Original Article

Posterior Tibial Nerve Ultrasound Assessment of Peripheral Neuropathy in Adults with Type 2 Diabetes Mellitus

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Abstract

Background: Diabetic peripheral neuropathy (DPN) is a common and debilitating complication of type 2 diabetes mellitus (T2DM). Early detection and prompt institution of appropriate therapy could prevent undesirable outcomes such as paresthesia, pain, and amputation. Although the gold standard for diagnosing DPN is nerve conduction studies, high-resolution peripheral nerve ultrasonography may serve as a noninvasive and low-cost alternative for diagnosing and staging DPN. This study investigated the clinical utility of sonographic posterior tibial nerve cross-sectional area (PTN CSA) for diagnosing DPN in individuals with T2DM. **Methods:** Eighty consecutive adults with T2DM and 80 age-/sex-matched controls were recruited. Clinical information was obtained, including symptoms, disease duration, Toronto clinical neuropathy score (TCNS), and biochemical parameters. The left PTN CSA at 1 cm, 3 cm, and 5 cm above the medial malleolus (MM) was measured with a high-frequency ultrasound transducer and compared to the detection of DPN using the TCNS. **Results:** Based on the TCNS, 58 (72.5%) of the T2DM group had DPN. Of these, 14 (24.1%), 16 (27.6%), and 28 (48.3%) participants had mild, moderate, and severe DPN, respectively. All the mean PTN CSA (aggregate, 1 cm, 3 cm, and 5 cm above MM) of the participants with T2DM and DPN (T2DM-DPN) were significantly higher than those of T2DM without DPN (WDPN) and controls. All the PTN CSA increased significantly with increasing severity of DPN. The PTN CSA at 3 and 5 cm levels correlated weakly but significantly with fasting plasma glucose and glycated hemoglobin levels. **Conclusion:** The PTN CSA is significantly larger in T2DM-DPN than in T2DM-WDPN and healthy controls. PTN ultrasonography can be an additional tool for screening DPN in patients with T2DM.

Keywords: Diabetes mellitus, neuropathy, posterior tibial nerve, ultrasonography

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from impaired insulin secretion, ineffective insulin action, or both.[1] The chronic hyperglycemia often leads to long-term microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (peripheral vascular, cerebrovascular, and coronary artery diseases).[2] Type 1 diabetes mellitus is secondary to beta-cell destruction, leading to absolute insulin deficiency, while type 2 DM (T2DM) is due to progressive insulin deficiency and insulin resistance.[3,4]

Neuropathy is the most common complication of diabetes resulting from direct nerve damage by hyperglycemia and indirect damage by decreased blood flow to the nerves (secondary to damaged small blood vessels).[3] Diabetic neuropathy could be peripheral, autonomic, proximal, or focal in manifestation.[5,6] Peripheral neuropathy, the most common type of diabetic neuropathy, is defined as symptoms and/or signs of peripheral nerve dysfunction in people with DM after excluding other causes. Peripheral neuropathy causes pain or loss of sensation in the toes, feet, legs, hands, and arms.[5-10] Diabetic peripheral neuropathy (DPN) is responsible for substantial morbidity, increased mortality, and impaired quality

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of life in diabetic patients. DPN is a distressing health problem and a financial burden on the patient and society. Therefore, early detection and prompt institution of management could prevent undesirable outcomes associated with DPN.[11,12]

Electro-neurophysiological methods such as electroneuromyography and nerve conduction studies are still the gold standard for diagnosing DPN.[7,13] However, these methods are time-consuming, expensive, and assess peripheral nerve function only without providing data on their morphology or the pathomorphology of the surrounding structures and tissues. Furthermore, electroneuromyography studies can be equivocal or have technical limitations.[7,13]

With the remarkable improvement in the resolution of modern diagnostic ultrasound scanners, the revelation of minute peripheral nerve details has become possible.[14-16] Ultrasonography is widely available, dynamic/real-time, mobile, rapidly performed, noninvasive, and relatively cheap compared to magnetic resonance imaging (MRI). Although very accurate and superior for imaging soft tissues, MRI is expensive, time-consuming, patient-selective, often not readily available, and prone to magic angle artifacts.[16,17] Using high-resolution ultrasound, the shape, size, and echotexture of the posterior tibial nerve (PTN) can be examined along its course in the leg.[16] Due to its large diameter, linear course, and accompanying neurovascular bundle, the PTN is easily identified on high-frequency ultrasound.[18,19]

Some previous studies found peripheral nerve ultrasound useful for the diagnosis of diabetic neuropathy.[16,19,20] This study aimed to investigate the clinical utility of ultrasonographic PTN cross-sectional area (CSA) for detecting DPN in patients with T2DM in our locality and to correlate PTN CSA with the severity of DPN.

