Distal symmetrical polyneuropathy detected by vibration perception threshold among adults with and without diabetes attending a general outpatient clinic in Ilorin, Nigeria

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Abstract

The aim of this study is to compare the prevalence, severity, and symptoms of Distal Symmetrical Polyneuropathy (DSP) among adult patients with diabetes and those without diabetes in a primary care clinic. It was a cross-sectional comparative study involving 72 adults of between 40-60 years of age living with diabetes and 72 age-matched adults without diabetes. DSP was assessed with a biothesiometer device, and data analysis was performed using the SPSS Version 21 statistical software. The overall prevalence of neuropathy among the participants was 68.1% for those living with diabetes and 38.9% for the other group. Furthermore, 22.3% of the diabetes group had severe neuropathy compared with 8.3% of the other group. These differences were found to be statistically significant with p=0.001 (df = 2, X2 = 14.07). We reported higher prevalence and severity of DSP in those living with diabetes. We also found significant association between high VPT (≥25V) and presence of neuropathic symptoms thereby enhancing the use of the biothesiometer device in the diagnosis of adults with DSP in the primary care setting.

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Key words: Distal polyneuropathy; diabetes; biothesiometer; vibration perception threshold.

Conflict of interest: The authors declare no conflict of interest.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate: The Ethics Committee of General Hospital Ilorin approved this study (GHI/ADM/134/ VOLI-II/380). The study is conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights. All patients participating in this study signed a written informed consent form for participating in this study.

Informed consent: Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Received for publication: 15 August 2021.
Revision received: 1 November 2021.
Accepted for publication: 17 February 2022.

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Licensee PAGEPress, Italy
Annals of African Medical Research 2022; 5:159
doi:10.4081/aamr.2022.159

Introduction

Distal Symmetrical Polyneuropathy (DSP) is one of the most common neurologic problems seen in primary care setting posing diagnostic and evaluation challenges to clinicians because of its diverse ways of presentations.[1] There are different aetiological factors responsible for DSP but the most common is diabetes accounting for about 32 to 53% of cases.[2,3] Therefore, DSP is also commonly referred to as chronic sensorimotor neuropathy or diabetic polyneuropathy.[4] It is estimated that 90% of people with diabetic peripheral neuropathy have Distal Symmetrical Polyneuropathy (DSP) with the involvement of multiple nerve groups.[5] The prevalence of diabetic polyneuropathy ranges from 2.4% to 78.8% worldwide depending on the diagnostic method and the population assessed.[6] In Nigeria, the prevalence of DSP among patients living with diabetes ranges from 31.2% to as high as 71.1%.[7,8] Kaoje *et al.* in Zaria in North-West Nigeria found a prevalence of 39.7% among diabetic patients as against 6.1% among healthy controls.[9] In Ilorin North-Central Nigeria, Bello *et al*. found DSP prevalence of 41.7% among diabetic patients attending a specialist diabetic clinic.[10] It is clear from available literature that diabetes is responsible for most distal symmetrical polyneuropathy.

Other known causes of peripheral neuropathy include medications such as chloroquine, systemic conditions such as chronic lymphocytic leukemia and renal failure, infections such as herpes zoster, autoimmune disorders, toxins, trauma and inherited conditions such as Charcot Marie Tooth disease. Others include vitamin B12 deficiency, excessive alcohol consumption, uraemia, paraneoplastic syndromes, paraproteinaemia, hypothyroidism and idiopathic cases.[2,3,11]

The symptoms of DSP usually have mild insidious onset with predominance of sensory features over motor symptoms.[12] They are present in 10% of diabetic patients at the time of diagnosis of type 2 diabetes mellitus.[11] The symptoms can be either positive or negative.[11,13] The positive type include sensation of burning or knife-like pain, electrical sensations, squeezing, constricting, freezing or throbbing, and allodynia.[11,13] The negative symptoms include swelling, prickling, numbness, a feeling of walking on cotton wool or dead limb.[11,13] The severity of peripheral neuropathy

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can be mild, moderate and severe. This can be measured using screening tools like the Neuropathy Disability Score, Toronto Clinical Scoring Scale, United Kingdom Screening Tool, and also the biothesiometer device.[9,14,15]

