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Peripheral sensory neuropathy is associated with circulating angiopoietins in type 2 diabetes patients in Ghana

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ABSTRACT

Objective: Peripheral sensory neuropathy (PSN) is a common complication of type 2 diabetes (T2DM) that can lead to frequent ulcerations, lower extremities, and reduced quality of life. Imbalance in the circulating levels of angiogenic growth factors, notably, angiopoietin (Ang)-1, Ang-2 and vascular endothelial growth factor (VEGF) may be among the underlying mechanisms of PSN in T2DM patients. We studied the association between PSN and angiogenic growth factors, Ang-1, Ang-2 and VEGF in T2DM patients in Ghana.

Methods: In a case-control study design, PSN was evaluated in 160 patients with T2DM and 108 nondiabetic controls using vibration perception threshold (VPT) and diabetic neurological examination (DNE). The definition of PSN was abnormal VPT ($\geq$25 mV) or the presence of neuropathic symptoms on examination (DNE score $>$ 3). In addition, fasting venous blood samples were collected to measure circulating levels of Ang-1, Ang-2 and VEGF.

Results: Compared to non-diabetic controls, patients with T2DM had a higher prevalence of PSN using abnormal VPT (20.6 % vs 2.8 %, $p < 0.001$) or neuropathic symptoms (35.6 % vs 3.7 %, $p < 0.001$). Compared to nondiabetic controls, patients with T2DM had increased levels of Ang-2 [597 (274 – 1005) vs 838 (473 – 1241) ng/ml, $p = 0.018$] and VEGF [48.4 (17.4 – 110.1) vs 72.2 (28 – 201.8), $p = 0.025$] and decreased Ang-1 levels [41.1 (30 – 57.3) vs 36.1 (24.7 – 42.1) ng/ml, $p = 0.01$]. In regression analyses, an increase in Ang-1 levels was associated with decreased odds, while an increase in Ang-2 levels was associated with increased odds, of abnormal VPT and neuropathic symptoms in T2DM patients.

Conclusion: In our study population, PSN was associated with reduced plasma levels of Ang-1 and increased plasma levels of Ang-2 in patients with T2DM. Therefore, an imbalance of angiopoietins may be associated with PSN in T2DM.

Introduction

Damage to the peripheral nerves is a common and intractable complication of diabetes with the sensory and autonomic nerves generally affected [1]. Diabetic peripheral sensory neuropathy (PSN) is estimated to affect 7 % of patients within the first year of diabetes diagnosis and this can rise to about 50 % for those living with diabetes for over 25 years [2]. When we consider patients with asymptomatic neuropathic abnormalities as well, the prevalence of PSN might even exceed 90 % [3]. Compared to patients without PSN, patients with PSN had increased mortality [4] and lower limb amputation, which occurs in 1 to 2 % of diabetes patients at an extreme economic cost [3,5]. In Ghana, data from the main referral hospital indicate that diabetes is a major cause of nontraumatic lower limb amputation, accounting for $>$ 90 % of such amputations [6]. Several efforts have been made to diagnose PSN early to slow its progression in diabetes patients; however, there is presently no effective treatment available except for tight control of risk factors. This may be due to vague mechanisms and presentations of PSN that do not reflect the clinical course of the disease [1,7]. The manifestations of PSN in diabetes patients depend on the type of nerve fibre involved (small or large) and the organs that these nerves supply. PSN may be presented as symmetric sensory-motor axonal neuropathy, proximal asymmetric painful motor neuropathy, mononeuropathy, and autonomic neuropathy which mainly involves small nerve fibres [6,8]. There have been several metabolic, inflammatory and cellular signalling defects have been postulated to underline the

Abbreviations: PSN, peripheral sensory neuropathy; Ang, angiopoietins; VEGF, vascular endothelial growth factor; VPT, vibration perception threshold.

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development of PSN in diabetes patients. Prominent among these pathophysiological processes of nerve damage in diabetes patients include microangiopathy leading to disruption of the blood-nerve barrier, lipid peroxidation and oxidative stress [8,9].

Angiogenic growth factors are synthesised and released by body tissues to regulate the growth and proliferation of small blood vessels [10]. The widely reported angiogenic growth factors in medical research include vascular endothelial growth factor (VEGF), angiopoietin 1 (Ang-1) and angiopoietin 2 (Ang-2) [11]. Ang-1 is secreted primarily by non-endothelial cells, including pericytes, whereas Ang-2 is predominantly expressed in endothelial cells, stored in Weibel-Palade bodies, and is rapidly released in response to specific stimuli [10,11]. Ang-1 regulates the circumferential growth required for vessel maturation and stabilisation, while Ang-2 / VEGF promotes vessel proliferation. Vascular dysfunction has been involved in the pathogenesis of PSN in diabetes patients [12], as demonstrated by high-grade microangiopathic changes in endoneurial microvessels from nerve biopsy predict the development of evident neuropathy in people with abnormal glucose metabolism [13]. Abnormalities in endoneurial capillaries are related to the expression of angiogenic growth factors [14]. Furthermore, angiopoietins and VEGF have been reported to have direct effects on neurons in the peripheral and central nervous system, such as inhibition of neuronal apoptosis and promotion of neurite outgrowth [15]. Therefore, we studied the plasma levels of angiogenic growth factors in T2DM patients with PSN diagnosed using vibration perception threshold (VPT) and diabetic neurological examination (DNE). We hypothesized that, compared to T2DM patients without PSN, those with PSN would have an imbalance in the circulating levels of angiogenic growth factors.

