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Original Research

Peripheral sensory neuropathy in type 2 diabetes patients: A case control study in Accra, Ghana

Kwame Yeboah [a,*], Peter Puplampu [b], Vincent Boima [b], Daniel A. Antwi [a], Ben Gyan [c], Albert G.B. Amoah [b,d]

[a] Department of Physiology, School of Biomedical & Allied Health Sciences, University of Ghana, Accra, Ghana
[b] Department of Medicine & Therapeutics, School of Medicine & Dentistry, University of Ghana, Accra, Ghana
[c] Department of Immunology, Noguchi Memorial Institute of Medical Research, University of Ghana, Accra, Ghana
[d] National Diabetes Management & Research Centre, Korle-Bu Teaching Hospital, Accra, Ghana

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ABSTRACT

Objective: Peripheral sensory neuropathy (PSN) is a common cause of ulceration and amputation in diabetes (DM) patients. The prevalence of PSN in DM patients is largely undetermined in sub-Saharan African population. We studied the burden of PSN in DM patients using a validated questionnaire and quantitative sensory test.

Methods: In a case-control design, PSN was measured in 491 DM patients and 330 non-DM controls using Michigan neuropathy screening instrument (MNSI) and vibration perception threshold (VPT). PSN was defined as MNSI symptom score ≥7, MNSI examination score ≥2 or VPT ≥25V.

Results: The prevalence of PSN screened by MNSI symptom score, MNSI examination score and VPT was 7.1%, 51.5% and 24.5% in DM patients; and 1.5%, 24.5% and 8.5% in non-DM participants respectively. The major determinants of PSN screened by MNSI examination score were diabetes status [OR (95% CI): 4.31 (2.94–6.31), $p < 0.001$], age [1.03 (1.01–1.05), $p < 0.001$], previous [4.55 (2.11–9.82), $p < 0.001$] and current [8.16 (3.77–17.68), $p < 0.001$] smoking status. The major determinants of PSN screened by VPT were diabetes status [1.04 (1.02–1.06), $p < 0.001$], age [1.02 (1.01–1.03), $p = 0.047$], heart rate [1.78 (1.08–2.92), $p = 0.023$], second-hand smoking [3.66 (2.26–5.95), $p < 0.001$] and body height [3.28 (1.65–8.42), $p = 0.015$].

Conclusion: Our study has shown high burden of PSN in DM patients in Ghana using simple, accurate, and non-invasive screening tools like MNSI and neurothesiometer.

Introduction

Epidemiological transition has been under way in sub-Saharan Africa and this is in association with the dramatic increase in diabetes (DM) and accompanying vascular and neurological complications [1,2]. Peripheral sensory neuropathy (PSN) is a common microvascular complication of both type 1 and type 2 DM, and a major cause of morbidity and mortality [3,4]. PSN plays a major contributing role in the initiation of foot ulceration and non-traumatic lower-extremity amputation, resulting in severe disability, reduced quality of life, and significant economic burden to the health care system [5]. From the theatre records at the Department of Surgery, Korle-Bu Teaching Hospital, the main referral hospital in Ghana, out of 518 non-traumatic limb amputations performed within the period of January, 2014 through May, 2016, 467 (90.1%) were DM-related cases, with 318 (68.1%) below the knee amputations performed in DM patients.

Diagnosis of PSN is often made in clinical practice based on the presence of signs and symptoms of peripheral nervous system after other causes of neuropathy are excluded [3,6]. However, in up to 50% of DM patients, PSN may have no symptoms consistent with neuropathy, and hence, further neurological examination may be required for definite diagnosis [7,8]. Screening of PSN requires an appropriate tool that can detect mild form of the disease in high risk patients such as DM patients, and also, in low risk population with high sensitivity. Hence, the Michigan neuropathy screening instrument (MNSI), which is widely used for the evaluation of PSN in diabetes, was designed for such purpose [9]. Also, quantitative vibration testing is recommended in the screening and diagnosis of PSN [7]. However, this form of assessment is rarely performed in studies reporting the burden of PSN in sub-Saharan Africa.