Peripheral polyneuropathy is a disabling disease and has a negative impact on a person's quality of life.[16] Previous studies have shown that physicians tend to underestimate neuropathy in patients when using perception alone rather than a diagnostic tool or device.[17,18] The biothesiometer has been found to be a standard screening method of measuring Vibration Perception Threshold (VPT) as a measure of peripheral neuropathy.[18] The use of VPT for the diagnosis of neuropathy has been well validated by clinical studies with a sensitivity and specificity of 80 and 98%, respectively.[19] The biothesiometer was used as a standard to compare the sensitivities of other methods in detecting peripheral neuropathy in a study by Tanveer *et al*. in North India.[15] In the study, the assessment of neuropathy with biothesiometer was found to be the most sensitive compared to the use of monofilament, use of tuning fork, or the Diabetic Neuropathy Symptom Scores.[15]

There are few studies on the assessment and comparison of DSP among older adults living with diabetes and those living with other chronic diseases, and also fewer studies where the highly sensitive biothesiometer was used to detect DSP in the primary care setting. Therefore, the aim of this study is to compare the prevalence, severity, and symptoms of undiagnosed Distal Symmetrical Polyneuropathy (DSP) among older adult patients with diabetes and those without diabetes.

Materials and Methods

Study site

The study was conducted at the General Outpatient Unit of the Family Medicine Department in General Hospital Ilorin, an accredited academic center for family medicine residency training. The hospital is located in Ilorin metropolis and offers primary, secondary, and tertiary medical services. Ilorin is the capital of Kwara State, in the North-central geopolitical zone of Nigeria.

Study design

The study was a hospital-based, comparative cross-sectional study. The sample size was calculated using the OpenEpi version 4.04.15 calculator for cross-sectional comparative studies to be 72 patients living with diabetes and 72 other adult patients.[20] Those living with diabetes were selected consecutively while those without diabetes were selected by systematic random sampling using standard procedure. The inclusion criteria for patients living with diabetes were adult patients between 40-60 years of age who have been receiving treatments for diabetes for more than 3 months and who gave written informed consent to participate in the study. The inclusion criteria for the other group were middle-aged adults between 40-60 years of age who did not have diabetes and have been receiving treatments at the hospital for non-diabetic related conditions for at least 3 months duration, and who gave written informed consent to participate in the study. The exclusion criteria for the study were patients living with diabetic or non-diabetic leg ulcers, leprosy or HIV, patients with suspected hereditary or toxic peripheral neuropathy, patients on treatment for peripheral neuropathy, acutely ill patients requiring emergency care and patients on cytotoxic drugs. Ethical clearance was secured from the Institutional Review Board of the General Hospital Ilorin before commencement of the study and the study was conducted in line with the principles of the Helsinki Declaration.

Study instruments

A structured interviewer-administered questionnaire was used to obtain socio-demographic and clinical information from the participants, including presence of neuropathic symptoms in the legs. The questionnaire was developed by the authors for the purpose of the study. The patients' hospital records were also used to assess their eligibility for the study. Kodys™ biothesiometer digital vibration perception threshold analyzer (model Biothezi-VPT, Kodysmedical, Chennai, Tamil Nadu, India) was used to assess for DSP in all participants. It vibrates at 100Hz with amplitude of vibration ranging from 0-25μ.[21] The device has been validated for use to measure vibration perception much more accurately, and has been proven to detect distal polyneuropathy in both non-diabetics and people living with diabetes earlier than most clinical tools and validated neuropathy detecting questionnaires.[15] It has also been proven to accurately predict the risk of future foot ulceration in patients living with diabetes.[18] An experienced technician operated the device by applying the tactor at the plantar aspect of the great toe opposite the nail bed, the plantar aspect of the medial distal end of the first metatarsophalangeal joint, and the plantar surface of the lateral distal end of the fifth metatarsophalangeal joint of both feet in all participants in the sitting position. The sensitivity of the test was improved by applying the tactor firmly but with minimum pressure against the skin at the selected points. The test was also conducted in an air-conditioned room with room temperature of 25°C. Participants were familiarized with the sensation of the device by turning the applied voltage to the maximum (50Hz) and then to the minimum (0Hz). Voltage was then gradually increased from zero until the subjects signified perception of vibration in each of the three points in both feet. The average of the three readings per foot was recorded as the VPT.