Methods

Study design and subjects

This study was a case-control design, conducted from December 2019 to August 2020, at the Korle-Bu Teaching Hospital in Accra, which is a tertiary hospital and serves as the main referral hospital in Ghana. The study population was selected from two sources: (1) diabetes patients, selected systematically as every 3rd consecutive patient visiting the diabetes clinic and consented to take part in the study, and (2) non-diabetic individuals, invited from the surrounding communities and conveniently recruited into the study. Individuals with non-traumatic limb amputation and those unable to comprehend and comply with the protocol requirements (psychological and/or cognitive disorders, failure to cooperate, and failure to sign the informed consent document) were excluded from the study. In all, 268 subjects, comprising 160 diabetes patients and 108 non-diabetic individuals were screened for PSN. The study was approved by the University of Ghana Medical School Ethical and Protocol Review Committee (Protocol ID number: MS-Et/M.2 – P.4.10/2016–2017) and all participants gave their written informed consent after thoroughly explaining the procedures involved in the study, following the general recommendations of the Declaration of Helsinki.

Anthropometry and BP measurement

We measured body weight, height, waist and hip circumferences using standard protocol [16]. Briefly, body weight was determined twice using a homologated electronic scale (Seca 770) following due calibration (precision $\pm$ 0.1 kg), with the patient wearing light clothing with shoes removed. Height was also measured with a portable system (Seca 222) with the patient without shoes in an upright position. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured with a nonelastic tape measure at the upper border of the iliac crest, parallel to the floor without compressing the skin. Blood pressure was measured three times, with a validated Blood Pressure Monitor (Omron 991X, Omron Health Care, Japan), at the right upper arm of participants with an appropriate cuff size, after at least 5 mins rest, seated comfortably with arm and back support. Hypertension was defined as subjects with BP $\geq$ 140/90 mmHg and/or on antihypertensive medication.

Neurothesiometry and diabetic neurological examination

Neurothesiometry was performed using a handheld neurothesiometer (Horwell Neurothesiometer, Scientific Laboratory Supplies Ltd, Nottingham, UK) to read the vibration perception threshold (VPT) from the apex of the big toe of both legs, with the subject in a supine position, feet elevated with pillow support, and eyes closed as we previously reported [6,17]. Participants who failed to provide 3 consistent values of VPT within 5 V after seven measurements were excluded from the analysis as having conflicting VPTs. The higher VPT values between the left and right legs were used as the VPT value for the patient and the cut-off points for abnormal VPT were calculated as the VPT $\geq$ 25 mV.

Diabetic neuropathy examination (DNE) was performed on all T2DM patients by an experienced clinician on the dominant foot. The DNE is a hierarchical physical examination consisting of eight items with a total score of 16. The DNE score involved the summation of outcomes of eight series of assessments that include muscle strength by extension of the knee and dorsiflexion of the foot, tricep surae reflex, pinprick to test the sensitivity on the finger and sensitivity of the toes assessed by pinprick, vibration sensation, sensitivity to touch and joint sensitivity. Each assessment was scored 0 – 2, with zero being normal, one representing mild–moderate impairment and two being severe impairment. A DNE score $>$ 3 defines the presence of neuropathy [18].

Biochemical analysis

Venous blood samples were collected early morning after fasting overnight and processed to measure plasma glucose (FPG), plasma glucose 2 h after glucose load (2 h PPG) for nondiabetic controls, glycated haemoglobin (HbA1c), total lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL), and triglyceride using a biochemical analyser (BC 400, Contec, China) and commercial reagents (Randox Laboratory Reagents, UK). Low-density lipoprotein cholesterol levels were calculated using Friedewald's formula.

Plasma levels of Ang-1, Ang-2, and VEGF were measured by sandwich enzyme-linked immunosorbent assay using commercially available enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN). The assays were performed according to the manufacturer's recommendations and the total inter-assay coefficient of variation for the three assays was $<$ 7 %. The lowest detection limits for the various analytes were 0.03 ng/ml for VEGF, 0.16 ng/ml for Ang-1 and 100 pg/ml for Ang-2.

Statistical analysis

Continuous data were analysed with the Shapiro-Wilk test to determine their distribution, and skewed variables were logarithmically transformed before analysis. Data for angiogenic growth factors were skewed, and hence logarithm transformation was applied before incorporation into regression models. Variables with normal distribution were presented as mean $\pm$ standard deviation and analysed using the student's *T*-test or analysis of variance, as appropriate. Variables with non-normal distribution were presented as median and interquartile range and analysed using the Mann-Whitney *U* test or Kruskall Wallis test, as appropriate. Categorical data were analysed using the χ^2 test. Logistic regression models were performed to compute adjusted and unadjusted odd ratios between PSN and angiogenic growth factors.