A recent review of literature on PSN concluded that there is paucity of up-to-date epidemiological data on PSN worldwide [10], with only

Abbreviations: DM, diabetes mellitus; MNSI, Michigan neuropathy screening instrument; PSN, peripheral sensory neuropathy; VPT, vibration perception threshold.

* Corresponding author.
E-mail address: melvinky@gmail.com, kyeboah@ug.edu.gh (K. Yeboah).

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one outdated study reported in African population [11]. From our own literature search, we found a few current studies that reported the burden of PSN in DM patients in African population to be 27.3–48.2% [4,12,13]. In this study, we investigated into the burden and determinants of PSN in DM patients and non-DM participants using MNSI and vibration perception threshold (VPT).

Methods

The study was case control design conducted at National Diabetes Management and Research Centre, Korle-Bu Teaching Hospital in Accra, Ghana, from June 2009 to May 2010. The centre is Ghana's main referral clinic and operates ambulatory DM services and research. DM patients were recruited by systematic sampling, as every 3rd consenting patient visiting the clinic. The controls were recruited afterwards and matched with the DM patients by gender and age-decade. The controls were non-DM with normal fasting glucose (<6.9 mmol/l) and post-glucose load plasma glucose (<7.2 mmol/l), recruited randomly from the communities around the hospitals. Out of 1000 volunteers (600 DM and 400 non-diabetes) invited, 866 (516 DM and 350 non-diabetes) consented to participate in the study. In the final analysis, 31 diabetes (11 did not complete the questionnaire and 20 had conflicting VPT results) and 20 non-diabetes participants (9 had impaired glucose metabolism and 11 had conflicting VPT results) were excluded. Ethical approval for this study was obtained from the University of Ghana Medical School Ethical and Protocol Review Committee (Protocol ID number: MS-Et/M.2 – P.4.10/2009–2010) and all participants gave written informed consent after the procedures involved in the study were thoroughly explained to them. A structured questionnaire was administered to all the participants to collect information on age, gender, education, employment status, duration of DM, DM medication, pre-existing hypertension, smoking and alcohol status. Second-hand smoking was assessed as living with a smoking relative or co-worker. Hypertension was defined as subjects with BP ≥140/90 mmHg and/or on antihypertensive medication.

Michigan neuropathy screening instrument

The MNSI questionnaire was administered to all participants by a trained assistant. Responses were added to obtain a total score; 'Yes' responses to questions 1–3, 5–6, 8–9, 11–12, 14–15 were each counted as one point and 'No' responses to questions 7 and 13 likewise counted as one point. Question 4 was considered to be a measure of impaired circulation and question 10 a measure of general asthenia and were excluded in the published scoring algorithm [9]. A score of ≥7 was considered abnormal. In the MNSI examination, a physician inspected each foot for deformities, dry skin, calluses, infections and fissures, and the presence of any abnormality was scored as 1. Also, ulceration on each foot was scored as 1. The ankle reflexes were elicited and if absent, the patient was asked to perform the Jendrassik manoeuvre. If the reflex was present upon the Jendrassik, it was designated as present with reinforcement and scored as 0.5. In the absence of reflex after the Jendrassik manoeuvre, a score of 1 was assigned. Vibration sensation was then tested on the great toe using a 128-Hz tuning fork. Generally, the vibration is felt in the examiner's hand for 5 seconds longer than the a normal person can feel at the great toe. Vibration was scored as present, if the examiner sensed the vibration on his or her hand for not up to 10 s longer than the period the subject felt that vibration on the great toe (scored as null); as decreased if the vibration is sensed for ≥10 s (scored as 0.5); or absent (scored as 1) if no vibration was felt at all. The total possible score is 8 points and, in the published scoring algorithm, a score of ≥2.5 is considered abnormal [6].

