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Role of high-resolution ultrasonography in the evaluation of the tibial and median nerves in diabetic peripheral neuropathy

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diabetes; peripheral neuropathy; ultrasonography

Abstract

Aim: To evaluate and measure the mean cross-sectional area of the tibial and median nerves in patients with diabetic peripheral neuropathy, and to study the association between high-resolution ultrasonographic findings in diabetic peripheral neuropathy with the duration of illness, glycosylated haemoglobin values, random blood sugar levels, and aesthesiometry (using monofilament examination). **Material and methods:** A prospective observational study was conducted among 63 patients who were diagnosed with type 2 diabetes mellitus and underwent ultrasound and monofilament examinations. The cross-sectional area of the median nerve of the dominant hand and the tibial nerves was calculated on ultrasound examination. **Results:** The mean cross-sectional area of the median and tibial nerves was higher in patients with poor glycaemic control, with the mean cross-sectional area of the median nerve being 10.9, 12.8, 13.0, and 12.9 mm^2 at various points in the leg in cases where the monofilament examination was negative, as compared to 7.30, 7.78, 7.91, 7.87 mm^2 in patients with positive monofilament examination results. There was a significant positive correlation between the cross-sectional area of the tibial and median nerves and HbA_{1c}, duration of diabetes, aesthesiometry, and random blood sugar levels. With an increase in HbA_{1c}, duration of diabetes, and random blood sugar levels, there was a corresponding increase in the cross-sectional area of the nerves. These findings helped us to identify diabetic peripheral neuropathy. **Conclusions:** High-resolution ultrasonography along with aesthesiometry and HbA_{1c} values can be an effective and easily available tool for detecting changes secondary to diabetic peripheral neuropathy. The method has a potential to replace or substitute nerve conduction tests in the near future.

Introduction

Diabetes mellitus (DM) is a disease characterised by hyperglycaemia due to impaired insulin secretion, resistance to the effects of insulin, or both. Poor blood glucose control can lead to microvascular and macrovascular complications. Diabetic peripheral neuropathy (DPN) is one of the major and common complications of DM, and its prevalence in the diabetic population is estimated at approximately 30%[1]. Almost half of the diabetic population develop diabetic neuropathy during the course of their disease[2].

Uncontrolled diabetes is a major risk factor for the development of DPN. Osmotic swelling of nerves occurs due to hyperglycaemia, causing further damage to the axons and the myelin sheath of nerves, and ultimately leading to DPN[3]. Patients with DPN usually present with a sensation of numbness, tingling, sharpness or burning pain. DPN is a progressive disease which, if left untreated, can lead to ulceration and even gangrene, which may lead to the amputation of the affected limb[4]. Lower extremities tend to be more commonly affected than the upper extremities.

The lack of ankle reflexes is the most common sign. The vibration in toes along with pinprick, temperature and high touch sensation are prevalent sensory disturbances. There are many clinical scoring systems available for the evaluation of DPN. The Toronto Clinical Neuropathy Score (TCNS) is one such scoring system which helps to assess the symptoms, sensory tests, and reflex scores of the body[5].

Prevention of complications can improve the overall quality of life in diabetic patients[6], with screening and prompt diagnosis of DPN playing a crucial role in the process. Acral peripheral neuropathy should be evaluated once a year in patients with type 2 diabetes mellitus (T2DM)[7,8].

DPN is diagnosed mostly based on symptoms, with a nerve conduction study (NCS) used to confirm the diagnosis[9–12]. NCS takes a longer time to perform, and in patients with advanced DPN, the action potential in the lower limbs is often more difficult to elicit[13]. Ultrasonographic (US) scans are increasingly used for diagnosing peripheral neuropathy in the diabetic population[14–19].

High-resolution ultrasonography (HRU) can be used to assess nerves adequately in a very short time without causing patient discomfort. With HRU, the entire course of the nerves can be evaluated within a short period of time. The technique can also be used to evaluate smaller nerves. Nerves appear more echogenic than muscles and less echogenic than tendons on standard ultrasound scans. In a longitudinal view, a nerve appears as a hypoechoic stripe (nerve fascicles) partitioned by hyperechoic lines (perineurium). A nerve has a fascicular shape on transverse scans. It has a honeycomb appearance because of the organisation of numerous roundabout hypoechoic fascicles encompassed by the hyperechoic perineurium and epineurium[1].

When compared to NCS, the main advantages of ultrasound imaging are that it is non-invasive, readily available, well tolerated by patients, and inexpensive. Ultrasonography comes with dynamic evaluation and real-time imaging capabilities. The goal of this study was to determine whether ultrasonography could be used to diagnose DPN among diabetic patients suffering from peripheral neuropathy.

