabetes are expensive and a substantial burden for patients, potentially leading to devastating outcomes such as lower limb amputation and death (Vadivelooet al., 2018). These painful symptoms are commonly severe and often lead to depression, anxiety and sleep disorders, and reduced quality of life (Sloan et al., 2018).

Diabetic peripheral neuropathy leads to distressing and expensive clinical sequel such as foot ulceration, leg amputation, and neuropathic pain. A common and significant symptom of diabetic peripheral neuropathy is pain (Peltier et al., 2014). A community-based population study in the UK reported that around one-third of all diabetic patients have pain (UK diabetics care, 2011). Studies have also shown that up to half diabetic patients who experience diabetic peripheral neuropathy (DPN) suffer painful neuropathic symptoms (painful-DPN). Dyck et al., (1993), found that two thirds of patients with diabetes had objective evidence of some form of neuropathy. The most common was DPN, affecting ~50%. The duration of diabetes and glycemic control is the most significant risk factors for DPN (Callaghanet al., 2018). Other risk factors for cardiovascular disease are also associated with DPN, including: obesity, hypertension, smoking, and dyslipidemia (Andersen et al., 2018). Approximately 50% of people with DPN suffer with peripheral neuropathic pain (Alleman et al., 2015). The prevalence of neuropathy in patients with diabetes is 7% at 1 year, increasing to 50% at 25years for both type 1 and type 2 DM (Vinik et al., 2003).

Painful diabetic peripheral neuropathy (PDPN) is a common, predominantly chronic, complex and worrisome complication of diabetes mellitus (DM), whose symptoms and signs typically reside in the toes, feet and legs; affects a significant number of individuals with DM and impacts negatively on their quality of life (Jacovides et al., 2014; Sadosky et al., 2014). Although the pathophysiology of PDPN is not yet fully clarified, it is thought that an initial axonopathy of

the affected sensory neurons gives rise to the hyperexcitability seen in these neurons due to some changes in gene expression and abnormal proliferation and misregulation of Na+ and Ca2+ ion channels (Themistocleous et al., 2016). The complex nature of PDPN is supported by the fact that some individuals have been found to have mainly differentiation of nerves i.e. freeing of the motor nerve from its sensory component and hence, loss of sensory function while some others have more of hypersensitivity of nerves in the presence of preserved nerve integrity (Themistocleous et al., 2016b). Painful diabetic peripheral neuropathy usually arises in an individual with background diabetic peripheral neuropathy (DPN) (Petropoulos et al., 2016). Clinically, PDPN tends to be described as burning, shooting or aching and may be accompanied by increased sensitivity to pain numbness (Argoff et al., 2006).

Many risk factors for painful-DPN have been postulated such as the severity of neuropathy, hyperglycemic burden, and obesity. The epidemiology of painful diabetic neuropathy has not been studied. However, recent studies have demonstrated strong evidence that female sex is a risk factor for painful-DPN (Shillo et al., 2019). Indeed, female gender was the only risk factor identified in a large cross-sectional study (n = 816) performed by Truini et al., (2018), which diagnosed painful-DPN using widely agreed criteria. It is estimated that around half of patients with chronic diabetic neuropathy experience pain and the majority have features of chronic sensorimotor peripheral neuropathy. The diagnosis relies on both clinical signs as well as quantitative testing, and may be present despite a lack of reported symptoms (Pop-Busui et al., 2017). The primary symptom of diabetic peripheral neuropathy (DPN) is abnormal or loss of sensation in the toes, which extends to involve the feet and leg in a stocking distribution (Morkrid et al., 2008). DPN predisposes to substantial morbidity, which includes not only susceptibility to foot or ankle fractures and ulceration leading to lower-limb amputations, but also neuropsychiatric co-morbidity such as depression (Genuth et al., 2003).These situations can negatively impact the quality of life of affected individuals. In general, however, the magnitude of diabetic neuropathy in sub-Saharan Africans with diabetes has been less reliably quantified. Although most patients with DPN do not have pain, approximately 11% of patients with DPN have chronic, painful symptoms that diminish quality of life, disrupt sleep, and can lead to depression. Despite the number of patients affected by DPN pain, little consensus exists about the pathophysiology, best diagnostic tools, and primary treatment choices.

