Comparison of Cross Sectional Area of Posterior Tibial Nerve in Diabetic Peripheral Neuropathy Patients with That of Healthy Controls Using High Resolution Ultrasonography - A Cross Sectional Comparative Descriptive Study from Bangalore

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ABSTRACT

BACKGROUND

Patients with diabetic peripheral neuropathy (DPN) suffer from numbness, burning feet, lightning pain, and pins-and-needles sensations. Recently, High resolution ultrasonography is commonly used for evaluation of peripheral nerve diseases because of its easy availability, time saving and non-invasiveness of the procedure. This study intended to compare the cross sectional area (CSA) of posterior tibial nerve (PTN) in type 2 diabetic patients with peripheral neuropathy with that of non-diabetic healthy adults using high resolution ultrasonography (HRU) and study the role of increase in HbA1c level and severity of DPN comparing with CSA of PTN.

METHODS

A cross sectional comparative descriptive study was conducted from November 2018 to May 2020 with 50 type 2 diabetic patients and 50 healthy adults. 50 type 2 diabetic patients, clinically diagnosed with DPN were analysed and using the Toronto Clinical Neuropathy Score (TCNS) System, the severity of neuropathy was determined. HbA1c level and other demographic data were collected. 50 healthy adults were taken as controls. The CSA of posterior tibial nerve was measured 3 cm proximal to the medial malleolus in both lower limbs using HRU.

RESULTS

The mean CSA of posterior tibial nerve in healthy subjects was 6.0 + / - 0.142 mm^2, and in diabetic patients with peripheral neuropathy was 11.77 + / - 0.291 mm^2. Upon comparing the mean CSA of posterior tibial nerve of diabetic subjects with peripheral neuropathy and control subjects were statistically significant ($P < 0.001$) in unpaired 't' test. In our study, CSA of the posterior tibial nerve correlated significantly with TCNS and HbA1c levels, at $P < 0.001$.

CONCLUSIONS

This study showed that there is a significant difference between the cross sectional areas of posterior tibial nerve in diabetic subjects with peripheral neuropathy and healthy adult subjects. HRU can detect cross sectional area changes in the posterior tibial nerve early. Thus, ultrasonography can be used as a good screening tool in these patients.

KEYWORDS

Diabetic Peripheral Neuropathy, Posterior Tibial Nerve, High Resolution Ultrasonography

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BACKGROUND

Diabetes mellitus (DM) has worldwide prevalence with a rapid rate of growth. In India it has arrived at epidemic proportions.[1,2] According to International Diabetes Federation(IDF) Diabetes atlas, it is estimated that currently there are 463 million people with diabetes worldwide and by year 2030 this can be set to extend to 578 million and by 2045 extend to 700 million.[3] In India about 80 million population is estimated to be suffering with type 2 DM by the year 2030.[4] The prevalence of diabetic peripheral neuropathy varies greatly, ranging from 8 to 59% in various different studies.[5,6,7]

Poor control of blood glucose level is most commonly associated with Diabetic peripheral neuropathy and patients suffer with difficulty in controlling their lipid content in the blood, blood pressure and body mass within normal range.[8]

Electro-diagnostic testing, quantitative sensory tests, physical examination procedures and symptom questionnaires likewise many methods are established for screening and epidemiological research of peripheral neuropathy. Each of above methods have both strengths and limitations.[9,10] To assess the presence and severity of diabetic peripheral sensorimotor neuropathy several scoring systems are developed, including the Toronto clinical neuropathy scoring system which encompasses the symptoms, sensory tests and reflex scores for the assessment.[11]

Recently ultrasound is predominantly used in the evaluation of peripheral nerves. Ultrasonography of the posterior tibial nerve is a fast real time tool for detecting diabetic neuropathy. There is no patient discomfort, nor any radiation exposure. On transverse scans, peripheral nerves have a typical 'honeycomb' appearance, with ovoid hypoechoic fascicles dispersed within a milieu of hyperechoic perineural connective tissue. Peripheral nerves are located superficially making them easily assessable by HRU.

This study was intended to compare the cross sectional area (CSA) of posterior tibial nerve (PTN) in type 2 diabetic patients with peripheral neuropathy and those of non-diabetic healthy adults using high resolution ultrasonography (HRU) and also to study the role of increase in HbA1c level and severity of DPN comparing with CSA of PTN.