Neurothesiometry

Neurothesiometry was performed using hand-held neurothesiometer (Horwell Neurothesiometer, Scientific Laboratory Supplies Ltd, Nottingham, UK) to read vibration perception threshold (VPT) from the apex of the big toe of both legs, with subject in a supine position, feet elevated with pillow support and eyes closed. The neurothesiometer is a validated battery-operated diagnostic instrument that assesses sensitivity thresholds at various sites on the body surface. On the basis of the method of limits, participants were asked to indicate when they first perceived vibration sensation after stimulus was applied to the distal pulp of the toe. The intensity of the stimulus was gradually increased at a rate of 0.5 V/s from null to a voltage at which vibration was first detected. VPT was performed on each participant about 3–5 times and, at least, three VPTs the differed ≤5 V were averaged and used for analysis. A null stimulus test was added randomly to ensure participant adherence and understanding of the test requirements. Participants who failed to provide 3 consistent values of VPT within 5 V after several measurements were excluded from the analysis as having conflicting VPTs.

Statistical analysis

The data was analysed using IBM SPSS Version 20. Differences in mean values of continuous were assessed using student's *t*-test, and distribution of categorical variables with χ^2 test. Binary logistic regression model was used to determine independent clinical factors associated with PSN. $p < 0.05$ was considered statistically significant.

Results

DM patients were older, with higher proportion of hypertension, alcohol intake, and fewer current smokers than non-DM controls. Also, DM patients had higher means of BMI, heart rate, systolic, diastolic, mean and pulse blood pressures, as well as higher level of unemployment. Majority of the DM patients were on oral hypoglycaemic medication. Compared to non-DM controls, prevalence of PSN screened by MNSI symptom score, examination scores and VPT was higher in DM patients (Table 1). Among DM and non-DM participants with PSN screened by the MNSI examination score, majority were with the age range of 40–69 years, and predominantly females (Fig. 1a,b). However, when PSN was screened by VPT, the proportion of females with neuropathy was higher in DM patients, and the proportion of males was higher in non-DM participant; majority of PSN patients were likewise within the age range of 40–69 years (Fig. 2a,b).

Multivariable backward conditional logistic regression models were constructed with PSN screened by MNSI symptoms, MNSI examination and VPT as dependent variables. In all participants, DM status, age, heart rate, second-hand smoking and body height increased the odds of abnormal VPT after multiple adjustments of risk factors. In DM patients, age, duration of DM, heart rate and body height increased the risk of prevalence of abnormal VPT; and in non-DM controls, heart rate, body height increased the odds, whereas being fully employed decreased the odds of abnormal VPT. With respect to PSN screened by MNSI examination, DM status, age, female gender, cigarette smoking and working part-time increased the odds, whereas working full-time decreased the odds of PSN in all participants. In DM patients, age and female gender increased the odds of PSN, whereas diastolic pressure decreased the odds of PSN. In non-DM controls, alcohol use, cigarette smoking and working part-time increased the odds of PSN, whereas working full-time decreased the odds of PSN (Table 2).