Peripheral nerve damage in diabetic patients is mostly irreversible. This has led health care professionals to focus on prevention as well as the identification of modifiable risk factors (Won and Park, 2016). Studies suggest that numerous risk factors are responsible for DPN in DM patients including age, gender, duration of diabetes, the presence of microvascular complications, hypertension, area of residence, body mass index, glycated haemoglobin (HbA1c) level, alcohol intake, hyperglycaemia, cigarette smoking, physical inactivity, and marital status(Liu et al., 2019; Bansal et al., 2014). The personal impact of NP is often devastating and patients mostly generate high health costs. Diabetes caused at least 727 billion dollars in health expenditure in 2017, about 12% of total spending on adults (international Diabetes Federation, 2017). In another study by Ipingbemi and Erhun, (2015), on 52 diabetic patients, it was estimated that over 8 million naira was spent on medication alone.

DIABETES PREVALENCE

According to World Health Organization, the number of people with diabetes rose from 108 million in 1980 to 422 million in 2014. Between 2000 and 2016, there was a 5% increase in premature mortality from diabetes, in 2012, 2.2 million deaths were attributed to high blood glucose and in 2019 an estimated 1.5 million deaths were directly caused by diabetes (WHO, 2018, 2019). In the international diabetes federation latest estimated data, 382 million people worldwide are currently affected by diabetes (International Diabetic Federation [IDF], 2013), about 425 million adults in 2017 were living with diabetes globally; by 2045, this number is projected to rise to 629 million. In Africa, by 2017, 39 million people were living with diabetes and by 2045, this number is projected to rise to 82 million (IDF, 2017). Diabetic Mellitus is estimated to significantly cause millions of death around the world. Previous Studies highlighted the prevalence of diabetes and its excruciating symptoms.

Diabetes Mellitus is becoming more prevalent owing to the increasing rates of obesity, physical inactivity, and urbanization. (Nathan et al., 2005; Fox et al., 2007). It has also been found that the prevalence of diabetes has risen faster in low and middle-income countries than in high-income countries (Roglic, 2016). The greatest increase will be in developing countries (69%) compared with developed countries (20%) (Shaw et al., 2010). Factors such as poor health sector, poor quality of life, low or no access to health care, increased cost of treatment, inactivity, poor diet, improper management and more contribute to the increase of prevalence of diabetes in low and middle-income countries.
Furthermore, neuropathy has been discovered to be a common symptom associated with diabetes. American Diabetes Association discovered the rate of diabetic neuropathy to range from 8% to 63% in type1 diabetes and from 13% to 51% in type2 diabetes (America Diabetes Association, 2020).The overall peripheral neuropathy prevalence among patients with diabetes is high (40.3%) and patients with type 2 diabetes (42.2%) are more often affected than those with type 1 diabetes (29.1%) (Pfannkuche et al., 2020).

Studies conducted revealed the various DPN prevalence in different countries; 8.4% in China (Lu et al., 2013), 48.1% in Sri Lanka, 29.2% in India (Katulanda et al., 2012), 56.2% in Yemen (Al Washali et al., 2014), 39.5% in Jordan (Khawaja et al., 2018), 71.1% in Nigeria (Owolabi & Ipadeola, 2012), 16.6% in Ghana (Yeboah et al., 2018), and 29.5% in Ethiopia (Worku et al., 2010). From the above study, Nigeria had the highest prevalence of DPN, reasons attributing to low access to quality of care, increased cost of treatment, increase in obesity and ignorance. This result was evident in the research