Results

Characteristics of study participants

T2DM patients were similar to nondiabetic controls in terms of average age, sex, hypertension, anthropometric indices, blood pressure indices and plasma triglyceride levels. T2DM patients had higher levels of VPT, FPG, HbA1c and plasma cholesterol. Regarding angiogenic growth factors, T2DM patients had higher levels of Ang-2 and VEGF, and lower levels of Ang-1 compared to non-diabetic controls (Table 1). Concerning the management of T2DM, 38 (23.8 %) patients were on lifestyle and diet, 101 (63.1 %) patients were on oral hypoglycaemics only and 21 (13.1 %) patients were on both insulin and oral hypoglycaemics management.

Prevalence of PSN

Concerning PSN, T2DM patients had a higher prevalence of abnormal VPT (VPT $\geq$ 25 mV) and neuropathic symptoms (DNE > 3) (Fig. 1). Concerning the various components of DNE, 59 (36.9 %) and 60 (37.9 %) T2DM patients had reduced muscle strength in the quadriceps femoris and tibialis anterior muscles respectively, as well as 39 (24.4 %) T2DM patients had decreased triceps surae reflex. Sensitivity to touch on the index finger and toe, as well as sensitivity to pinpricks on the toe, were decreased in 21 (13.1 %), 37 (23.1 %) and 11 (6.9 %) T2DM patients respectively, and absent in 5 (3.1 %), 9 (5.6 %) and 6 (3.8 %) of T2DM patients respectively. Perception of vibration on the big toe was diminished in 45 (28.1 %) and absent in 35 (21.3 %) T2DM patients. Joint position sensation was reduced in 18 (11.3 %) and absent in 3 (1.9 %) T2DM patients. In the non-diabetic controls, 8 (7.4 %) and 5 (4.6 %) had reduced muscle strength in the quadriceps femoris and tibialis anterior muscles respectively; 4 (3.7 %) had decreased triceps surae reflex. Sensitivity to touch on the index finger and toe, as well as sensitivity to pinpricks on the toe, were decreased in 5 (4.6 %), 10 (9.3 %) and 9 (8.3 %) participants, respectively; perception of vibration on the big toe was decreased in 13 (12 %) participants and position sensation was reduced in 2 (1.9 %) participants. None of the nondiabetic participants had any insensitivity to touch, pinpricks and vibration.

Table 1
General characteristics of study participants by diabetes status.

	All participants (n = 268)	T2DM patients (n = 160)	Non-diabetic controls (n = 108)	p
Age, yrs	54.1 ± 10.2	53.7 ± 10.1	54.6 ± 10.3	0.54
Females, n (%)	134 (50)	72 (45)	61 (56.5)	0.065
Hypertension, n (%)	164 (61.2)	104 (61.9)	39 (36.1)	0.12
Diabetes management				
Lifestyle & diet		38 (23.8)		
Oral hypoglycaemics		101 (63.1)		
Insulin and oral hypoglycaemics		21 (13.1)		
Weight, kg	79.5 ± 14.9	79.9 ± 15.5	79 ± 14.3	0.672
Height, cm	166 ± 8.4	167 ± 8	164 ± 9	0.061
BMI, kg/m^2	29.1 ± 5.7	28.9 ± 5.9	29.4 ± 5.5	0.571
Waist circumference, cm	98 ± 14	99 ± 12	96 ± 15	0.073
Waist-hip ratio	0.91 ± 0.11	0.92 ± 0.07	0.9 ± 0.14	0.382
Systolic BP, mmHg	139 ± 30	141 ± 26	135 ± 34	0.174
Diastolic BP, mmHg	83 ± 13	83 ± 13	82 ± 14	0.594
Pulse BP, mmHg	59 ± 14	59 ± 14	58 ± 13	0.485
Heart rate, bpm	71 ± 17	75 ± 13	65 ± 19	<0.01
FPG, mmol/l	6.9 ± 3.2	8.4 ± 2.9	5 ± 2.5	<0.01
2 h-PPG, mmol/l	7.8 ± 1.4		7.8 ± 1.4	
Triglycerides, mmol/l	1.1 ± 0.5	1.1 ± 0.5	1.2 ± 0.6	0.586
Total cholesterol, mmol/l	4.7 ± 1.5	5.5 ± 1.4	3.9 ± 1.1	<0.001
HDL cholesterol, mmol/l	0.9 ± 0.2	0.7 ± 0.2	1.2 ± 0.4	0.025
LDL cholesterol, mmol/l	3.2 ± 1.4	3.9 ± 1.3	2.7 ± 1.4	<0.001
HbA1c, %	7.8 ± 3.2	9.7 ± 3.4	5.3 ± 1.6	<0.001
Angiopoietin-1, ng/ml	38.2 (25.7 – 47.9)	36.1 (24.7 – 42.1)	41.1 (30 – 57.3)	0.01
Angiopoietin-2, ng/ml	740 (392 – 1107)	838 (473 – 1241)	597 (274 – 1005)	0.018
VEGF, pg/ml	63.2 (21.2 – 157.8)	72.2 (28 – 201.8)	48.4 (17.4 – 110.1)	0.025
VPT, mV	8.9 ± 6.2	18.1 ± 7.8	6.3 ± 3.8	<0.001