METHODS

After obtaining approval from the institute ethical review committee, a cross sectional comparative descriptive study was conducted from November 2018 to May 2020 in the Department of Radio-diagnosis, Victoria hospital, Bangalore medical college and research institute, Bangalore. Based on the previous study by Watanabe T,[12] cross sectional area of posterior tibial nerve in diabetic peripheral neuropathy patients were 18 + / - 4 mm^2 and in control was 10 + / - 3 mm^2. Expecting a minimum difference between the two groups will be 2 mm^2.

Sample size calculation was done suing the formula

$$n = \frac{2\,(Z\alpha + Z_{1-\beta})^2\,\sigma^2}{d^2}$$

where,
n is the sample size for each group.
Z_α is standard table value for 95 % confident interval = 1.96.
$Z_{1-\beta}$ is standard table value for 80% power = 0.84.
σ is standard deviation = 3.5.
d is the expected minimum difference between the two groups.

$$N = \frac{2\,(1.96 + 0.84)^2\,(3.5)^2}{2^2}$$

n = 50 in each group.

The study group consisted of 50 cases with DPN and 50 healthy controls. We excluded patients with clinically suspected peripheral neuropathy due to other causes such as vitamin deficiency, drugs, and trauma. Demographic information, including age, sex, weight, blood pressure, fasting blood sugar level (FBS) and post-prandial blood sugar (PPBS) was recorded for all patients and normal subjects. Duration of Diabetes and HbA1c level of Diabetic patients were collected. Cross sectional area of bilateral posterior tibial nerve of DPN patients and normal subjects was measured using linear probe (5 – 12 MHz) of the Philips affinity 50 G High resolution Ultrasonography machine. Ultrasound studies were performed by radiologist blinded about subject's information.

Toronto Clinical Neuropathy Score (TCNS) was used to calculate the severity of DPN. Out of 19 score. 0 - 5 score - absent, 6 - 8 score- mild, 9 - 11 score - moderate and > 12 score - severe.

The examination was performed with the patient lying in a lateral position for easy assessment of the medial aspect of the distal leg and ankle. The cross sectional area of bilateral posterior tibial nerves was recorded 3 cm above the medial malleolus. An image of the posterior tibial nerve was visualized, captured and stored. Short (a) and long (b) axis of the nerve was recorded. The cross sectional area of the posterior tibial nerve was calculated using cross sectional area formula (a x b x 3.14) / 4. CSA of bilateral posterior tibial nerve of patients and normal subject was compared. Correlation of CSA of bilateral posterior tibial nerve of patients with FBS, PPBS, HbA1c and TCNS was studied.

Statistical Analysis

Results were presented as Mean, Standard deviation and range values for continuous measurements and frequencies as number and percentages. Intergroup comparisons were done by unpaired t test. Categorical data was analysed by chi-square test. Simultaneous multiple group comparisons done by One - way ANOVA. A P value of 0.01 or less was considered to be statistically significant. Pearson correlation coefficient was used to calculate the correlations of CSA of

PTN with HbA1c level and TCNS. Data was analysed by SPSS software.

RESULTS

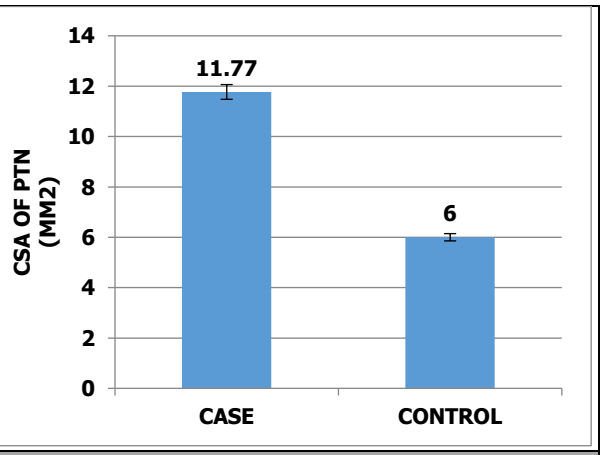
Our study consisted of 50 subjects with diabetic peripheral neuropathy comprising the case group and 50 normal healthy adults comprising the control group. Case group consisted of 30 male and 20 female subjects. Control group consisted of 27 male and 23 female subjects. (Refer to Table 1)

Sex	Control	Case
Male	27 (54 %)	30 (60 %)
Female	23 (46 %)	20 (40 %)
Total	**50 (100 %)**	**50 (100 %)**