Study protocol

Each selected participant signed an informed consent form and was asked to complete the study questionnaire. Thereafter, the participant was sent to the technician in the study room for VPT assessments. For the purpose of this study; patients living with diabetes were those who had a fasting plasma glucose of ≥7mmol/L or glycated haemoglobin ≥6.5% at the time of their first diagnosis, and have been on treatment for more than 3 months.[22] Also, absence of Distal Polyneuropathy (DP) was defined as average VPT voltages in both feet ≤15V, mild DP was average VPT between 16-24V, severe DP was average VPT ≥25V, symmetrical DP was defined as VPT values of ≥16V in both feet, and symptomatic DP was defined as presence of core neuropathic symptoms (tingling, burning, or numbness sensation) in any participants with at least average VPT value ≥16V in the symptomatic foot.[23,24] All the data were analyzed using SPSS Version 21 statistical software.

Results

Socio-demographic characteristics of the study participants

A total of 144 adult patients between the ages of 40-60 years participated in the study. Out of the total number, 72 participants were those living with diabetes while the other 72 were not, therefore the comparison ratio was 1:1. The mean ages among the study groups were 53.0±5.3 and 53.3±6.2 years for those living with diabetes and for the control group respectively. The highest percentage of the participants was that between the 55-60 age group

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(43.1%) and majority of the participants were women (75%). The female to male ratio was 2:1 and 5:1 for the diabetic group and the control group respectively. The mean and median durations of diabetes among participants with the disease were 5.9 (±2.1) years and 7.5 years respectively. The results are presented in Table 1.

Prevalence and severity of distal symmetrical polyneuropathy

The overall prevalence of neuropathy among the participants was 68.1% for those living with diabetes while the control group had 38.9%. Furthermore, 22.3% of the diabetes group had severe neuropathy compared with 8.3% of the control group. These differences were found to be statistically significant with p=0.001 (df=2, X2=14.07). There was also a statistically significant difference in the mean VPT of the two groups with P <0.0001 (df=142, t=4.8). The prevalence of DSP was 63.9%, and 29.2% for the diabetic and the non-diabetic group respectively. Also, 29.2% of the diabetic group had symptomatic DSP compared to 11.1% for the control group. The results are presented in Table 2.

Table 1. Socio-demographic characteristics of the participants (N = 144).

Variables	Diabetes group [n (%)] N^a =72	Non-diabetes group [n (%)] Nb = 72	Total [n (%)] N = 144
Age groups			
40-45 years	8 (11.1)	11 (15.3)	19 (13.2)
46-50 years	19 (26.4)	11 (15.3)	30 (20.8)
51-55 years	16 (22.2)	17 (23.6)	33 (22.9)
56-60 years	29 (40.3)	33 (45.8)	62 (43.1)
Total	72 (100.0)	72 (100.0)	144 (100.0)
Mean age (SD)	53.0 (±5.3)	53.3 (±6.2)	
Gender			
Female	48 (66.7)	60 (83.3)	108 (75.0)
Male	24 (33.3)	12 (16.7)	36 (25.0)
Total	72 (100.0)	72 (100.0)	144 (100.0)
Religion			
Islam	46 (63.9)	54 (75.0)	100 (69.4)
Christianity	26 (36.1)	18 (25.0)	44 (30.6)
Total	72 (100.0)	72 (100.0)	72 (100.0)
Duration of diabetes			
3 months - <1 year	12 (16.7)		
1 - 5 years	16 (22.2)		
5 - 10 years	35 (48.6)		
>10 years	9 (12.5)		
Total	72 (100.0)		
Mean duration	(SD): 5.9 (±2.1) years		
Median duration	7.5 years		

N = Total number of respondents. Na = Number in diabetes group. N^b = Number in non-diabetes group. n = Number of respondents in each cell. SD = Standard deviation of the mean.

Table 2. Prevalence and severity of distal symmetrical polyneuropathy among the participants.