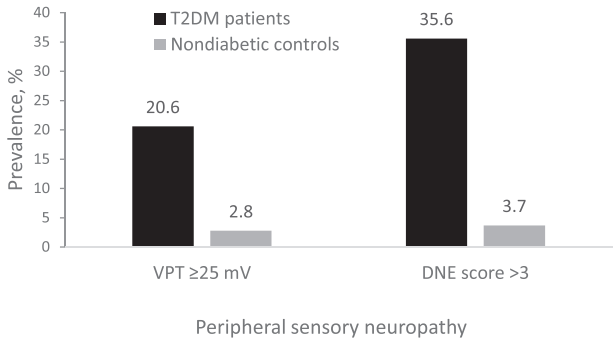

Fig. 1. Prevalence of peripheral sensory neuropathy among study participants.

PSN and angiogenic growth factors

Compared to patients with VPT < 25 mV, T2DM patients with VPT $\geq$ 25 mV had lower levels of Ang-1 and higher levels of Ang-2. No significant difference in VEGF levels was observed between T2DM patients with and without abnormal VPT (Fig. 2). Similarly, compared to patients without overt neuropathic symptoms, T2DM patients with neuropathic symptoms (DNE score > 3) had lower levels of Ang-1 and higher levels of Ang-2. There was no significant difference in VEGF levels between T2DM patients with and without neuropathic symptoms (Fig. 3).

Association between PSN and angiogenic growth factors

In both univariate and multivariate logistic regression analyses, an increase in log Ang-1 level was associated with decreased odds of abnormal VPT, while an increase in log Ang-2 was associated with increased odds of abnormal VPT. In addition, an increase in log Ang-1 levels was associated with decreased odds of neuropathic symptoms and an increase in log Ang-2 was associated with increased odds of neuropathic symptoms in unadjusted and adjusted models. There was no association between VEGF and abnormal VPT or neuropathic symptoms in T2DM patients (Table 2).

Discussion

The findings of this study are (1) PSN, assessed abnormal VPT or DNE, was common in T2DM patients in Ghana, (2) T2DM patients had decreased plasma Ang-1 levels and increased plasma levels Ang-2 and VEGF, and (3) in T2DM patients, Ang-1 was associated with decreased odds of having PSN whereas Ang-2 was associated with increased odds of having PSN. Previous studies in Ghana have reported an imbalance in angiogenic growth factors in T2DM patients and associated it with reduced glomerular filtration rate [19] and peripheral arterial disease [20]. The current study is among the few reported study that has investigated the association between angiopoietins and PSN assessed by VPT and neuropathic symptoms in T2DM.

In this study, the prevalence of PSN by VPT and DNE were 20.6 % and 35.6 % in T2DM patients and 2.8 % and 3.7 % in nondiabetic