Materials and Methods

This prospective descriptive comparative study was conducted from February 2020 to August 2020 at the radiology department of a tertiary hospital. The hospital's Ethics committee approved the study protocol (ADM/DCST/HREC/APP/2993). Written informed consent was obtained from all participants.

The study population comprised eighty adults (>18 years) with T2DM who were recruited consecutively from the endocrinology clinic of our institution. Eighty healthy age-matched and sex-matched controls (with fasting plasma glucose [FPG] of 4.0–5.6 mmol/L and no history suggestive of peripheral neuropathy) were also recruited.

The participants with T2DM had been diagnosed based on FPG of ≥126 mg/dL (≥7.0 mmol/L) on two separate tests or glycated hemoglobin (HbA1c) of ≥48 mmol/L (≥6.5%).[1] The exclusion criteria for the T2DM group were: Polyneuropathy due to other etiologies (such as hereditary, metabolic, inflammatory, or toxic factors excluded based on history, physical examination, and laboratory findings), intake of >20 g of alcohol per day (risk of alcohol-induced peripheral neuropathy), symptomatic carpal tunnel syndrome or tarsal tunnel syndrome (TTS), and other causes of peripheral nerve enlargement (hereditary neuropathies, neuropathy in Refsum's disease, neuropathy in familial amyloidosis, inflammatory neuropathies, chronic inflammatory demyelinating neuropathy, Guillain–Barré syndrome, multifocal inflammatory demyelinating neuropathy).[19,21] Preliminary sonography was also done to screen for space-occupying lesions (tumors, ganglion cysts, and varicose vessels) that may predispose to other focal neuropathy.

Clinical and sonographic methods were used to distinguish DPN from TTS. DPN typically affects both feet symmetrically and progresses gradually over time, while TTS can affect one or both feet and may have a more acute onset. In TTS, the pain and sensory deficits are typically localized to the medial aspect of the ankle and foot, while in DPN, the symptoms can be more diffuse and involve other areas of the lower limbs. In DPN, there may be decreased or absent reflexes, decreased sensitivity to touch or pinprick, and decreased vibration sense in the feet, whereas in TTS, there may be tenderness over the tarsal tunnel, and the symptoms may be reproduced with Tinel's sign (tapping over the tarsal tunnel).[22]

Clinical and laboratory evaluation

The age, sex, duration of T2DM, height in meters, weight in kilograms (SERICO Stadiometer model number RGZ-120 with sitting and standing weighing scale), body mass index (BMI), waist–hip ratio, alcohol intake, and duration of smoking of the participants were recorded. Relevant clinical history and physical examination were done to identify any exclusion criteria in the participants. Capillary blood from a finger prick was taken for FPG (in all participants) and HbA1c (in the T2DM group only) using portable kits, i.e., Accucheck active glucometer (model no 07133766200) and PTS Diagnostics Multi-test A1C System (Match Code L7, HemoCure HB 201), respectively.

DPN was assessed clinically using the Toronto clinical neuropathy score (TCNS) as follows:[16,23]

Symptom scores

1. Pain: Pain in the feet of neuropathic type (including "burning," "stabbing," or "electric-like shock") = 1
2. Numbness (loss of sensation on the feet) = 1
3. Tingling sensation = 1
4. Weakness in the limb = 1
5. Ataxia (imbalance when walking or standing) = 1
6. Upper limb (presence of any leg symptoms listed above in the upper limb) = 1.

Reflexes scores

The patellar tendon and Achilles tendon reflexes were examined (using a Queen square tendon hammer with Neurotip) in the sitting position with the legs resting on the examination couch. If the reflex is obtained, it is graded as present. If the reflex is absent, the participant was asked to perform the Jendrassik maneuver (i.e., hooking the fingers

together and pulling). Reflexes elicited with the Jendrassik maneuver alone are designated "reduced." If the reflex is absent, even with the Jendrassik maneuver, the reflex is considered absent.

Sensory test scores

Pinprick, temperature, vibration, and light touch were first demonstrated over the chest, while joint position sense was demonstrated on the thumb. Afterward, the participants were asked to close their eyes while each test was demonstrated on the big toe on either side.