Materials and methods

It was a prospective observational study conducted in the Department of Radiodiagnosis following the approval of the Institutional Ethics Committee. The study was done on 63 patients over a period of 18 months. Patients with the clinical diagnosis of T2DM who were referred to the radiology department and gave their consent to participate were enrolled in our study, while those who refused to give their informed consent were excluded. HRU and monofilament examinations were done, and the blood investigations including the RBS levels and HbA_{1c} were also collected during the same hospital visit/stay. Diabetic patients without DPN served as the control group.

High-resolution ultrasonography (HRU)

HRU was performed using SIEMENS S2000/S3000 Acuson or Juniper US scanner (Siemens Medical Systems) equipped with 4–9 MHz and 5–14 MHz linear transducers, by a single observer (a trained radiologist with more than 10 years of experience). We did not include two radiologists for performing the HRU examination to maintain consistency and ensure that the examination would be objective and simple. The right-sided nerves were selected for evaluation to retain uniformity among all the patients.

The patients were first placed in the lateral position, so that the medial area of the ankle and the distal leg could be examined more thoroughly. The cross-sectional area (CSA) of the tibial nerve of the right limbs were measured at 1 cm, 3 cm and 5 cm proximal to the medial malleolus.

For the calculation of the CSA of the median nerve, the patient was placed in the sitting position, with the hands supinated, and the CSA was calculated 5 cm proximal to the wrist.

The values were designated as MN 5 cm, TN 1 cm, TN 3 cm, and TN 5 cm, and expressed in mm^2.

Monofilament examination

Monofilament examination was also done among all the subjects who underwent HRU examination using the Semmes-Weinstein monofilament 10g in the Medicine Department by a single observer (resident) who was trained by a physician with more than 10 years of experience. We placed the monofilament perpendicular to the skin, and pressure was applied until there was buckling. The pressure was released thereafter. The selected sites included the plantar aspect of the great toe, and the base of the first, third and fifth metatarsals in both feet. A score of one was given to each site. The patient was asked to close his/her eyes and to say "yes" if pressure was felt.

Statistical analysis

The data was collected and subjected to statistical analysis using the SPSS software version 24. Pearson's correlation test was used to correlate the nerve CSA and the diabetic profile. Correlations were considered significant at the 0.01 level (2-tailed).

Results

The present prospective study was conducted in the Department of Radiodiagnosis among 63 patients with clinically diagnosed T2DM.

Most of the patients, i.e. 52.38%, had been suffering from diabetes for 5–10 years. Only 6.35% of the patients had been suffering from diabetes for more than 15 years.

Tab. 1. *HbA_{1c} among the study subjects*

HbA_{1c} (in %)	Number of patients	% of patients
≤6.5	3	4.76
>6.5–9	48	76.19
>9	12	19.05
Total	63	100

In our study, 63.5% of the subjects (n = 40) showed negative monofilament examination and only 37.5% showed positive monofilament examination. Mean ± SD RBS (mg/dl) among the study subjects was 303.86 ± 72.83, with minimum and maximum values of 205 and 450, respectively. The CSA of the median and tibial nerves (mean ± SD) including MN 5 cm, TN 1 cm, TN 3 cm and TN 5 cm among the study subjects was 9.59 ± 2.44, 10.97 ± 3.355, 11.16 ± 3.313, and 11.06 ± 3.296, respectively.

Tab. 2. *Mean description of MN 5 cm, TN 1 cm, TN 3 cm and TN 5 cm (CSA of the nerves in mm^2 at various levels)*

Variables	Minimum	Maximum	Mean	Std. deviation
MN 5 cm	5	15	9.59	2.440
TN 1 cm	5	18	10.97	3.355
TN 3 cm	6	18	11.16	3.313
TN 5 cm	5	19	11.06	3.296

Correlation between the HbA_{1c} levels and the CSA of the nerves using Pearson's coefficient shows a statistically significant positive correlation between the two parameters: as the levels of HbA_{1c} increase, the CSA of the nerves also increases. All the nerve parameters, including MN 5 cm, TN 1 cm, TN 3 cm and TN 5 cm, showed a positive correlation with RBS i.e. as the nerve thickness increases, RBS increases as well.