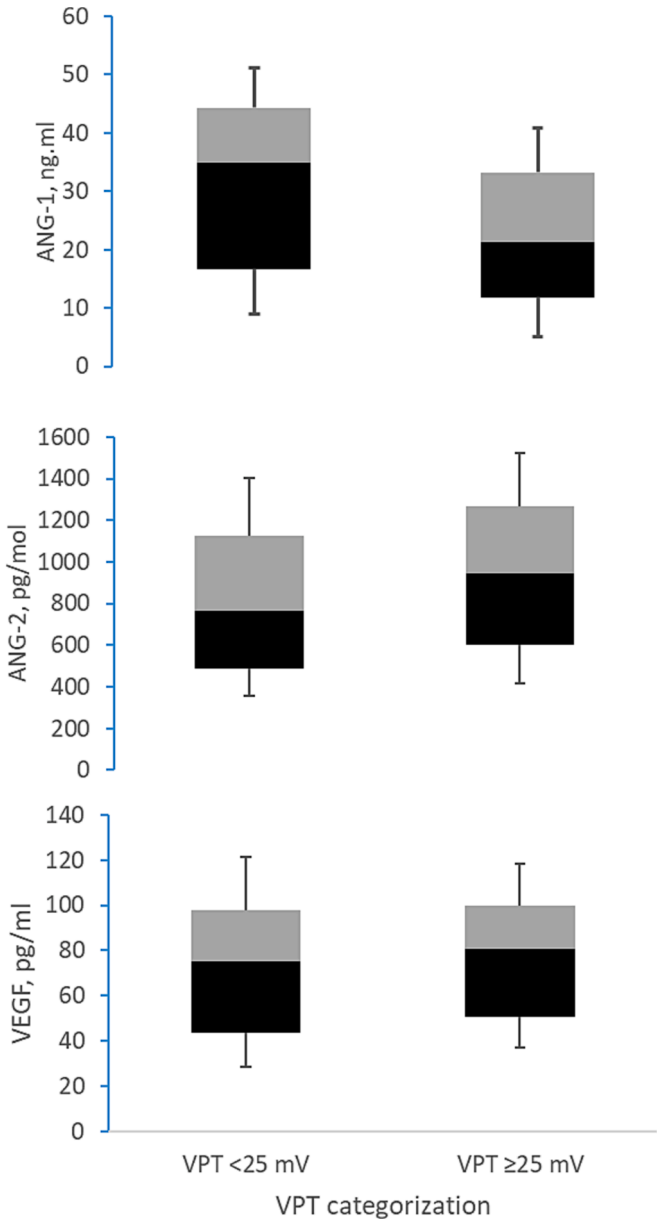

Fig. 2. Levels of angiogenic growth factors by VPT categorization among T2DM patients.

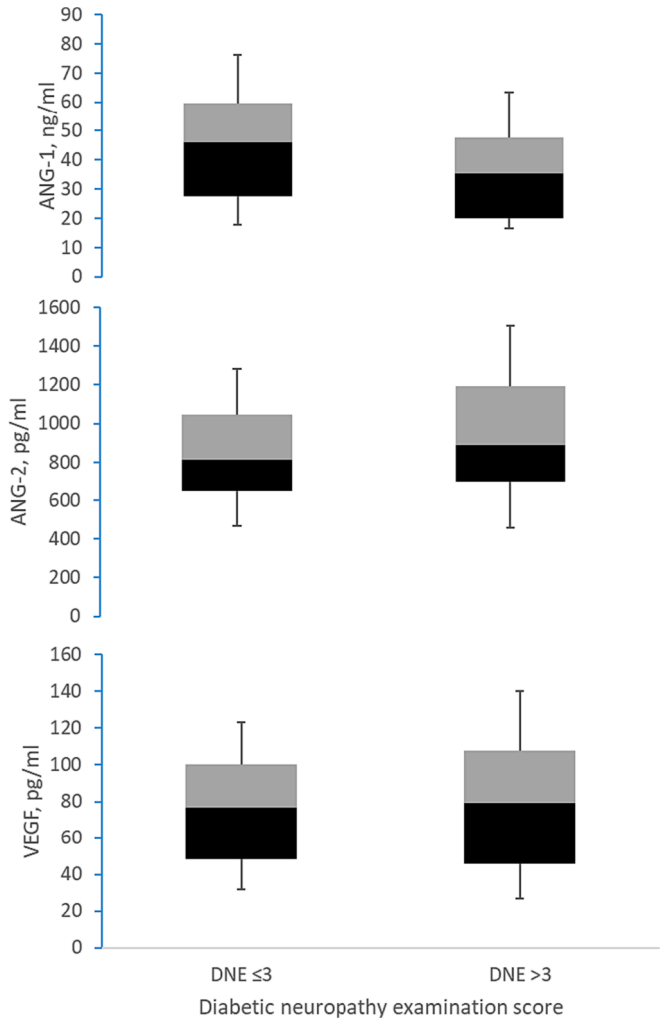

Fig. 3. Levels of angiogenic growth factors by DNE scores among T2DM patients.

Table 2
Association between vascular growth factors and abnormal VPT in T2DM patients (n = 160).

	Angiogenic growth factors	Odds ratio (95 % CI)	p
VPT > 25 mV			
Unadjusted model	Ang-1	0.73 (0.36 – 0.92)	0.002
	logAng-2	2.41 (1.19 – 5.69)	0.006
	logVEGF	1.51 (0.73 – 5.81)	0.201
Adjusted model	Ang-1	0.87 (0.28 – 0.98)	0.018
	logAng-2	1.93 (1.04 – 4.69)	0.031
	logVEGF	2.65 (0.87 – 4.85)	0.139
DNE score > 3			
Unadjusted model	Ang-1	0.84 (0.37 – 0.91)	0.031
	logAng-2	2.63 (1.28 – 4.07)	<0.001
	logVEGF	2.11 (1 – 7.61)	0.067
Adjusted model	Ang-1	0.88 (0.32 – 0.97)	0.044
	logAng-2	1.75 (1.05 – 4.01)	0.045
	logVEGF	1.96 (0.94 – 5.02)	0.098

The adjusted model includes age, gender, hypertension, BMI, diabetic medication/management, total cholesterol and triglyceride levels.

controls respectively. The prevalence of PSN in non-diabetic controls in our study is consistent with the report of peripheral neuropathies in the general population, which is within the range of 1 – 7 % [21], and this has been attributed to alcoholism [22], vitamin deficiency [23], chronic exposure to recreational drugs and heavy metal [24] and medications [8,21]. The prevalence of PSN in T2DM patients in the current study is consistent with our previous studies in T2DM patients that reported the prevalence of PSN to be 15.2 % using VPT ≥ 25 [6] and 16.6 % using VPT > 97.5th percentile of age and gender-adjusted cut-off [17]. Similarly, the prevalence of PSN was reported in Cameroonian T2DM patients to be 33.3 % by the DNE score > 3 [18]. A recent *meta*-analysis estimated the prevalence of PSN in diabetes patients in sub-Saharan Africa to be 46 %; however, most of the studies included in this analysis used standardised neuropathy questionnaires that have not been validated for the local populations [25]. The use of a neuropathic symptoms questionnaire without appropriate psychometric testing and validation may result in erroneous scoring and categorization of study participants [26–28]. This is the reason we chose to employ VPT and DNE to screen for PSN in this study instead of a symptomatic score.