Table 1
General characteristics of study participants

	All participants (n = 821)	Diabetes patients (n = 491)	Non-diabetes controls (n = 330)	p
Age, yrs	52.6 ± 10.5	54.4 ± 10.4	51.9 ± 10.2	0.101
Gender (male), n (%)	368 (45.1)	212 (26)	156 (19.1)	0.79
Duration of diabetes, yrs		7.1 ± 6.2		
Hypertension, n (%)	399 (48.7)	324 (39.6)	75 (9.1)	<0.001
BMI, kg/m^2	27.9 ± 7.8	29 ± 8.7	26.3 ± 5.8	<0.001
Height, cm	163 ± 11	162 ± 13	164 ± 8	0.038
Waist girth, cm	94 ± 24	95 ± 12	93 ± 34	0.442
Waist–hip ratio	0.93 ± 0.21	0.94 ± 0.07	0.91 ± 0.31	0.061
Systolic BP, mmHg	135 ± 26	144 ± 24	121 ± 22	<0.001
Diastolic BP, mmHg	80 ± 13	84 ± 13	74 ± 10	<0.001
Pulse BP, mmHg	55 ± 19	60 ± 18	48 ± 18	<0.001
Mean BP, mmHg	98 ± 15	104 ± 15	90 ± 11	<0.001
Heart rate, bpm	80 ± 13	82 ± 13	76 ± 12	<0.001
Smoking, n (%)				0.034
Current	36 (4.4)	10 (1.2)	26 (3.2)	
Former	140 (17.1)	102 (12.4)	38 (4.7)	
Never	635 (77.3)	367 (44.7)	268 (32.6)	
Second-hand smoking	121 (14.7)	73 (8.9)	48 (5.8)	0.078
Alcohol, n (%)	225 (27.4)	115 (14)	110 (13.4)	0.002
Educational level				0.344
Up to elementary school	496 (60.5)	302 (36.9)	194 (23.6)	
Higher than elementary	322 (39.5)	185 (22.7)	137 (16.8)	
Employment				0.043
Unemployed	322 (39.2)	208 (25.3)	114 (13.9)	
Part-time employment	49 (6)	27 (3.3)	22 (2.7)	
Full-time employment	450 (54.8)	257 (31.3)	193 (23.5)	
Diabetes medication, n (%)				0.012
Oral hypoglycaemics		318 (38.7)		
Insulin		68 (8.3)		
Insulin and oral hypoglycaemics		103 (12.5)		
MNSI symptom score	2.5 ± 2.1	2.9 ± 1.8	2 ± 1.5	<0.001
MNSI examination score	2.2 ± 1.9	2.7 ± 2	1.5 ± 1.5	<0.001
Leg-specific VPT				
Left great toe	16.1 ± 8.9	18.2 ± 9.1	13 ± 7.5	<0.001
Right great toe	15.3 ± 8.6	17.5 ± 9.2	12.2 ± 6.3	<0.001
Neuropathy, n (%)				
VPT ≥25 V	163 (18.6)	125 (15.2)	28 (3.4)	<0.001
MNSI symptom score ≥7	40 (5.3)	35 (4.7)	5 (0.6)	<0.001
MNSI examination score ≥2.5	334 (40.7)	253 (30.8)	81 (9.9)	<0.001

Table 2
Determinants of peripheral sensory neuropathy from multivariable logistic regression model

	All participants		Diabetes patients		Non-diabetes	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Abnormal VPT (≥25 V)						
Diabetes	3.66 (2.26–5.95)	<0.001				
Age	1.04 (1.02–1.06)	<0.001	1.05 (1.03–1.07)	0.001		
Duration of diabetes			1.19 (1.03–2.140	0.021		
Heart rate	1.02 (1.01–1.03)	0.047	1.03 (1.01–1.05)	0.019	3.17 (1.15–8.7)	0.025
SHS	1.78 (1.08–2.92)	0.023	–	–		
Height	3.28 (1.65–8.42)	0.015	2.33 (1.47–5.69)	0.01	2.01 (1.24–6.1)	0.006
Employed (reference: unemployed)						
Part-time					2.84 (0.97–10.1)	0.067
Full-time					0.37 (0.14–0.95)	0.043
Abnormal MNSI examination score (≥2.5)						
Diabetes	4.31 (2.94–6.31)	<0.001				
Age	1.03 (1.01–1.05)	<0.001	1.03 (1.01–1.06)	0.002		
Female	1.33 (0.96–1.83)	0.085	1.48 (1.01–2.18)	0.046		
Insulin use	1.59 (0.92–2.77)	0.1	1.68 (0.96–2.92)	0.068		
Alcohol	1.44 (1–2.08)	0.051			2.21 (1.15–4.25)	0.017
Systolic BP			1.01 (1–1.02)	0.077		
Diastolic BP			0.98 (0.95–0.99)	0.018		
Smoking (reference: non-smoking)						
Previous	4.55 (2.11–9.82)	<0.001			4.81 (1.98–11.66)	0.001
Current	8.16 (3.77–17.68)	<0.001			9.53 (4.1–22.15)	<0.001
Employment status (reference: unemployed)						
Part-time	2.46 (1.23–4.92)	0.011			3.45 (1.29–9.21)	0.014
Full-time	0.77 (0.54–1.11)	0.155			0.48 (0.25–0.94)	0.032