Tab. 3. *Correlation between the nerve CSA and HbA_{1c}, RBS and duration of illness (DOI)*

Parameters		HBA_{1c}	RBS (mg/dl)	DOI (years)
MN 5 cm	Pearson's correlation	0.621*	0.491*	0.652*
	Sig. (2-tailed)	0.000	0.000	0.000
TN 1 cm	Pearson's correlation	0.714*	0.512*	0.704*
	Sig. (2-tailed)	0.000	0.000	0.000
TN 3 cm	Pearson's correlation	0.701*	0.507*	0.712*
	Sig. (2-tailed)	0.000	0.000	0.000
TN 5 cm	Pearson's correlation	0.700*	0.502*	0.705*
	Sig. (2-tailed)	0.000	0.000	0.000

* Correlation is significant at the 0.01 level (2-tailed).
All the nerve parameters, including MN 5 cm, TN 1 cm, TN 3 cm and TN 5 cm, showed a positive correlation with the duration of diabetes (DOI – duration of illness) i.e. as the duration of diabetes increases, the nerve thickness also increases. The nerve thickness was found to be less among the subjects with positive monofilament examination, as compared to negative monofilament examination, with a statistically significant difference (p <0.01).

More than two-thirds, that is 76.19% of the subjects, were found to have HbA_{1c} values between 6.5 and 9%. Only in 4.76% of the subjects, HbA_{1c} was less than 6.5% (Tab. 1).

In our study, 63.5% of the subjects (n = 40) showed negative monofilament examination, and only 37.5% showed positive monofilament examination.

The mean ± SD RBS (mg/dl) among the study subjects was 303.86 ± 72.83, with the minimum and maximum values of 205 and 450, respectively.

The CSA of the median and tibial nerves (mean ± SD, MN 5 cm, TN 1 cm, TN 3 cm and TN 5 cm) among the study subjects was 9.59 ± 2.44, 10.97 ± 3.355, 11.16 ± 3.313, and 11.06 ± 3.296, respectively (Tab. 2).

The analysis of correlations between the HbA_{1c} levels and the CSA of the nerves using Pearson's coefficient shows that there was a statistically significant positive correlation between these two parameters: as the level of HbA_{1c} rises, the CSA of the nerves increases (Tab. 3).

All the nerve parameters, including MN 5 cm, TN 1 cm, TN 3 cm and TN 5 cm, showed a positive correlation with RBS i.e. as the nerve thickness increases, RBS increases as well (Tab. 3).

All the nerve parameters, including MN 5 cm, TN 1 cm, TN 3 cm and TN 5 cm, showed a positive correlation with the duration of diabetes (DOI – duration of illness) i.e. as the duration of diabetes increases, the thickness of the nerves also rises (Tab. 3).

The nerve thickness was found to be less among the subjects with positive monofilament examination as compared to negative monofilament examination, with a statistically significant difference (p <0.01) (Tab. 4).

Discussion

DPN is a distressing complication for patients with diabetes. It is diagnosed mostly based on the patient's reported symptoms and confirmed using NCS[13].

Tab. 4. *Nerve parameters according to monofilament examination results*

Monofilament examination		MN 5 cm	TN 1 cm	TN 3 cm	TN 5 cm
Negative	Mean	10.90	12.80	13.02	12.90
	SD	1.892	2.503	2.370	2.362
Positive	Mean	7.30	7.78	7.91	7.87
	SD	1.363	1.976	1.905	1.984
t test		63.82	67.89	77.91	74.10
p-value		<0.01*	<0.01*	<0.01*	<0.01*

* Statistically significant. Monofilament examination was found to be statistically significant at all the levels of nerve examination.