The findings of this study indicate disruption of the balance in the levels of angiogenic growth factors in T2DM patients leading to increased expression of Ang-2 and VEGF and inhibition of Ang-1 expression, and this is consistent with our previous studies in T2DM

patients in Ghana [19,20]. The reduction in Ang-1 levels and increase in Ang-2 levels observed in T2DM patients with PSN in this study is consistent with the findings in Austrian [29], British [30] and Saudi [31] T2DM patients. Hyperglycemia and inflammation, common in T2DM disease, increase the expression and release of Ang-2 and this suppresses the expression of Ang-1, resulting in decreased neuroprotection activity. Concerning VEGF levels, regardless of higher levels in T2DM patients compared to non-diabetic controls, we did not find any differences in VEGF between T2DM with and without PSN. This is consistent with a study in Greek T2DM patients that reported no difference in circulating VEGF levels between patients with and without peripheral polyneuropathy [32]. In contrast to our findings, Sugimoto et al reported that the expression of immunoreactive VEGF in the skin microvessels was lower in T2DM patients with PSN compared to those without PSN [33].

Angiopoietins have direct effects on nerve functioning and survival, and imbalance may result in neuropathy [15]. For example, Ang-1 has been reported to be neuroprotective by suppressing neural apoptosis through the activation of phosphatidyl-inositol 3-kinase [34] and favours neurite outgrowth in cultured dorsal root ganglion cells [35]. In addition, Ang-1 can oppose cell death in neurons exposed to oxygen-glucose deprivation/recovery [9] and in nerve injury, there is microRNA-targeted Ang-1 mRNA to reduce Ang-1 expression [36]. Therefore, reduced levels of Ang-1 may have adverse effects on nerve function as observed in T2DM patients with PSN in this study. Indirect effects of angiopoietins may also be through their effects on the microvessel, with imbalanced levels of Ang-1 and Ang-2 leading to microvascular disorganization which can affect nutrient and oxygen delivery to nerves [11,15]. As demonstrated in ultrastructural morphometric analysis, diabetic patients with neuropathy have abnormalities in the capillaries that supply the main peripheral nerves, such as a significant reduction in the endoneurial capillary density and thickening of the capillary basement membrane [13,37]. Peripheral nerves have few transperineurial arterioles penetrating their endoneurium, resulting in sporadic arteriolar perfusion of peripheral nerves and this can be severely compromised when there is an imbalance in angiopoietins levels in diabetes [38]. Furthermore, the mechanisms of PSN are similar to that of renal dysfunction which has been reported to cause an imbalance in the levels of circulating angiogenic growth factors [39]. Further studies can investigate the expression of the angiogenic growth factors in PSN patients with and without renal dysfunction.

Limitations of the study

The objective assessment of PSN may include nerve conduction studies and skin biopsies, which are physician/patient independent [7]. However, these methods may require sophisticated equipment and set-up that may limit their application in the poor-resourced sub-Saharan African setting. In this study, we used DNE and VPT independently for the diagnosis of PSN. The DNE has been reported to have comparable discriminatory potential as nerve conduction studies in diabetes patients [40]. Neurological findings associated with nerve functions performed on DNE tests may account for the morbidity associated with PSN in T2DM patients [1,7]. In addition, abnormal VPT values have been reported to predict the long-term complications of ulceration and amputation [41,42], and hence, they can be employed in epidemiological studies. However, the utility of VPT for the diagnosis of PSN may be limited by the bias of the device used [43] and patient factors such as attention, motivation, and fatigue [44]. In our study, a deliberate effort was made to ensure that the participants understood the procedure and cooperated fully during VPT measurements.

The design of this study, cross-sectional data collection, implies that we cannot infer causality; whether an imbalance of angiogenic growth factors results in PSN or PSN precedes aberration in circulating levels of angiogenic growth factors. Additionally, the diabetes patients were recruited from tertiary health institutions, and therefore, the findings may differ from diabetes patients recruited from primary health care centres across Ghana. In addition, we did not collect information on all medications used by T2DM patients and non-diabetic controls. It may be possible that current or previous medications taken by T2DM patients and non-diabetic controls may have potentially impacted the angiogenic factor levels.

Conclusion

In this study, compared to nondiabetic controls, T2DM patients had a high prevalence of PSN assessed by VPT and DNE. T2DM patients had low Ang-1 levels and high Ang-2 and VEGF levels compared to nondiabetic controls. Furthermore, a decrease in Ang-1 levels and an increase in Ang-2 levels were associated with a higher probability of PSN.