Table 1. Sex Distribution between Control and Case Group

Clinical and Demographic Characteristics	Control Mean +/- SD	Case Mean +/- SD
Age (years)	54.18 + / - 0.999	56.36 + / - 1.038
Weight (kilogram)	62.64 + / - 1.126	64.76 + / - 1.447
Duration of DM (years)	0	8.34 + / - 0.557
Systolic blood pressure(mmHg)	119.08 + / - 0.813	137.04 + / - 0.850
Diastolic blood pressure(mmHg)	80.04 + / - 0.326	85.44 + / - 0.662
FBS (mg/dl)	84.38 + / - 0.826	173.24 + / - 5.995
PPB S(mg/dl)	112.28 + / - 1.474	232.16 + / - 8.495
CSA OF PTN (mm^2)	6.0 + / - 0.142	11.77 + / - 0.291

Table 2. Clinical, Demographic details and CSA Measurement of Control and Cases



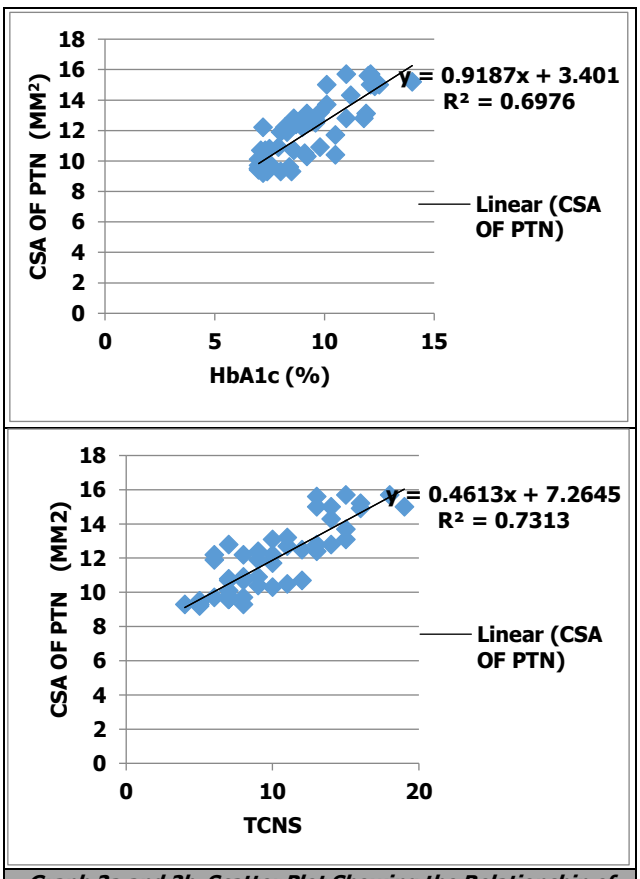
Graph 1. CSA of PTN of Cases and Control

Cases	HbA1c (%) Mean +/-SD	TCNS Mean +/-SD	CSA OF PTN (mm^2) Mean +/-SD
50	9.11+/-1.872	9.78+/-3.819	11.77+/-2.059

Table 3. Mean value of HbA1c level, TCNS and CSA of PTN of Cases

Mean HbA1c obtained was 9.11 + / - 1.872. (Refer to Table 3) r value 0.835 and P value < 0.01 was obtained from comparison between HbA1c with CSA of PTN, suggestive of existence strong positive correlation. Similar manner upon comparison of TCNS score with CSA of PTN r value of 0.855 and P value < 0.01 was obtained, suggestive of existence of strong positive correlation. (Refer to Graph 2 a and 2 b).

In this study, mean age of case was 56.36 + / - 1.038 year and that for control was 54.18 + / - 0.999 year. Mean weight was 64.76 + / - 1.447 kg in case group and 62.64 +/- 1.126 kg in control group. Mean duration of diabetes was 8.34 + / - 0.557 years of the patients. Mean FBS was 84.38 + / - 0.826 mg/dl in control group and 173.24 + / - 5.995 mg / dl in case group. Mean PPBS was 112.28 + / - 1.474 mg / dl in control group and 232.16 + / - 8.495 mg / dl in case group. The mean CSA of posterior tibial nerve in control group was 6.0 + / - 0.142 mm^2 and in case group was 11.77 + / - 0.291 mm^2. Cross sectional area of PTN obtained in bilateral limbs was same. Mean CSA of PTN in DPN patients was significantly more than normal subjects with P value < 0.01. (Refer to Table 2, Graph 1)