Pinprick

Using the Neurotip, the participants, whose eyes are closed, were asked to respond yes if they feel the pain. Four locations were tested in each big toe. Significant abnormality (score = 1) indicates one or more abnormal responses in each toe or two or more abnormalities on one toe.

Temperature

A cold roller (or stem of a 128 Hz tuning fork) elicited a cold sensation. Each toe was tested twice. Significant abnormality (score = 1) indicates one or more abnormal responses in either toe.

Light touch

Using a 10 g monofilament, the same areas tested for pinprick are evaluated for light touch. Significant abnormality (score = 1) indicates one or more abnormal responses in each toe or two or more abnormalities on one toe.

Vibration sensation

Vibration sensation was tested bilaterally using a 128 Hz tuning fork placed over the dorsum of the great toe on the bony prominence of the distal interphalangeal joint. The participants, whose eyes were closed, were asked to indicate when they could no longer sense the vibration from the vibrating tuning fork after the examiner deliberately stopped it. Each toe was tested twice. Significant abnormality (score = 1) indicates one or more abnormal responses (inability to feel the vibration or stopping) in either toe.

Position

With their eyes closed, the participants were asked to tell if the toe was bent "up" or "down." Each toe was tested twice. Significant abnormality (score = 1) indicates one or more abnormal responses in either toe.

The participant's TCNS scores were documented out of a total of 19. Based on the scores, DPN severity was classified as no neuropathy (TCNS = 0–5), mild DPN (TCNS = 6–8), moderate DPN (TCNS = 9–11), and severe DPN (TCNS = 12–19).[16,23]

Sonographic examination of the posterior tibial nerve

Since the PTN dimensions show no statistically significant difference between the right and left lower limbs in published studies,[24,25] the left PTN CSA was used in this study (for convenient scanning and ease of participant positioning). The participants' left lower limbs were scanned using the 7–12 MHz Toshiba Xario 200 ultrasound scanner transducer with Doppler facilities (Toshiba, Minato City, Tokyo, Japan).

Each participant lay supine on the examination couch with the medial aspect of the leg exposed by partial knee flexion and hip abduction/external rotation. After gentle palpation, the cephalad border of the medial malleolus (MM) was identified, and the "0 cm" mark of the plastic ruler was placed at this level. Then, the 1 cm, 3 cm, and 5 cm marks were indicated on the leg more proximally using the skin marker [Figure 1]. The participant was instructed not to move the toes during the examination period.

Following adequate positioning, the coupling gel was applied over the scan area. The PTN was identified based on its speckled sonographic pattern, and the angle of the transducer was adjusted until it was perpendicular to the nerve to obtain the smallest cross-sectional image. The transducer was applied transversely with minimal pressure to the area of interest to avoid potential nerve compression. The major/long axis and minor/short axis of the PTN were measured inside the hyperechoic border of the nerve at the levels indicated on the

Table 1: Clinical and demographic characteristics of the study population

Parameters	Mean±SD		*P*
	T2DM (*n*=80)	Controls (*n*=80)	
Age (years)	60.09±7.79	59.97±6.22	0.08
BMI (kg/m^2)	27. 33±6.21	26.43±3.86	<0.0001
FPG (mg/dL)	7.50±2.74	4.70±3.32	0.001
T2DM duration (years)	12.61±6.92	NA	
Waist–hip ratio	41.16±6.89	34.16±7.79	<0.0001
Alcohol intake (g), median (IQR)	10 (4.00–22.50)	0	
Duration of smoking (pack year), median (IQR)	2.50 (0.25–18.00)	0	
HbA1c (%)	7.89±2.18	-	
CSA (mm^2) at 1 cm	18.40±9.80	10.77±6.13	<0.0001
CSA (mm^2) at 3 cm	18.02±6.94	10.27±6.08	<0.0001
CSA (mm^2) at 5 cm	16.97±6.39	8.94±5.53	<0.0001
Aggregate CSA (mm^2)	17.93±7.05	10.02±5.55	<0.0001

BMI: Body mass index, CSA: Cross-sectional area (posterior tibial nerve), FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, IQR: Interquartile range, NA: Not applicable, T2DM: Type 2 diabetes mellitus, SD: Standard deviation

Table 2: Characteristics of the type 2 diabetes mellitus group according to the presence of diabetic peripheral neuropathy