Declarations

Ethics approval and consent to participate

The study was conducted in conformity with the Helsinki Declaration on Human Experimentation, 1964 with subsequent revisions, latest Seoul, October 2008. Ethical approval for the study was granted by the Ethics and Protocol Review Committee of the College of Health Science, the University of Ghana (Protocol ID number: MS-Et/M.2 – P.4.10/2016–2017). All the participants provided voluntary written consent before being recruited into the study.

Consent for publication

Not applicable.

Availability of data and materials

The data set supporting the conclusion of this study is available for systematic review and *meta*-analysis upon request.

Funding

There was no funding for this study.

Authors' contributions

KY contributed to the conception, design, data collection & and analysis and bears the primary responsibility for the content of the manuscript. JAA performed laboratory analysis, curated the data and drafted the initial manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Boulton AJM, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: A statement by the American Diabetes Association. Diabetes Care 2005;28(4):956–62.
[2] Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973. Diabetes Care 1978;1(3):168–88.
[3] Vinik AI, Holland MT, Beau JML, Liuzzi FJ, Stansberry KB, Colen LB. Diabetic neuropathies. Diabetes Care 1992;15(12):1926–75.
[4] Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation 2007;115(3):387–97.
[5] Rodríguez-Sánchez B, Sinclair A. Chapter 13 - Health economics of diabetic foot disease: costs of diabetic neuropathy and diabetic foot. In: Tavakoli M, editor. Diabetic neuropathy. Elsevier; 2022. p. 211–21.
[6] Yeboah K, Puplampu P, Boima V, Antwi DA, Gyan B, Amoah AG. Peripheral sensory neuropathy in type 2 diabetes patients: A case control study in Accra, Ghana. J Clin Transl Endocrinol 2016;5:26–31.
[7] Tesfaye S, Boulton AJM, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010;33(10):2285–93.