conducted by Shiferaw et al., (2020), on a systematic review and meta-analysis using twenty-three studies which included 269,691 participants. The overall pooled prevalence of DPN was 46% (95% CI; 36.21 – 55.78%) based on the sub-group analysis, the highest prevalence of DPN in DM patients was reported in West Africa at 49.4% (95% CI; 32.74, 66.06) and the lowest was observed in Central Africa (35.9%; 95% CI: 29.51, 42.32). In a study by Oguejiofor et al., (2009), in Nnewi, Nigeria, diabetic peripheral neuropathy was present in 69.3% of patients when the United Kingdom Screening Test (UKST) tool was applied, although PDPN particularly, was not assessed. The prevalence of diabetic peripheral neuropathy using monofilament testing was reported to be as high as 59.2% in the Diabcare Nigeria study (Uloko et al., 2012), while Otu et al., (2013), reported that 29.9% of patients with diabetic mellitus foot ulcer had underlying diabetic peripheral neuropathy, as measured using a 10 g monofilament.
Patients with DPN often suffer from the loss or absence of a protective sensation in the lower extremities leading to balance problems (Herrera-Rangel et al., 2014), risk of foot ulcerations, pain and disrupted sleep patterns (Hoffman et al., 2009), cardiovascular morbidity and mortality (Bello et al., 2019), reduced quality of life and increased cost of treatment (Mehra et al., 2014). Despite these symptoms experiences, studies have also revealed that early screening and management can reduce occurrence. Previous studies have indicated that for those with high-risk diabetic neuropathy, proper management and early screening can minimize the occurrence of ulcers by 60% and amputations by 85% (Hoffman et al., 2009).

Among diabetic patients that experience DPN, neuropathy is the most common and some patient experience painful neuropathy. It was established that the prevalence of pain is 10% to 20% in patients with diabetes and from 40% to 50% in those with diabetic neuropathy (Veves et al., 2008). In recent years, approximately 50% of people with DPN suffer with peripheral neuropathic pain (Alleman et al., 2015). Painful diabetic poly-neuropathy has a prevalence of 16–26%, and up to 80% of patients may have moderate or severe pain (Davies et al., 2006). An objective neuropathy with pathological changes in a nerve and even a nerve injury does not necessarily cause pain. It should be remembered that NP may present long after the initial nerve injury and that genetic, psychosocial and other factors are relevant in the pathogenesis (Herr 2004; Dworkin et al., 2003). Painful diabetic peripheral neuropathy usually arises in an individual with background diabetic peripheral neuropathy (DPN). In the US the estimated prevalence of peripheral neuropathy among adults with diabetes is 28% (Pop-Busui et al., 2017; Gregg et al., 2007).

Young et al., (2018), conducted a study on the prevalence of painful diabetes peripheral neuropathy (PDPN) in Nigeria revealed in a total of 272 patients used, (46.3%) males were recruited; Type 2 diabetes was present in 95.6% and 57.4% had hypertension. Poor glycemic control was present in 79.2% and 44.5% had PDPN. In addition, PDPN was more prevalent in those on insulin (P =.007, OR =1.96) and diabetes duration more than 10 years (P = .004, OR = 1.92), Painful diabetic peripheral neuropathy was more common in the subjects who had had diabetes for more than 10 years, compared to those who had had diabetes for less than 10 years (P = 0.015, OR = 1.9). The study population had more females than males, reflecting the higher prevalence of diabetes in females in Nigeria, as reported in some community and hospital-based studies on DM (Ahmed, 2017: Akinkingbe, 1997). This supports the study on gender as a risk factor for painful diabetic peripheral neuropathy. There was a record of high prevalence of PDPN among the subjects, with almost half (44.5%) of the study population being affected. The long duration of diabetes in the study subjects was a factor that accounted for the high prevalence of PDPN in the patients. This high prevalence of PDPN, using the DN4 score, has also been reported in other studies (Halawa et al., 2010; Jambart et al., 2011). DN4 is Diabetes Mellitus simple validated questionnaire administered to diabetic patients to measure diabetic neuropathy.

A study conducted in Saudi Arabia, where the DN4 questionnaire was also utilized, and a prevalence of 65.3% was reported for PDPN (Halawa et al., 2010b). Similarly, in a larger study conducted among out-patient subjects with diabetes, in some select countries of the Middle East region; including Egypt, the Gulf States, Jordan and Lebanon, a prevalence of 53.7% was recorded for PDPN (Jambart et al., 2011b). However, Jacovides et al., (2014), in their study in South Africa, recorded a lower prevalence of 30.3%, while PDPN was prevalent in 14.4% of Type 2 DM subjects in Korea (Kim et al., 2013). The wide variations in prevalence may be accounted for by the different diagnostic tools employed by the various researchers, in addition to possible differences in ethno-cultural pain perceptions, among the different populations cited (Abbott et al., 2011; Shavers et al., 2010).