Graph 2a and 2b. Scatter Plot Showing the Relationship of CSA of PTN with HbA1c and TCNS Respectively

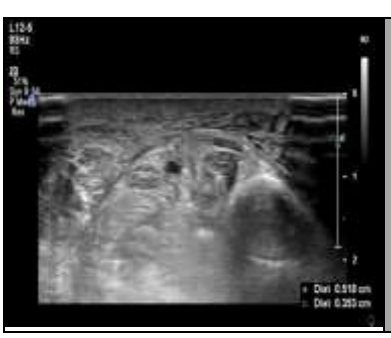


Figure 1. Ultrasound Image showing the Posterior Tibial Nerve in DPN Patient

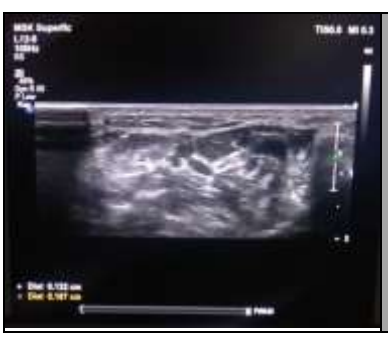


Figure 2. Ultrasound Image Showing PTN in Control Subject

Using TCNS scoring system, cases were classified according to the grades into 4 groups. First group consisted of 7 out of 50 cases; second group consisted of 16 out of 50 cases, third group 11 out of 50 cases and fourth group 16 cases out of 50 cases.

In first group, mean age was 51.71 + / - 4.889 years, mean weight was 58.7 + / - 2.752 kilogram, Duration of DM was 6.14 + / - 1.069 years, mean FBS was 149.71 + / - 53.962 mg / dl and mean PPBS was 218.43 + / - 69.536 mg/dl. In the second group, mean age was 56.19 + / - 8.175 years, mean weight was 63.25 + / - 7.767 kilogram, Duration of DM was 7.69 + / - 4.453 years, mean FBS was 148.50 + / - 9.661 mg / dl and mean PPBS was 189.44 + / - 18.829 mg / dl. In third group, mean age was 56.91 + / - 6.949 years, mean weight was 63.27 + / - 4.361 kilogram, Duration of DM was 7.45 + / - 2.697 years, mean FBS was 172.36 + / - 36.065 mg / dl and mean PPBS was 230.64 + / - 49.579 mg / dl. In fourth group, mean age was 58.19 + / - 7.323 years, mean weight was 69.94 + / - 14.708 kilogram, Duration of DM was 10.56 + / - 4.131 years, mean FBS was 208.88 + / - 38.464 mg / dl and mean PPBS was 281.94 + / - 56.399 mg / dl.

Mean value of CSA of right and left PTN in Grade 0 group was 9.35 + / - 0.113 mm 2 and 9.35 + / - 0.113 mm 2 respectively, grade 1 group was 10.60 + / - 1.125 mm 2 and 10.52 + / - 0.990 mm 2 respectively, grade 2 group was 11.75 + / - 1.081 mm 2 and 11.74 + / - 1.094 mm 2 respectively and grade 3 group was 14.02 + / - 1.486 mm 2 and 14.11 + / - 1.432 mm 2 respectively. In our study it was confirmed that increase in severity of DPN in patients based on TCNS scoring system, significant increase in the CSA of PTN.

DISCUSSION

Before the advancement of uses of imaging modalities, initially peripheral nerve disorder evaluation was based on clinical symptoms and signs, neurological examination and other diagnostic tests such as nerve conduction studies, F-waves and electromyography.[13] In patient management, nerve imaging plays an important role by providing information on lesion characteristics, location, relationship with surrounding anatomical structures, and evaluation of areas not reachable from electro diagnostic tests. Ultrasonography (US) and magnetic resonance imaging are the most common and widely used methods for assessing peripheral nerves. In everyday practice, US is used as a supporting modality in the neurological assessment, and this confirms the increasing usage of US in the evaluation of the peripheral nervous system disorders.[14]

Haemoglobin A1c and Fasting Plasma Glucose

HaemoglobinA1C (HbA1c) and fasting blood glucose constitute important laboratory screening tests. HaemoglobinA1C measurement reflects the adequacy of recent diabetes control; that is past three months which in turn is lifespan of RBC. These levels are mostly elevated in patients with diabetic neuropathies.