[8] Galiero R, Caturano A, Vetrano E, Beccia D, Brin C, Alfano M, et al. Peripheral neuropathy in diabetes mellitus: pathogenetic mechanisms and diagnostic options. Internat J Mol Sci 2023;24(4):3554.
[9] Sabirzhanov B, Faden AI, Aubrecht T, Henry R, Glaser E, Stoica BA. MicroRNA-711–induced downregulation of angiopoietin-1 mediates neuronal cell death. J Neurotrauma 2018;35(20):2462–81.
[10] Koh GY. Orchestral actions of angiopoietin-1 in vascular regeneration. Trends Mol Med 2013;19(1):31–9.
[11] Fagiani E, Christofori G. Angiopoietins in angiogenesis. Cancer Lett 2013;328(1):18–26.
[12] Yeboah K. Arterial stiffness in type 2 diabetes patients in Ghana. PhD dissertation. Accra, Ghana: University of Ghana Library; 2013.
[13] Thrainsdottir S, Malik RA, Dahlin LB, Wiksell P, Eriksson KF, Rosén I, et al. Endoneurial capillary abnormalities presage deterioration of glucose tolerance and accompany peripheral neuropathy in man. Diabetes 2003;52(10):2615–22.
[14] Kusano KF, Allendoerfer KL, Munger W, Pola R, Bosch-Marce M, Kirchmair R, et al. Sonic hedgehog induces arteriogenesis in diabetic vasa nervorum and restores function in diabetic neuropathy. Arterioscler Thromb Vasc Biol 2004;24(11):2102–7.
[15] Yin J, Gong G, Liu X. Angiopoietin: A novel neuroprotective/neurotrophic agent. Neuroscience 2019;411:177–84.
[16] World Health Organization: Waist circumference and waist-hip ratio: Report of a WHO expert consultation. In: 8-11 December 2008 2011; Geneva: WHO; 2011.
[17] Yeboah K, Agyekum JA, Owusu Mensah RNA, Affrim PK, Adu-Gyamfi L, Doughan RO, et al. Arterial stiffness is associated with peripheral sensory neuropathy in diabetes patients in Ghana. J Diab Res 2018;2018:1–8.
[18] Kuate-Tegueu C, Temfack E, Ngankou S, Doumbe J, Djientcheu VP, Kengne AP. Prevalence and determinants of diabetic polyneuropathy in a sub-Saharan African referral hospital. J Neurol Sci 2015;355(1):108–12.
[19] Yeboah K, Kyei-Baafour E, Antwi DA, Asare-Anane H, Gyan B, Amoah AGB. Circulating angiogenic factors in diabetes patients in a tertiary hospital in Ghana. J Diabetes Metab Disord 2016;15(1):44.
[20] Yeboah K, Agyekum JA, Baafour EK, Antwi DA, Adjei AB, Boima V, et al. Circulating angiogenic growth factors in diabetes patients with peripheral arterial disease and exertional leg pain in Ghana. J Vasc Med 2017;2017:1–7.
[21] Castelli G, Desai KM, Cantone RE. Peripheral neuropathy: evaluation and differential diagnosis. Am Fam Physician 2020;102(12):732–9.
[22] Julian T, Glascow N, Syeed R, Zis P. Alcohol-related peripheral neuropathy: a systematic review and meta-analysis. J Neurol 2019;266(12):2907–19.
[23] Stein J, Geisel J, Obeid R. Association between neuropathy and B-vitamins: A systematic review and meta-analysis. Eur J Neurol 2021;28(6):2054–64.
[24] Grisold W, Carozzi V. Toxicity in peripheral nerves: an overview. Toxics 2021;9(9):218.
[25] Shiferaw WS, Akalu TY, Work Y, Aynalem YA. Prevalence of diabetic peripheral neuropathy in Africa: a systematic review and meta-analysis. BMC Endocr Disord 2020;20(1):49.
[26] Menezes Costa LdC, Maher CG, McAuley JH, Costa LOP, Maher CG, McAuley JH, et al. Systematic review of cross-cultural adaptations of McGill Pain Questionnaire reveals a paucity of clinimetric testing. J Clin Epidemiol 2009;62(9):934–43.
[27] Attal N. Screening tools for neuropathic pain: are they adaptable in different languages and cultures? Pain Med 2010;11(7):985–6.
[28] Shaikh A, Bentley A, Kamerman PR, Forloni G. Symptomatology of Peripheral Neuropathy in an African Language. PLoS One 2013;8(5):e63986.
[29] Rasul S, Reiter MH, Ilhan A, Lampichler K, Wagner L, Kautzky-Willer A. Circulating angiopoietin-2 and soluble Tie-2 in type 2 diabetes mellitus: a cross-sectional study. Cardiovasc Diabetol 2011;10(1):55.
[30] Jaumdally RJ, Lip GY, Varma C, Blann AD. Impact of high-dose atorvastatin on endothelial, platelet, and angiogenic indices: effect of ethnicity, cardiovascular disease, and diabetes. Angiology 2011;62(7):571–8.
[31] Siddiqui K, Joy SS, Nawaz SS. Serum Angiopoietin-2 levels as a marker in type 2 diabetes mellitus complications. Internat J Diab Dev Count 2019;39(2):387–93.
[32] Eleftheriadou I, Dimitrakopoulou N, Kafasi N, Tentolouris A, Dimitrakopoulou A, Anastasiou IA, et al. Endothelial progenitor cells and peripheral neuropathy in subjects with type 2 diabetes mellitus. J Diabetes Complications 2020;34(4):107517.
[33] Sugimoto K, Murakami H, Deguchi T, Arimura A, Daimon M, Suzuki S, et al. Cutaneous microangiopathy in patients with type 2 diabetes: Impaired vascular endothelial growth factor expression and its correlation with neuropathy, retinopathy and nephropathy. J Diab Investig 2019;10(5):1318–31.
[34] Valable S, Bellail A, Lesné S, Liot G, MacKenzie ET, Vivien D, et al. Angiopoietin-1-induced phosphatidyl-inositol 3-kinase activation prevents neuronal apoptosis. FASEB J 2003;17(3):1–19.
[35] Kosacka J, Figiel M, Engele J, Hilbig H, Majewski M, Spanel-Borowski K. Angiopoietin-1 promotes neurite outgrowth from dorsal root ganglion cells positive for Tie-2 receptor. Cell Tissue Res 2005;320(1):11–9.
[36] Yin Z, Gong G, Zhu C, Wang B, Sun C, Liu X, et al. Angiopoietin-1 protects neurons by inhibiting autophagy after neuronal oxygen-glucose deprivation/recovery injury. Neuroreport 2020;31(11):825–32.
[37] Malik RA, Newrick PG, Sharma AK, Jennings A, Ah-See AK, Mayhew TM, et al. Microangiopathy in human diabetic neuropathy: relationship between capillary abnormalities and the severity of neuropathy. Diabetologia 1989;32(2):92–102.
[38] Smith DR, Kobrine AI, Rizzoli HV. Absence of autoregulation in peripheral nerve blood flow. J Neurol Sci 1977;33(3):347–52.
[39] Anderson CE, Hamm LL, Batuman G, Kumbala DR, Chen C-S, Kallu SG, et al. The association of angiogenic factors and chronic kidney disease. BMC Nephrol 2018;19(1):117.
[40] Meijer J-W-G, Bosma E, Lefrandt JD, Links TP, Smit AJ, Stewart RE, et al. Clinical diagnosis of diabetic polyneuropathy with the diabetic neuropathy symptom and diabetic neuropathy examination scores. Diabetes Care 2003;26(3):697–701.
[41] Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. J Am Med Assoc 2005;293(2):217–28.
[42] Young MJ, Breddy JL, Veves A, Boulton AJ. The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds. A prospective study. Diabetes Care 1994;17(6):557–60.
[43] Chong PST, Cros DP. Technology literature review: Quantitative sensory testing. Muscle Nerve 2004;29(5):734–47.
[44] Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. Diabetes Care 2000;23(5):606–11.