Variables	Diabetes group [n (%)] N^a =72	Non-diabetes group [n (%)] N^b = 72	Total [n (%)] N = 144
VPT categories (Volts)		df = 2, X^2 = 14.07, P = 0.001	
≤15 (No neuropathy)	23 (31.9)	44 (61.1)	67 (46.5)
16-24 (Mild neuropathy)	33 (45.8)	22 (30.6)	55 (38.2)
>25 (Severe neuropathy)	16 (22.3)	6 (8.3)	22 (15.3)
Total	72 (100.0)	72 (100.0)	144 (100.0)
Mean VPT (SD)	21.2 (±7.0)	15.9 (±6.4) t = 4.8, df = 142, P = <0.0001	
Distal symmetrical polyneuropathy			
Present	46 (63.9)	21 (29.2)	67 (46.5)
Absent	26 (36.1)	51 (70.8)	77 (53.5)
Total	72 (100.0)	72 (100.0)	144 (100.0)
Symptomatic DSP			
Present	21 (29.2)	8 (11.1)	29 (20.1)
Absent	51 (70.8)	64 (88.9)	115 (79.9)
Total	72 (100.0)	72 (100.0)	144 (100.0)

df = Degree of freedom; X^2 = Chi-square. P = P-value, t = Student t-test.

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Association between VPT categories and presence of neuropathic symptoms

The test of association between VPT categories and presence of neuropathic symptoms among participants was found to be statistically significant by Fisher's exact test (df=2, F=90.13, p<0.0001). Also, 75.9% of those who had neuropathic symptoms had VPT ≥25V. The results are presented in Table 3.

VPT categories by participants' clinical diagnoses

Sub-group analysis of the participants' VPT records revealed that only participants who were receiving treatments for diabetes and systemic hypertension had VPT ≥25V (severe neuropathy) at 72.7% and 27.3% respectively. However, the Fisher's Exact test for association between VPT categories and participants' clinical diagnosis was not statistically significant (df=24, F=31.67, p=0.34). The results are presented in Table 4.

Discussion

This comparative cross-sectional study has reported the overall prevalence of previously undiagnosed distal polyneuropathy based on detection of abnormal VPT in either of the feet, the prevalence of DSP based on detection of abnormal VPT in both feet, and the prevalence of symptomatic DSP based on the combination of abnormal VPT in both feet and presence of neuropathic symptoms, in those living with diabetes and their age-matched adults living with other chronic illness except diabetes. There was a level of inconsistency in the description of distal polyneuropathy or DSP among researchers which led to the issuance of a consensus statement by the American Academy of Neurology and others on the case definition of DSP in 2005.[24] The report recommended the combination of symptoms, signs, and validated electrodiagnostic methods to detect DSP in clinical research which in itself is not flawless because of the imperfect diagnostic correlations of the three modalities.[25]

It is pertinent to mention that distal polyneuropathy is complex and can be symmetrical or asymmetrical, it can also be symptomatic or asymptomatic.[25] Therefore, it is important to completely describe the spectrum of the disease along these lines, especially in the primary care setting where many older adults' patients usually have asymptomatic and undiagnosed distal polyneuropathy.[26] As reported in this study, 46.5% of the entire study population had DSP but only 20.1% had symptomatic DSP. Early detection of those with undiagnosed DSP provides a window of opportunity to offer foot care education and prophylactic treatments to further reduce their risks of developing symptomatic DSP and severe foot complications. This comprehensive care approach was offered to those diagnosed with DSP in this study.

While there are widespread variations in the level of prevalence of diabetic DSP reported in various studies, the 63.9% prevalence reported in this study is well within ranges of values reported in Nigeria and Africa, but higher than the 30%-50% range reported in the United States.[7,8,27] This difference may be due to not only methodological and study population differences but also as a result of late detection of patients with diabetes in Nigeria and most African countries.[28] When compared with the 29.2% prevalence of DSP among age-matched adults not living with diabetes reported in this study, the difference was found to be significantly higher with the ratio of at least 2:1 in those living with diabetes (X^2=17.445, df=1, p=<0.0001). This 2:1 ratio in the prevalence of DSP in those living with diabetes and older adults without diabetes respectively, is consistent with those reported from the developed countries with prevalence of about 30% and 15% respectively.[29]