	DPN		*P*
	Without DPN (*n*=22), *n* (%)	With DPN (*n*=58), *n* (%)	
Gender			
Male	8 (36.4)	20 (34.5)	0.875
Female	14 (63.6)	38 (65.5)	
Mean age (years)	57.14±5.66	61.10±8.28	0.058
Age group (years)			
<50	1 (4.5)	5 (8.6)	0.293
50–69	21 (95.5)	44 (75.9)	
≥70	-	9 (15.5)	
Age at diagnosis (years)	48.41±8.77	47.93±8.89	0.830
T2DM duration (years)	10.14±7.25	13.55±6.61	0.048
Alcohol intake			
No	16 (72.7)	41 (70.7)	0.857
Yes	6 (27.3)	17 (29.3)	
Duration of alcohol (years)	7.50 (3.75–26.25)	12 (4.00–25.00)	0.791
History of smoking			
No	21 (95.5)	51 (87.9)	0.434
Yes	1 (4.5)	7 (12.1)	
Duration of smoking (years)	0.08	3.00 (0.25–20.00)	0.250
BMI (kg/m^2)	27.30±5.38	27.34±6.55	0.981
Waist–hip ratio	0.98±0.07	0.95±0.08	0.067
FPG (mg/dL)	6.28±1.48	7.96±2.97	0.013
HbA1c (%)	6.84±1.63	8.29±2.24	0.002
CSA (mm^2) at 1 cm	14.69±5.64	19.81±10.68	0.007
CSA (mm^2) at 3 cm	15.69±4.03	18.91±7.60	0.017
CSA (mm^2) at 5 cm	13.74±3.93	18.19±6.73	0.005
Aggregate CSA (mm^2)	14.76±3.94	19.13±7.61	0.001

BMI: Body mass index, CSA: Cross-sectional area (posterior tibial nerve), FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, T2DM: Type 2 diabetes mellitus, DPN: Diabetic peripheral neuropathy

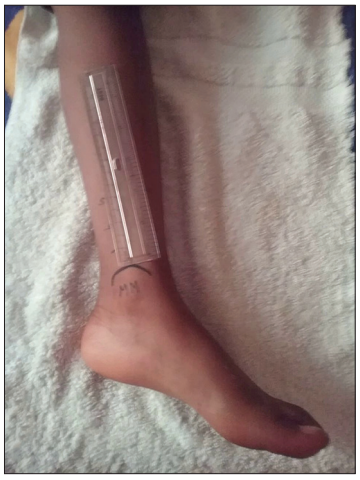

Figure 1: The transducer positions at 1, 3, and 5 cm proximal to the MM. MM: Medial malleolus

skin [Figure 2]. All the participants were scanned by the first author, who was a 5th year radiology resident, under the close supervision of two consultant radiologists with 5 years of experience in musculoskeletal sonography. The sonologist was not blinded to the participant's status. Intraobserver variability was minimized by taking three measurements and recording the mean value.

The CSA of peripheral nerves can be calculated using the indirect method (formula method) or the direct method (directly tracing the nerve's edge in the transverse plane). Previous studies showed that nerve CSA measurements are reproducible by either the direct or indirect method.[26] In addition, there is a high correlation ($r = 0.99$) between the nerve CSA obtained by the indirect and direct methods.[27] The PTN CSA in this study was calculated by the indirect method using the formula:[27]

$$\text{CSA (mm}^2\text{)} = \text{major (long) axis (a)} \times \text{minor (short) axis (b)}\ \pi \times \frac{1}{4}$$

Data analysis

The study data were analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA). Data Normality was tested with the Kolmogorov–Smirnov test. The categorical variables were subjected to a Chi-square test. Continuous variables were presented as mean ± standard deviation, while other data that significantly deviated from normal distribution were presented as median (interquartile range). Independent Student's *t*-test and One-way ANOVA were used for the parametric data, while the Mann–Whitney *U*-test and Kruskal–Wallis test were used for nonparametric data. The PTN aggregate CSA was calculated as the arithmetic average of the PTN CSA at 1 cm, 3 cm, and 5 cm. Spearman correlation analysis was used to determine the relationship between participants' characteristics and PTN CSA. The strength of the correlation coefficients was graded as follows: r = 0–0.2: Very low/negligible and probably meaningless correlation; $r \geq 0.2$–0.4: Low correlation; $r \geq 0.4$–0.6: Moderate