Chan et al., (1990), quoted a 7.5% prevalence rate for painful lower-limb symptoms in people with diabetes. Ziegler et al., (1992), also reported that painful lower limb symptoms occur in 11.6% of type 1 and 32.1% of type 2 diabetic patients. Recent community-based studies of patients with diabetes suggest that the prevalence of PDNP is around 16–26% (Jude & Schaper, 2007), and in one study, 80% of the patients with PDNP had moderate or severe pain (Daousi et al., 2004; Benbow et al., 1998) demonstrated the negative impact of pain on patients with DNP, and found a strong relationship between chronic pain and poor sleep quality, which was thought likely to be due to the worsening of pain symptoms at night. (Galer et al., 2000**)** found that over half of the patients whom they studied reported that pain interfered substantially with one or more aspects of their Quality of Life (namely mobility, employment, sleep, enjoyment of life and recreational and social activities). In a study on the prevalence and impact of pain in diabetic neuropathy by Geerts et al., (2009), 57.5% of the 219 patients used admitted to painful diabetic neuropathy from mild to severe.
Different primary studies been conducted in Africa aims to demonstrate the magnitude of PDPN as a health issue in this region. However, there seems to be a variation and as such this study was aimed to estimate the prevalence and associations of neuropathic pain in patients with Diabetes Mellitus in south-east Nigeria.

Hypothesis

1. There will be a significant relationship between positive pain and diabetic peripheral neuropathy among diabetic patients.
2. The existence of painful symptoms will not lead to significant growth in diabetic peripheral neuropathy severity among diabetic patients.
3. Certain lifestyle will significantly predict painful diabetic peripheral neuropathy among diabetic patients.

METHODS AND MATERIALS

The Enugu Diabetic Peripheral Neuropathy (EDIPEN) study was a cross sectional observational study of 422 type 1 and type 2 diabetic patients drawn from the Medical Outpatients (MOP) unit of Enugu State University Teaching Hospital (ESUTH) Parklane, Enugu. The data collection period lasted for six months (January to October 2022). The participants' ages were between 18 and 70 years, with mean age and mean duration of diabetes 57.6 ± 10.1 years and 7.4 ± 5.9 years respectively. Females were predominant (68.5%) and majority (97.2%) had type 2 diabetes. The study inclusion criteria include (1) must be at least 18 year and above, (2) participants must have been diagnosed of either type 1 or type 2 diabetes (3) the participant must express the willingness to participate in the study, (4) the participant must be an outpatient of the hospital. While the exclusion criteria included (1) pregnant women, (2) participants with bilateral lower limb amputation, (3) those with ulcer on both feet and the remaining foot of a one-limbed patient. The minimum sample was calculated using Fisher's formula (Fisher et al., 1980). Their socio-demographic variables including age, gender, smoking and alcohol habits were documented, and this was followed by clinical history including type and duration of diabetes, treatment type, history of hypertension, diabetic foot ulcer and lower limb amputation. The data was gathered using Diabetic Peripheral Neuropathy Questionnaire (Feldman & Stevens, 1994).

Weight and height were measured by standard methods and body mass index calculated as a ratio of weight to the square of height in kilogram per square meter (Meijer et al., 2002), and as well the measurement of vibration perception threshold (VPT/biothesiometry). A biothesiometer (Diabetik Foot Care Pvt Limited, India, 2005) was used to assess vibration perception threshold in both feet for each participant. The participants were examined in a supine position without their footwear or stocking. The procedure was first explained to the participant and a test demonstration made on the patient's hand to ensure comprehension before the actual testing was conducted. The tip of the biothesiometer probe was held one at a time on each of the 5 designated testing points on the sole of each foot at 90^0 to the skin with sustained pressure and the voltage was slowly increased from 0 volt. The VPT for each testing point was taken as the voltage at which the participant first reported perception of the vibration. The average VPT for the 5 test points was calculated and recorded as the VPT for that foot. Both feet were tested separately. A value below 15 volts indicated absence of neuropathy (normal sensation), between 16 and 20 volts indicated mild neuropathy, between 21 and 25 Volts indicated moderate neuropathy, and above 25 Volts indicated severe neuropathy. Serum B12 level, hemoglobin concentration were measured in all DM patients.