A glucose tolerance test (GTT) may be more helpful in borderline cases. Urine analysis is also helpful to screen for nephropathy and proteinuria. American Diabetes Association has recommended annual foot exam of diabetic neuropathy.

To evaluate a patient for neuropathy, clinicians needs to ask patients about signs and symptoms, perform a thorough physical exam, including deep tendon reflexes, motor strength and vibration; as well as perform diagnostic studies such as nerve conduction velocities (NCV).

Scoring System in Diabetic Neuropathy: Toronto Clinical Scoring System

The outcome, the clinical neuropathy score, is a continuous variable ranging from a minimum of 0 to a maximum of 19 points**.** Six points are derived from symptoms, eight from lower-limb reflexes and five from sensory examination distally at the toes.

Symptom Scores

Foot – Pain, Numbness, Tingling, Weakness Ataxia, Upper limb symptoms.

Reflexes

Knee reflex, Ankle reflex

Sensory Test Scores

Pinprick, Temperature, Light touch, Vibration and Position. Sensory testing was performed on the first toe.
Symptom scores: present = 1, absent = 0.
Reflex scores: absent = 2, reduced = 1, normal = 0.
Sensory test score: abnormal = 1, Normal = 0.
Total scores range from 0 to maximum of 19.

Scoring

Grade 0 – 0 -5 score,
Grade 1 - Mild neuropathy - 6 - 8 score,
Grade 2 - Moderate neuropathy - 9 - 11 score,
Grade 3 - Severe neuropathy - 12 - 19 score.

Nerve Ultrasound

Nerve imaging with US has become a valuable bedside tool for the clinical assessment of nerve structure, by providing real-time information about lesion morphology, anatomic location and relationship to surrounding structures.[15,16] US has been considered a diagnostic tool in neuromuscular medicine for over 30 years, however, its clinical utility has rapidly improved in the last decade due to the development of compact higher-frequency transducers, resulting in lower cost, better tissue resolution and increased sensitivity. US is now a routinely available, non-invasive, multiplanar, dynamic, and relatively inexpensive tool with high patient acceptability.[17] For these reasons, it has become a useful investigative tool that offers insights into the pathophysiological mechanisms underlying nerve injury. Nerve US typically relies on the use of high-frequency (12 – 18 MHZ) linear probes, except for the imaging of deeper

structures, such as the sciatic nerve, which requires a low frequency probe.[18] (2 to 6 MHZ)

Sonographic Features of Normal Peripheral Nerve

Most peripheral nerves of the upper and lower limbs can be easily imaged by US including cervical roots and brachial plexus. However, deeper nerves such as the proximal sciatic nerve and lumbosacral plexus are difficult to visualise. The appearance of peripheral nerves on US has been shown to correspond with their macroscopic and microscopic anatomy[18]. On transverse scans, peripheral nerves have a typical 'honeycomb' appearance, with ovoid hypoechoic fascicles dispersed within a milieu of hyperechoic perineural connective tissue. Longitudinally, the fascicles appear as linear hypoechoic bands. The epineurium usually appears hyperechoic due to its composition of dense connective tissue with high acoustic impedance. Its distinctive appearance helps to delineate nerves from their surrounding structures.

Anatomy of Posterior Tibial Nerve

Sciatic nerve terminates by dividing into posterior tibial nerve and common peroneal nerve at the level of upper end of popliteal fossa. PTN passes under tendinous arch formed between fibular and tibial heads of the muscle soleus and vertically passes through the deep region of the posterior compartment of leg on the surface of the tibialis posterior muscle with the posterior tibial vessels.[19]

Surface Marking of Posterior Tibial Nerve

Points to mark-

1. In the midline of back of the thigh at the junction of its upper two-thirds and lower one-third, i.e. at the apex of the popliteal fossa.
2. In the midline of back of the leg at the level of tibial tuberosity.
3. Midway between the medial malleolus and tendo calcaneous.

The line joining (1) and (2) represents the tibial nerve in the popliteal fossa, and the line joining (2) and (3) represents it in the back of the leg.[20]

Anatomical reference point for the nerve, the vessels accompanying the nerve was considered during US examination. At the level of the medial malleolus, posterior tibial nerve is accompanied by the posterior tibial artery and veins, along its medial aspect.[21] The diagnosis of diabetic neuropathy is usually done with Nerve conduction study (NCS), however that's time-consuming and invasive, and isn't feasible for repeated evaluations. US on other side, is often performed at the patient's little or no discomfort, and has already been used for evaluating peripheral neural pathologies.[22,23] DPN symptoms usually, initial site occurrence will be in the toes or the soles of the feet.[24] This was another point why we used the US evaluation of posterior tibial nerve in our study.