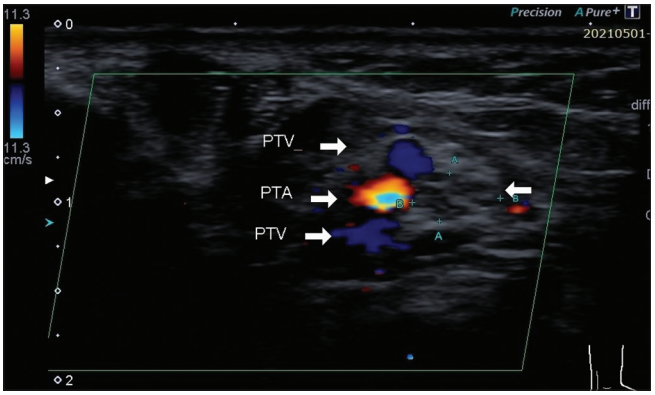

Figure 2: Transverse colour Doppler ultrasonogram of the PTN showing its minor axis (A-A) and major axis (B-B), with the accompanying PTA and paired PTVs. PTN: Posterior tibial nerve, PTA: Posterior tibial artery, PTV: Posterior tibial vein

Table 3: Characteristics of the type 2 diabetes mellitus group according to the severity of diabetic peripheral neuropathy

	DPN				*P*
	Absent (*n*=22), *n* (%)	Mild (*n*=14), *n* (%)	Moderate (*n*=16), *n* (%)	Severe (*n*=28), *n* (%)	
Gender					
Male	8 (36.4)	7 (50)	2 (12.5)	11 (39.3)	0.774
Female	14 (63.6)	7 (50)	14 (87.5)	17 (60.7)	
Mean age (years)	57.41±5.66	57.07±6.21	62.81±8.82	62.14±8.47	0.032
Age group (years)					
<50	1 (4.5)	2 (14.3)	1 (6.3)	2 (7.1)	0.054
50–69	21 (95.5)	12 (85.7)	12 (75.0)	20 (71.4)	
≥70	-	-	3 (18.8)	6 (21.4)	
Age at diagnosis (years)	48.41±8.77	47.50±6.14	46.69±7.99	48.86±10.56	0.876
T2DM duration (years)	10.14±7.23	9.64±3.34	16.75±5.49[a, b]	13.68±7.49	0.006
Alcohol intake					
No	16 (72.7)	9 (64.3)	12 (75)	20 (71.4)	0.940
Yes	6 (27.3)	5 (35.7)	4 (25)	8 (28.6)	
Duration of alcohol	7.5 (3.75–26.25)	12 (3.5–19)	8.0	15 (4–37.25)	0.901
History of smoking					
No	21 (95.5)	11 (78.6)	15 (93.8)	25 (89.3)	0.761
Yes	1 (4.5)	3 (21.4)	1 (6.3)	3 (10.7)	
Duration of smoking (years)	0.08	2.0	3.0	20.0	0.382
BMI (kg/m^2)	27.30±5.38	28.61±5.68	27.51±6.09	26.60±7.27	0.809
Waist–hip ratio	0.98±0.07	0.97±0.08	0.95±0.08	0.94±0.07	0.195
FPG (mg/dL)	6.28±1.48	7.60±1.57	8.08±2.53	8.08±3.72	0.094
HbA1c (%)	6.84±1.63	7.43±1.28	8.27±2.25	8.74±2.53[a]	0.013
CSA (mm^2) at 1 cm	14.69±5.64	16.09±8.10	16.78±8.35	23.39±12.01[a]	0.007
CSA (mm^2) at 3 cm	15.69±4.03	15.88±7.37	18.87±6.05	20.44±8.26	0.055
CSA (mm^2) at 5 cm	13.74±3.93	15.94±6.15	17.21±5.89	19.88±7.21[a]	0.006
Aggregate CSA (mm^2)	14.76±3.94	16.77±6.99	17.51±6.08	21.24±8.31	0.009

[a]Significantly different from the absent group (P <0.05), [b]Significantly different from the mild group (P <0.05). BMI: Body mass index, CSA: Cross-sectional area (posterior tibial nerve), FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, T2DM: Type 2 diabetes mellitus, DPN: Diabetic peripheral neuropathy

correlation; $r \geq 0.6$–0.8: High correlation; and $r \geq 0.8$–1.0: excellent/very high correlation.[28]

The receiver operating characteristic (ROC) curve was plotted to determine optimum cut-off points and evaluate sonographic measurements' diagnostic accuracy. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the sonographic measurements were determined. $P \leq 0.05$ was considered statistically significant.