Variables in the model included DM status, hypertension status, insulin therapy, age, body height, BMI, employment status, education, duration of DM (DM patient group), alcohol intake, smoking status, second-hand smoking, systolic, diastolic, mean and pulse BPs. Backward conditional logistic regression model was applied.

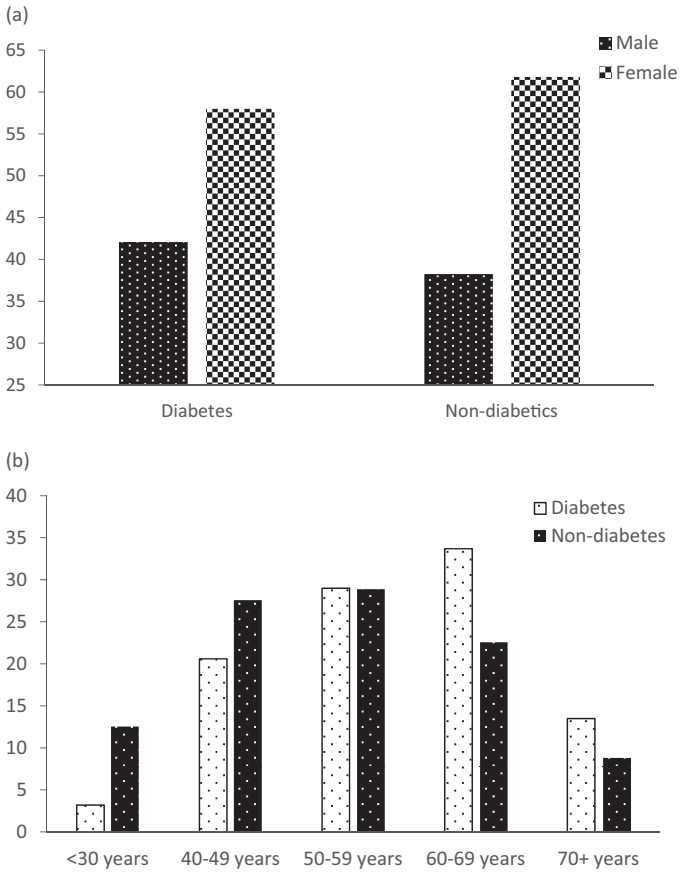

Figure 1. a). Gender distribution of peripheral sensory neuropathy by MNSQ examination score (≥2.5). b). Distribution of peripheral sensory neuropathy by MNSQ examination (≥2.5) across age decades.