Peripheral nerves have a characteristic US pattern that correlates with their histological structure: hypoechoic areas are separated by hyperechoic bands. The hypoechoic areas correspond to neuronal fascicles.[25,26]

Sheila Riazi et al. conducted study on 98 diabetic patients. Severity of DPN was determined using TCNS. At the level of the medial malleolus, 1 cm, 3 cm and 5 cm proximally the cross sectional area of PTN was measured. The result showed that optimal threshold value for diagnosing diabetic peripheral neuropathy was CSA measured at 3 cm above the medial malleolus, with a sensitivity and specificity of 0.69 and 0.77 respectively.[24] In our study, CSA of PTN was measured at the level of 3 cm proximal to the medial malleolus.

In our study CSA of PTN was 11.77 + / - 0.291 mm^2 in case group. CSA of PTN was 6.0 + / - 0.142 mm^2 and 6.0 + / - 0.145 mm^2 respectively in control group. We observed statistically significant increase in the CSA of PTN in cases when compared to that of control with P value < 0.001. (Figure 1 and 2).

Fukashi Ishibashi et al. studied CSA of the posterior tibial nerves in patients with or without diabetic neuropathy. They concluded that the CSA of examined nerves in patients with neuropathy were larger than those in the controls, with significant P - values.[27] The result was similar in our study, where CSA of PTN in DPN patients was increased when compared with the control group, with P < 0.001.

In our study CSA of posterior tibial nerve was measured in both left and right lower limb, and no significant difference was noted. Similar findings were obtained in the study conducted by Fukashi Ishibashi et al..[27]

Kunwarpal Singh et al. studied CSA of PTN in 75 patients with DPN and 75 control subjects. CSA of PTN in DPN patients was 22.63 + / – 2.66 mm^2 and in control subjects was 12.42 + / - 1.01 mm^2 which was statistically significant. Similar findings were obtained in our study (P < 0.001).[28]

HbA1c, which is an index of the blood glucose level average over the next weeks to months. Best way to monitor the glycaemic control in diabetic patients is measuring the HbA1c every quarterly. Onset and as well as progression of diabetic peripheral neuropathy result from the poor glycaemic control.[29]

In our study mean value of HbA1c obtained was 9.11 + / - 1.872 percent. We compared the HbA1c with CSA of PTN in cases. We found statistically significant correlation between them with Pearson coefficient of 0.835 and P value < 0.001. Watanabe et al. evaluated the role of ultrasonography in DPN patients, concluding that, between HbA1c levels and CSA of the peripheral nerves no statistically significant correlation existed.[12] However in our study, a significant correlation was observed between these two parameters, with P < 0.001.

In our study we studied the severity of DPN using TCNS scoring system and compared with the CSA of PTN. The mean value of TCNS was 9.78 + / - 3.819 score. There was significant correlation between the severity of DPN and CSA of PTN. As severity of the DPN increased we found that there was increase in the CSA of PTN in both the limbs. Between CSA of PTN and TCNS, r value was 0.855 and P value was < 0.001, suggesting existence of significant correlation. A

similar finding was observed in the studied conducted by Kunwarpal Singh et al..[28]

Further we classified the DPN patients according to the TCNS system into 4 groups, first group with grade 0 (0 - 5 score) constituted 7 out of 50, second group with grade 1 (6 - 8 score) constituted 16 out of 50, third group with grade 2 (9 - 11) constituted 11 out of 50 and fourth group with grade 3 (12 - 19 score) constituted 16 out of 50 cases. There was significant increase in the CSA of PTN with increase in the grade of severity of DPN was proved.

Due to easy availability, ultrasound machine has the strength of becoming the modality of choice in evaluation of peripheral nerves and can act like adjuvant to other diagnostic tools like NCS. Further studies with larger number of patients are probably required. Our study shows the usage of high resolution ultrasonography in illustrating DPN changes of peripheral nerve which have been previously evaluated in a few studies.

CONCLUSIONS

Thus our study confirmed the increase in CSA of PTN in diabetic peripheral neuropathy patients even with early mild signs and symptoms. We studied the existence of significant correlation with HbA1c levels and TCNS. Hence High Resolution Ultrasonography can be used as a screening and follow up tool in Diabetic Peripheral Neuropathy patients.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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