Baseline characteristics of the study population

A total of 422 diabetic subjects with mean age and mean duration of diabetes 57.6 ± 10.1 years and 7.4 ± 5.9 years respectively participated in the study. Females were predominant (68.5%) and majority (97.2%) had type 2 diabetes.

RESULTS

Table 1. Baseline Characteristics of the Study Population

Variable	Mean ± SD	n (%)
Age (years)	57.6 ± 10.1	
Female Gender		289 (68.5)
Cigarette Smoker		59 (14.0)
Alcohol User		178 (42.2)
Body Mass Index (kg/m^2)	27.8 ± 5.5	
Diabetes type (type 2)		410 (97.2)
Duration of Diabetes (years)	7.4 ± 5.9	
Hypertension		258 (61.1)
On Treatment with Insulin		113 (26.8)
On Vitamin Supplements		162 (38.4)
Presence of foot deformity		47 (11.1)
Peripheral artery disease		95 (22.5)
Previous Foot Ulcer		38 (9.0)
Previous Amputation		20 (4.7)
Glycated Hemoglobin (%)	8.4 ± 2.1	

Prevalence of Painful Symptoms and Painful Diabetic Peripheral Neuropathy

A total of 117 out of 422 subjects (27.7%) had positive pain score (PNS score ≥ 4). Of the 261 (61.8%) subjects who were confirmed to have DPN based on neuropathic tests, 105 (40.2%) had positive pain score and therefore met the diagnosis of Painful DPN. Painful DPN occurred in 20.0% and 40.6% of subjects with type 1 and type 2 DM respectively. Twelve

of the 117 subjects (10.3%) who had positive pain score did not have DPN. There was a significant association between having positive pain score and presence of DPN (OR = 4.5, 95% CI = 2.2 – 9.4, P <0.001). Figure 1 shows the prevalence of painful symptoms in subjects with and without neuropathy.

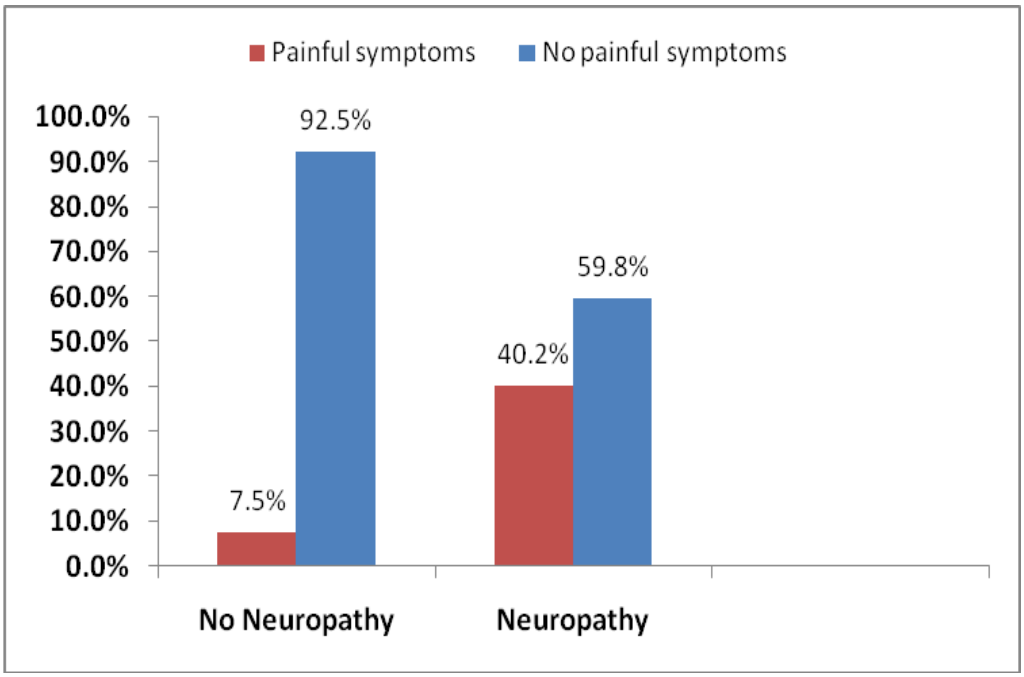

Figure 1. Prevalence of painful symptoms in subjects with and without diabetic peripheral neuropathy.