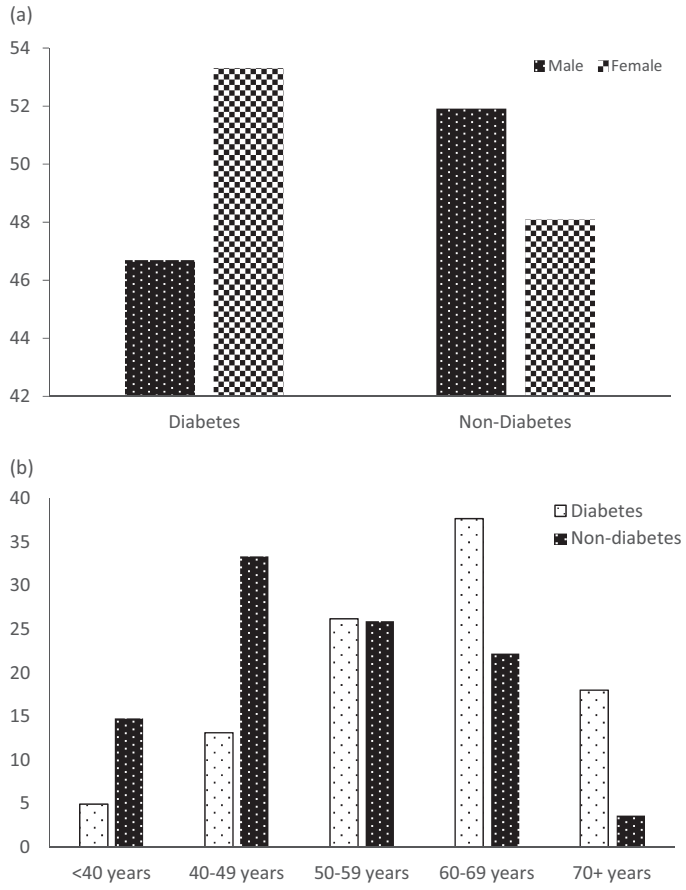

Figure 2. a). Gender distribution of peripheral sensory neuropathy by VPT (≥25V). b). Distribution of peripheral sensory neuropathy by VPT (≥25V) across age decades.

Discussion

PSN is a frequent complication of DM which has been diagnosed, historically, using symptoms, signs, quantitative sensory testing and electrophysiological studies [8]. In Africa, few studies that reported the burden of PSN in DM patients used questionnaire instrument or semi-quantitative methods [4]. These studies are normally cross-sectional survey without appropriate non-DM controls for comparison. In our study, we used case-control design for comparison of PSN burden in DM patients and non-DM controls. Also, PSN was simultaneously diagnosed using symptom score, physical examination and quantitative sensory test. The findings of this study shows that the prevalence of PSN screened by MNSI symptom score, MNSI examination score and VPT was 7.1%, 51.5% and 24.5% in DM patients and 1.5%, 24.5% and 8.5% in non-DM participants respectively. The major determinants of PSN by MNSI examination score were diabetes status, age, female gender, insulin therapy, alcohol use and employment status. Also, significant determinants of PSN by abnormal VPT were diabetes status, age, heart rate, second-hand smoking and body height in all the participants.

The prevalence of PSN in Africa varies widely partly due to design of the study, sample selection, and different diagnostic criteria employed (pin-prick perception, clinical signs and symptoms or semi-quantitative sensory tests). Similar to the findings of our study, the prevalence of PSN in diabetes patients was reported to be 48.2% and 47.1% in Ethiopia [12] and Libya [13], respectively, when screened with questionnaire instrument. However, in Cameroon, the prevalence of PSN was reported to be 28% using symptom score from clinical examination [14] and 27.3% using vibration perception from a tuning fork [15]. From our literature search, we found no study reporting the burden of PSN in non-DM sub-Saharan African population using quantitative sensory test like the VPT. Our findings indicate that, compared to DM patients, the prevalence of PSN in non-DM population is low, but gender and age-decade distribution of PSN in non-DM participants were similar to DM patients. The findings of this study also show that PSN patients are prone to work part-time, giving an indication that PSN may be associated with less productivity and economic cost [16].

The objective methods of assessing PSN are nerve conduction studies and skin biopsies [3]. However, these methods are robust requiring specially trained and experienced personnel, and may be invasive as well, precluding their utility in resource-deprived sub-Saharan African setting. Therefore, simple non-invasive clinical test, like the MNSI, that assesses symptoms and signs of PSN can be easily be applied in sub-Saharan African setting [17]. Since its introduction, the MNSI [9] has been widely used to assess PSN in clinical practice and in large clinical trials, including the DCCT/EDIC [18], ACCORD studies [19] and BARI 2D [20]. The MNSI has been validated to be accurate, reproducible, and well correlated with neurologist confirmed PSN [21]. Since the questionnaire items in MNSI depend on the ability of the patient to understand and recall appropriately the symptoms being described, patient-recall bias may affect the performance of MNSI in screening for PSN.