Results

The study population comprised 80 individuals (28 males and 52 females) with T2DM and 80 age-/sex-matched healthy controls. The T2DM group had significantly higher BMI, FPG, waist–hip ratio, and PTN CSA (aggregate CSA and CSA at 1 cm, 3 cm, and 5 cm) [Table 1]. The mean duration of diabetes mellitus in the T2DM group was 12.6 ± 6.92 years. The mean FPG of the participants with T2DM was 7.50 ± 2.74 mmol/L, while their mean HbA1c was 7.89% ± 2.18% [Table 1].

Using TCNS >5 as the diagnostic criterion for DPN, the prevalence of neuropathy in the T2DM group was 72.5% [Table 2]. The participants with T2DM and DPN had significantly higher T2DM duration, FPG, HbA1c, and all the four measurements of the PTN CSA than those with T2DM without DPN (WDPN) [Table 2]. The PTN aggregate CSA, CSA at 1 cm, and CSA at 5 cm increased significantly with increasing severity of DPN [Table 3]. Except for ataxia, weakness, and position, all the other parameters of the TCNS were abnormal in significantly higher proportions of T2DM-DPN than T2DM-WDPN [Table 4].

Only the FPG and HbA1c levels showed a weak positive but significant correlation with PTN CSA at all (except at 1 cm for FPG) anatomical levels of measurements, with the strongest association at 5 cm for both FPG and HbA1c [Table 5].

Using the TCNS as the gold standard, a ROC curve was plotted [Figure 3] to determine the optimum cut-off points of the CSA for diagnosing DPN. Table 6 shows the sensitivity and specificity of PTN CSA for the diagnosis of DPN at the different measurement levels proximal to the MM. A mean PTN CSA of 14 mm^2 at 5 cm above the MM was the optimal threshold for identification of DPN because it had the highest accuracy of 73.8% (62.7-83%) to correctly classify participants as having DPN [Table 6]. This cutoff value's sensitivity, specificity, PPV, and NPV were 77.6%, 63.6%, 84.9%, and 51.9%, respectively.

Table 4: Toronto clinical neuropathy scoring in the type 2 diabetes mellitus group

	DPN		*P*
	Without DPN (*n*=22), *n* (%)	With DPN (*n*=58), *n* (%)	
Pain			
Absent	16 (72.7)	20 (34.5)	0.002
Present	6 (27.3)	38 (65.5)	
Numbness			
Absent	19 (86.4)	13 (22.4)	<0.0001
Present	3 (13.6)	45 (77.6)	
Weakness			0.010
Absent	19 (86.4)	32 (55.2)	
Present	3 (13.6)	26 (44.8)	
Tingling			0.002
Absent	21 (95.5)	35 (60.3)	
Present	1 (4.5)	23 (39.7)	
Ataxia			
Absent	20 (90.9)	43 (74.1)	0.104
Present	2 (9.1)	15 (25.9)	
Upper limb symptom			
Absent	22 (100)	39 (67.2)	0.002
Present	-	19 (32.8)	
Knee reflex			
Normal	17 (77.3)	12 (20.7)	<0.0001
Reduced	5 (22.7)	37 (63.8)	
Absent	-	9 (15.5)	
Ankle reflex			
Normal	19 (86.4)	16 (27.6)	<0.0001
Reduced	3 (13.6)	16 (27.6)	
Absent	-	26 (44.8)	
Pinprick			
Normal	17 (77.3)	18 (31.0)	<0.0001
Abnormal	5 (22.7)	40 (69.0)	
Temperature			
Normal	19 (86.4)	18 (31.0)	<0.0001
Abnormal	3 (13.6)	40 (69.0)	
Light touch			
Normal	20 (90.9)	29 (50.0)	0.001
Abnormal	2 (9.1)	29 (50.0)	
Position			
Normal	20 (90.9)	42 (72.4)	0.079
Abnormal	2 (9.1)	16 (27.6)	
Vibration			
Normal	21 (95.5)	34 (58.6)	0.002
Abnormal	1 (4.5)	24 (41.4)	

DPN: Diabetic peripheral neuropathy

Discussion

In this study, the PTN CSA was significantly larger in T2DM-DPN than in T2DM-WDPN and healthy controls. The severity of DPN, FPG, and HbA1c levels correlated with PTN CSA.