The relationship between the frequency of painful symptoms and severity of clinical DPN (based on biothesiometry) is presented in figure 2. Prevalence of painful symptoms increased progressively as the severity of DPN increased, from 14.3% in subjects with no DPN to 43.2% in those with severe DPN (Chi-Square 30.273, P < 0.001). There was also a significant correlation between PNS and DNS scores (Pearson r = 0.73, P < 0.001).

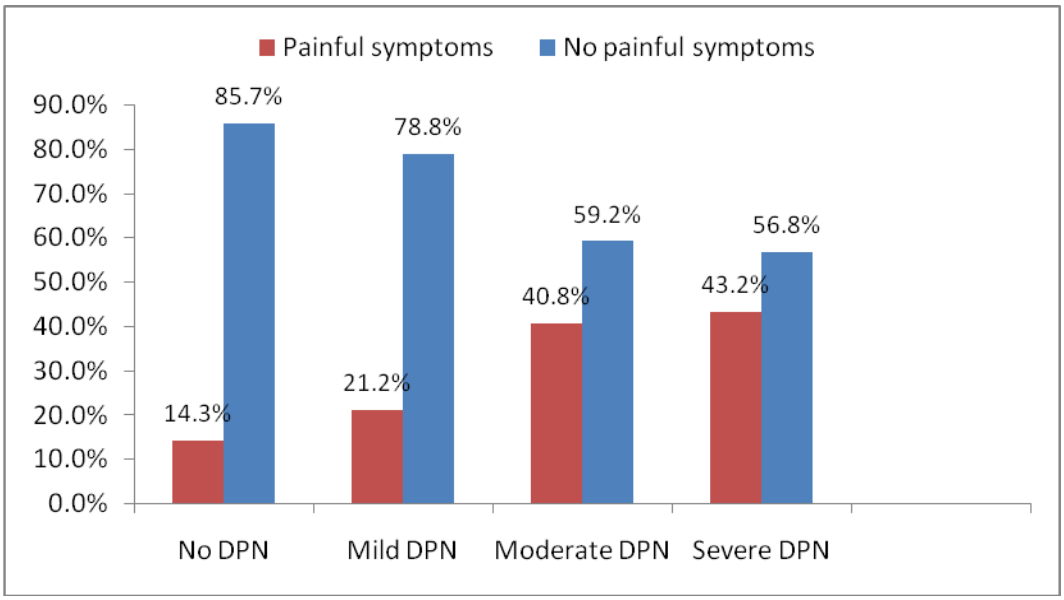

Figure 2. Frequency of painful symptoms according to severity of diabetic peripheral neuropathy. DPN = diabetic peripheral neuropathy

Risk factors of painful diabetic peripheral neuropathy among subjects with type 2 diabetes.

To determine the risk factors of PDPN in the 236 subjects who had confirmed DPN, we performed a binary logistic regression, with positive PNS score as the dependent variable, after excluding 4 type 1 DM subjects due to small number. The results showed that female gender (OR 3.9, 95% CI 1.7 – 8.8, P 0.001) and anemia (OR 2.7, 95% CI 1.2 – 5.5, P 0.015) were the significant predictors of PDPN. Painful diabetic peripheral neuropathy was not dependent on age, diabetes duration, smoking and alcohol habits, insulin use, glycemic control or vitamin B12 concentrations (table 2).

Table 2. Determinants of painful diabetic peripheral neuropathy in subjects with type 2 diabetes.