VPT is the recommended method of assessing PSN in populations-based studies. VPT may provide important, clinically meaningful information about large nerve fibre dysfunction in diabetes. The

neurological symptoms associated with large fibre neuropathy may account for about 80% of the morbidity associated with PSN in DM patients [3,8]. Abnormal VPT values had been shown to predict the long-term complications of ulceration and amputation [6,22]. Some critics of VPT testing suggest that it is not a sufficient measure of peripheral nerve dysfunction and the results may be device-biased [23], patient-dependent, affected by level of the patient's attentiveness, motivation, and fatigue [24]. In our study, to ensure full patient's cooperation, we thoroughly explained the procedure of neurothesiometry to the participants, the nature of vibration expected was demonstrated on the arm before the test began, and those with conflicting VPTs were excluded from analysis. VPT testing was simple, quick to perform, painless, and generally well tolerated by our study participants.

The results of this study indicate that in both diabetes and non-diabetes participants, MNSI examination score captured the highest number of participants with PSN, followed by VPT, with MNSI symptom score capturing the lowest number of PSN. As a questionnaire tool, MNSI symptom score may be limited by the patient's understanding and ability to appropriately recall the symptoms involved. MNSI symptom score assesses general symptoms like numbness, burning pain sensation, hypersensitivity and thermal sensitivity, generally associated with small fibre nerve damage [25]. Indeed, MNSI symptom score is reported to reflect loss of long nerve fibre bundle in the cornea and reduced corneal sensitivity [26], markers of damage of small unmyelinated fibres. In prediabetes patients, damage to small nerve fibres is more common, but in diabetes patients, large nerve fibre damage predominates sensory neuropathies [27]. Both MNSI examination and VPT involve assessment of large nerve functions, which are most vulnerable to infarction in diabetes patients. In MNSI examination, a physician specialist carefully examines foot symptoms, and also utilises standardised techniques to screen for nerve damage assessment. However, the outcomes of these screenings are binary (present or absent) and hence, cannot measure the degree of nerve damage. The VPT can independently assess the degree of large nerve damage and was previously used as the gold method for neuropathy assessment [8].

The limitations of this study include cross-sectional data collection, so we cannot infer causality or assess predictive utility of the methods used to screen for PSN. Also, diabetes patients in the study were recruited from a tertiary referral hospital and hence, the findings of this study cannot be generalised to the entire diabetes patients in Ghana. In addition, no plasma markers were measured to evaluate the pathophysiological mechanisms underlying PSN in sub-Saharan African population. The major strength of our study is large sample size, with DM patients systematically selected, and comparable age and gender of non-DM controls.

Conclusion

In summary, there is high burden of PSN in diabetes patients in our study sample, using simple, non-invasive screening tools, yet accurate tools such as MNSI and neurothesiometer. Future studies may investigate the utility of these assessment tools and the pathophysiological mechanisms underlying PSN in Ghanaian population.

Declarations

Ethics, consent and permissions

The study was conducted in accordance with the Declaration of Helsinki and ethical approval was granted by the University of Ghana Medical School Ethical and Protocol Review Committee (Protocol ID number: MS-Et/M.3 – P.2.10/2009–2010). All participants gave written informed consent after thorough explanation of the procedures involved.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KY cleaned the data, performed the statistical analysis, wrote the manuscript and takes overall responsibility of the content of the manuscript. PP collected data and critically reviewed the manuscript. VB assisted in preparation of manuscript and critically reviewed the manuscript. DAA assisted in the preparation and critically reviewed the manuscript. BG assisted in the preparation and critically reviewed the manuscript. AGBA designed the study, supervised data collection and reviewed the manuscript. All authors read and approved the manuscript.

Availability of data and materials

The dataset supporting the conclusions of this article is readily available for systematic review and meta-analysis upon request.

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Conflict of interest

The authors declare they have no conflicts of interest.

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