DPN is a common complication of T2DM.[29] Using the TCNS, the prevalence of DPN in this study was 72.5%. By contrast, sonographic PTN CSA detected DPN in 66.3% of the participants with T2DM with varying prevalence at the different anatomic points of measurements (56.3% at 1 cm, 53.8% at 3 cm, and 66.3% at 5 cm). The prevalence of DPN in people with T2DM is about 30% worldwide, with about 50% of the patients becoming symptomatic during their disease.[21] The prevalence of diabetic neuropathy is 6.6%–83.4% across Africa.[30]

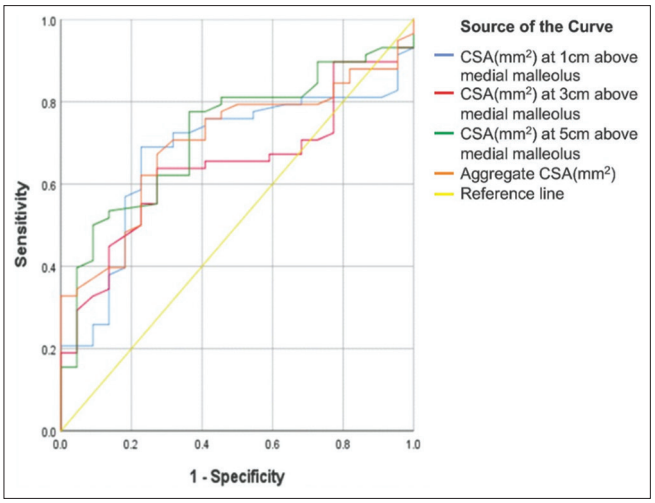

Figure 3: ROC curves to determine the sensitivity and specificity of CSA for the diagnosis of DPN at the different levels proximal to the medial malleolus. ROC: Receiver operating characteristic, CSA: Cross-sectional area, DPN: Diabetic peripheral neuropathy

The PTN is a good choice because DPN symptoms first appear in the soles of the feet, the nerve is the thicker branch of the sciatic nerve, its accompanying vessels can be taken as an anatomical reference point, and ultrasound can be performed on the patient with little or no discomfort to determine its CSA.[21] Riazi *et al*.[19] measured the PTN CSA at 1 cm, 3 cm, and 5 cm above the MM and found that the PTN CSA at 3 cm (19.01 mm^2) had optimal diagnostic value for diagnosing DPN, with a sensitivity and sensitivity of 69% and 77%, respectively. In contrast, this study measured the PTN CSA at the same three levels as Riazi *et al*., but the PTN CSA at 5 cm (14 mm^2) had the highest sensitivity (77.6%), PPV (84.9%) and accuracy (73.8%) for the identification of DPN.

This study found that the PTN CSA at all three points of measurement were significantly higher among participants with severe neuropathy than those with moderate neuropathy, mild neuropathy, and T2DM-WDPN. This finding is similar to that of Singh *et al*.[31] who recorded a higher mean PTN CSA in severe DPN than in moderate disease. The T2DM-WDPN group also had increased PTN CSA, suggesting that sonographic changes in the PTN can be detected before the onset of clinical symptoms. A previous study also described this observation of thickened PTN in T2DM-WDPN.[25]

The mean FPG and HbA1c showed a low positive and significant correlation with the mean PTN CSA measurements at 5 cm. This suggests that the PTN CSA measurements will increase as FPG and HbA1c levels rise. A few studies also interrogated the relationship between PTN CSA and HbA1c

Table 5: Correlation between participant's (type 2 diabetes mellitus) characteristics and posterior tibial nerve cross-sectional area (tibial nerve), at different levels

Parameters	*r* (*P*)			
	CSA at 1 cm	CSA at 3 cm	CSA at 5 cm	Aggregate CSA
Age (years)	0.071 (0.534)	0.047 (0.678)	0.129 (0.254)	0.096 (0.396)
Age at diagnosis (years)	−0.009 (0.934)	0.047 (0.679)	0.085 (0.453)	0.058 (0.609)
T2DM duration (years)	0.013 (0.912)	−0.012 (0.917)	−0.047 (0.679)	−0.026 (0.821)
BMI (kg/m^2)	0.053 (0.639)	0.003 (0.980)	−0.020 (0.858)	−0.002 (0.986)
Waist–hip ratio	0.079 (0.489)	0.098 (0.389)	−0.006 (0.957)	0.039 (0.731)
FPG (mg/dL)	0.291 (0.009)	0.313 (0.005)	0.349 (0.001)	0.347 (0.002)
HbA1c (%)	0.214 (0.06)	0.262 (0.019)	0.379 (0.001)	0.320 (0.004)