Furthermore, this study was able to demonstrate statistically significant higher level of severity of distal neuropathy experienced by those living with diabetes compared with the other group (22.3% *vs* 8.3%, X^2=14.07, df=2, p=0.001). This is in line with other studies globally where diabetes has been shown to be the leading cause of severe distal neuropathy with or without neuropathic pains.[1,3] In addition, we are able to establish that average VPT≥25V in the feet can be a good predictor to the presence of severe DSP with neuropathic symptoms. Majority of those who had neuropathic symptoms in our study had VPT ≥25V (75.9%), and the association between VPT categories and presence of neuropathic symptoms was found to be significant (df=2, F=90.13, p<0.0001). This finding is similar to those reported in other studies and will further enhance the use of the biothesiometer in the pri-

Table 3. Association between VPT categories and presence of neuropathic symptoms among the participants.

VPT Categories	Neuropatic symptoms		Total [n (%)]
	Present [n(%)]	Absent [n(%)]	
		df = 2, F = 90.13, P = <0.0001	
≤15 (No neuropathy)	1 (3.4)	66 (57.4)	67 (46.5)
16-24 (Mild neuropathy)	6 (45.8)	49 (42.6)	55 (38.2)
>25 (Severe neuropathy)	22 (22.3)	0 (0.0)	22 (15.3)
Total	29 (100.0)	115 (100.0)	144 (100.0)

F = Fisher's Exact test.

Table 4. VPT categories by participant's clinical diagnoses.

Clinical Diagnoses	VPT Categories (Volts)			Total
	≤15 [n (%)]	16-24 [n (%)]	≥25 [n (%)]	[n (%)]
Diabetes mellitus	23 (34.3)	33 (60.0)	16 (72.7)	72 (50.0)
Systemic hypertension	13 (19.4)	9 (16.4)	6 (27.3)	28 (19.4)
Peptic ulcer disease	6 (9.0)	6 (10.9)	0 (0.0)	12 (8.4)
Osteoarthritis	4 (6.0)	5 (9.1)	0 (0.0)	9 (6.3)
Others	21 (31.3)	2 (3.6)	0 (0.0)	23 (15.9)
Total	67 (100.0)	55 (100.0)	22 (100.0)	144 (100.0)

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mary care setting to detect patients that might need therapeutic treatments.[9,25]

A post hoc subgroup analysis done to compare the severity of neuropathy based on the chronic diseases present in the group without diabetes revealed that only patients receiving treatment for systemic hypertension had VPT values consistent with severe neuropathy among the group (27.3%). Although, this percentage is substantially lower than that reported in those living with diabetes (72.7%), it is a noteworthy finding in the evaluation of older adults with DSP. Pappanas and Ziegler, in their comprehensive review of significant risk factors for DSP, identified among others; systemic hypertension, prediabetes, age, height, obesity, and duration of diabetes as significant risk factors for DSP.[30] Consequently, a more rigorous and high-power study is desired in the future to explore the role of hypertension in the pathogenesis of DSP and to confirm if it can cause severe DSP alone.

While we tried to eliminate some of the confounders for DSP in this study we were not able to completely eliminate them due to the limited scope of the study and the resources available to us. Other limitations in our study included our use of the patients' hospital records to identify eligible participants in the study, which, though reliable, might not be perfectly accurate. Also, the cross-sectional comparative design of the study meant no cause-effect analysis could be done. Furthermore, the 40-60 years age range of participants used in the study means that the prevalence reported are age-specific and not totally generalizable in adults.

Conclusions

In this comparative cross-sectional study, we have been able to show that the prevalence of undiagnosed DSP is high in the study population. Participants living with diabetes had significantly higher prevalence and severity of DSP compared to those without diabetes. We were also able to demonstrate significant association between high VPT (≥25V) and presence of neuropathic symptoms thereby enhancing the use of the biothesiometer device in the diagnosis of adults with DSP in the primary care setting. We hypothesized based on our findings that systemic hypertension might be a cause of non-diabetic DSP and therefore hope for a robust randomized clinical trial to test this hypothesis in the future.

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