Variable	OR	95% C.I		P value
		Lower	Upper	
Age > 50 years	0.50	0.17	1.47	0.210
Female gender	3.87	1.70	8.84	**0.001**
Hypertension	0.81	0.41	1.61	0.545
Cigarette smoking	0.81	0.28	2.33	0.700
Alcohol use	1.48	0.74	2.98	0.266
Diabetes type 1	0.37	0.04	3.32	0.371
Diabetes duration > 10 years	0.56	0.28	1.10	0.093
Insulin use	1.08	0.51	2.30	0.838
Vitamin supplements use	0.80	0.42	1.53	0.495
Body mass index ≥ 25kg/m^2	0.57	0.26	1.26	0.163
Peripheral artery disease	1.57	0.77	3.23	0.215
Hemoglobin < 12g/dl	2.57	1.20	5.49	**0.015**
Glycated hemoglobin ≥ 7%	1.14	0.57	2.26	0.715
Vitamin B12 level < 200pg/ml	1.00	0.41	2.49	0.993

DISCUSSION

The study focused on prevalence and associations of neuropathic pain among subjects with diabetes mellitus. The results of the study showed that there is a significant association between having positive pain and presence of DPN. This shows that among patients with DM who noticed positive pain, diabetic peripheral neuropathy is inevitable. Hence, the hypothesis which stated that there will be significant relationship between positive pain and DPN is therefore supported. The outcome of this study is in line with previous studies (e.g., Baxi et al., 2020; Hussain et al., 2020; Abbott et al., 2011). The result also showed that prevalence of painful symptoms increased progressively as the severity of DPN increased. This indicates that among DM patients with existence of painful symptoms, there was an increase in the severity of their diabetic peripheral neuropathy. Thus, the study hypothesis which stated that the existence of painful symptoms will not lead to significant growth in the DPN severity was not supported. This outcome tallies with the results of other previous studies (e.g., Chaplin et al., 2017; Vinik et al., 2013; Pop-Busui et al., 2017). Also, the result showed a significant relationship between PNS and DNS. This indicates that existence of PNS may be triggered by the existence of DNS in patients (Dyck et al., 1993). Lastly, the study result showed that the gender (female) and anemia significantly predicted PDPN among diabetic patients, while age, diabetes duration, smoking, and alcohol habits, do not trigger nor influence PDPN. This shows that among diabetic patients, being a woman and the existence of anemia triggered PDPN, while patient's age, number of years they have suffered diabetes, smoking, and alcohol intake, didn't predict PDPN. Hence, the study hypothesis which states that certain lifestyle will significantly predict painful diabetic peripheral neuropathy was not supported. This outcome is in line with outcome previous studies (e.g., Truini et al., 2018; Young et al., 2018; Baxi et al., 2020).

IMPLICATIONS OF THE FINDINGS

Apparently, diabetes mellitus is regarded as one of the most expensive illness to manage due to its complications and effects on patient's quality of life (Ezaka et al., 2022). Suffering from this chronic illness comes with different complications and health challenges, one of which is painful diabetic peripheral neuropathy. The present study found that prevalence of painful symptoms increased progressively as the severity of DPN increased. This indicates that among DM patients who notice painful symptoms, there is an increase in the severity of their diabetic peripheral neuropathy. The study also found that the gender (female) and anemia significantly predicted PDPN among diabetic patients, while age, diabetes duration, smoking, and alcohol habits, do not trigger nor influence PDPN. This shows that among diabetic patients, being a woman and the existence of anemia triggered PDPN, while patient's age, number of years they have suffered diabetes, smoking, and alcohol intake, didn't predict PDPN.

LIMITATIONS

The limitations of this study can be viewed in terms of number of participants (422) used in the study, and the use of one hospital in carrying out a study of this nature, as these will affect the generalization of the study outcomes.

SUGGESTIONS FOR FUTURE STUDIES

The researchers suggest that the outcome of this study should stand as a working document in managing the physical complications and co-morbidities associated with living with a chronic illness such as diabetes. We therefore suggest that future researchers who wish to replicate a study of this nature should consider using more participants, and explore not only the physical symptoms associated with diabetes, but the psychological factors associated with it.

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The authors declare that they have no funding for this article and that they have no conflicts of interest regarding this work.

THE AUTHORS DECLARE AUTHORS' CONTRIBUTION

All the authors contributed equally to this study, they read and approved the final manuscript

ETHICAL CLEARANCE

Ethical clearance was obtained from the ethics committee of the ESUT Teaching Hospital, Parklane-Enugu, Nigeria.

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