BMI: Body mass index, CSA: Cross-sectional area (posterior tibial nerve), FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, T2DM: Type 2 diabetes mellitus

Table 6: Comparison of sensitivity and specificity of posterior tibial nerve cross-sectional area (tibial nerve) for detecting diabetic peripheral neuropathy in the type 2 diabetes mellitus group

	CSA at 1 cm	CSA at 3 cm	CSA at 5 cm	Aggregate CSA
AUC (95% CI)	0.678 (0.55–0.80)	0.643 (0.52–0.77)	0.721 (0.61–0.84)	0.701 (0.59–0.82)
P	0.015	0.049	0.002	0.006
Cutoff value (cm)	15.5	16.95	14.00	14.85
Sensitivity (95% CI)	69 (55.5–80.5)	63.8 (50.1–76.0)	77.6 (64.7–87.5)	75.9 (62.8–86.1)
Specificity (95% CI)	77.3 (54.6–92.2)	72.7 (49.8–89.3)	63.6 (40.7–82.8)	59.1 (36.4–79.3)
Positive likelihood ratio	3.03 (1.38–6.68)	2.34 (1.15–4.75)	2.13 (1.21–3.77)	1.85 (1.10–3.13)
Negative likelihood ratio	0.40 (0.26–0.63)	0.50 (0.32–0.76)	0.35 (0.20–0.63)	0.41 (0.23–0.72)
PPV (95% CI)	88.9 (78.4–94.6)	86.5 (75.2–92.6)	84.9 (76.1–90.9)	83.0 (74.4–89.2)
NPV (95% CI)	48.6 (37.7–59.6)	43.2 (33.2–53.9)	51.9 (37.8–65.7)	48.2 (34.4–62.2)
Accuracy (95% CI)	71.3 (60.1–80.8)	66.3 (54.8–76.5)	73.8 (62.7–83)	71.3 (60.1–80.8)

CSA of 14 mm^2 at 5 cm had the optimal threshold value with the highest accuracy and sensitivity. AUC: Area under the curve, CI: Confidence interval, CSA: Cross-sectional area (posterior tibial nerve), DPN: Diabetic peripheral neuropathy, PTN: Posterior tibial nerve, PPV: Positive predictive value, NPV: Negative predictive value

levels. Among these, Watanabe *et al*.[15] reported a very weak but significant association between the PTN CSA in DPN and HbA1c ($r = 0.2$, $P = 0.01$). Other researchers who evaluated multiple peripheral nerves (including the PTN) in patients with DPN also reported a significant correlation between HbA1c and CSA of some other nerves.[21,24,32] Unfortunately, some previous studies did not elaborate on the relationship between glycemic control (HbA1c level) and ultrasonographic changes. The mean PTN CSA at all anatomical measurement levels did not correlate with the duration since diagnosis of T2DM and BMI. This agrees with the study of Kelle *et al*.[33]

The main limitation of this study was that nerve conduction testing, which was unavailable in this setting, could not be done. However, the TCNS is a widely used, reliable, and validated diagnostic tool for various neuropathies.[34,35] In addition, while we have included a sex-/age-matched control group, still other factors including obesity, DPN severity, and T2DM duration can all affect the PTN CSA and may be adjusted for confounding effects. Finally, the study involved participants of African background, and therefore the findings may not apply to the broader global population due to the potential bias towards a specific group; however, studies done elsewhere have reported similar findings. Future research would include a longitudinal follow-up study of the PTN CSA of people with T2DM and an evaluation of PTN CSA utility in the pediatric age group.

In a nutshell, the PTN CSA is significantly larger in T2DM-DPN than T2DM-WDPN and healthy controls. It showed the highest sensitivity for detecting DPN at 5 cm proximal to the MM. PTN CSA correlated with the severity of DPN. PTN ultrasonography can be an additional tool for screening and monitoring DPN in individuals with T2DM. Early detection of DPN through routine screening and regular follow-up would help to reduce the burden of disability and improve the quality of life in patients with T2DM.

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Conflicts of interest

There are no conflicts of interest.

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