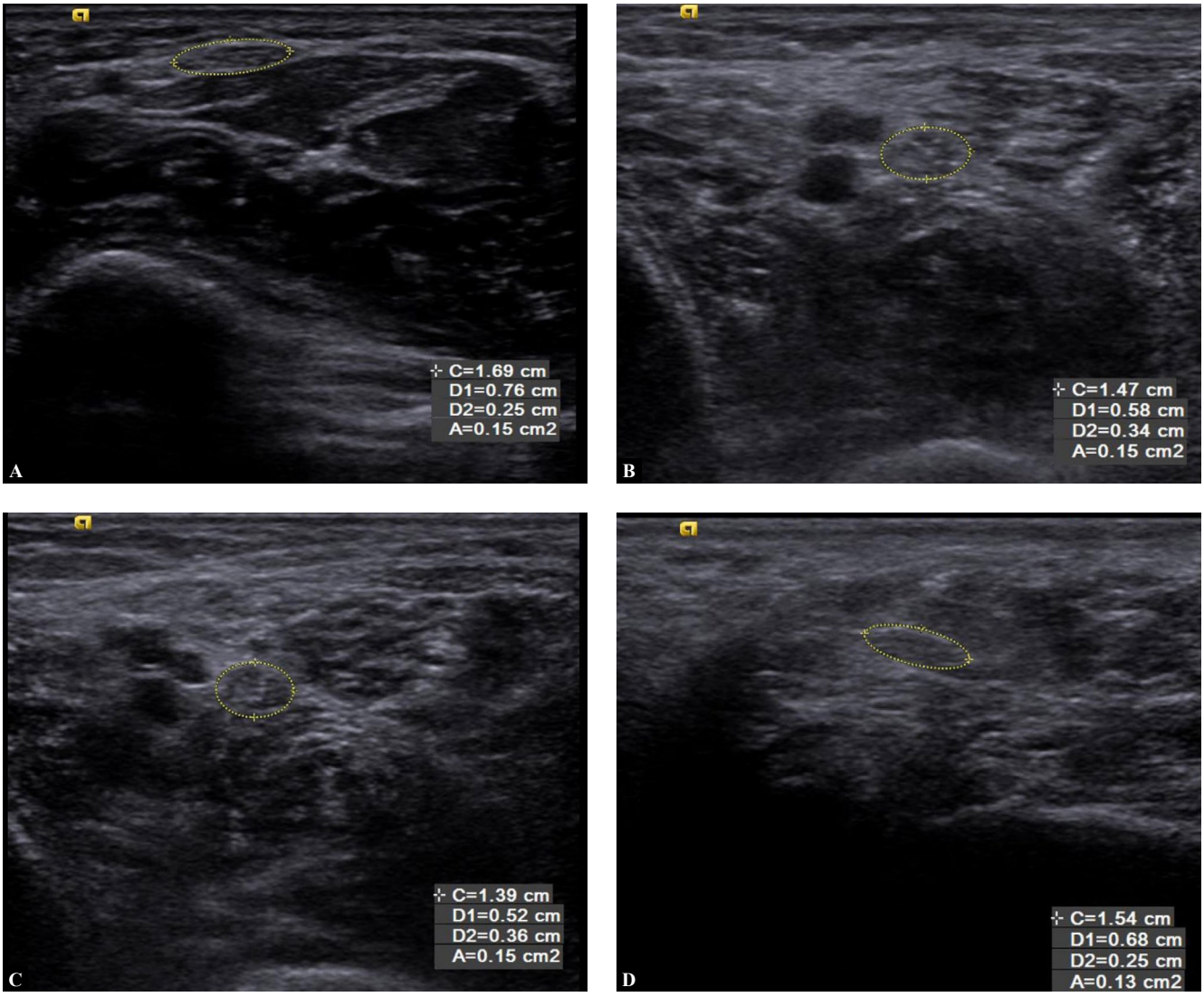

Fig. 1. *Transverse grey-scale ultrasound showing:* **A.** *Thickening of median nerve in a 65-year-old male patient diagnosed with T2DM 10 years previously. The patient had pain in both lower limbs. His HbA_{1c} was 9% and his random blood sugar value was 400 mg/dl. It shows mean cross-sectional area of 15 mm^2.* **B.** *Thickening of tibial nerve at 1 cm proximal to medial malleolus (in the same patient).* **C.** *Thickening of tibial nerve (in the same patient) at 3 cm proximal to medial malleolus.* **D.** *Thickening of tibial nerve (in the same patient) at 5 cm proximal to medial malleolus*

HRU is a relatively new technology for nerve imaging. It is a readily available, patient friendly and cost-effective tool suitable for examining the entire course of the nerve in a short duration of time[14–15].

The aim of our study was to assess the role of HRU in the evaluation of the median and tibial nerves in DPN. We also studied the association between the CSA of the median nerve and the tibial nerve with DOI, HbA_{1c} values, random blood sugar (RBS) levels, and monofilament examination.

The age of the patients included in our study ranged between 41 and 50 years. Only 4.76% were more over 70 years old. The percentages of male (49.2%) and female (50.8%) subjects in the study were almost equal. Our study also correlated a relationship between the duration of diabetes and the mean CSA of the median and tibial nerves. In the study, the majority of the patients, i.e. 52.38%, were suffering from diabetes for 15–20 years.

We measured the CSA of the median nerve at 5 cm proximal to the wrist (MN 5 cm) and the tibial nerve at 1, 3 and 5 cm (TN 1 cm, TN 3 cm, TN 5 cm) proximal to the medial malleolus, revealing a positive relationship between the duration of diabetes and the CSA of these nerves, i.e. as the duration of diabetes increased, the nerve thickness also increased. There was a positive correlation between the CSA of the two nerves and HbA_{1c} levels, duration of diabetes, RBS levels, and monofilament examination (Fig. 1A–1D). Subjects who had good glycaemic control and a shorter duration of diabetes showed no significant thickening of the nerves (Fig. 2A–2D).

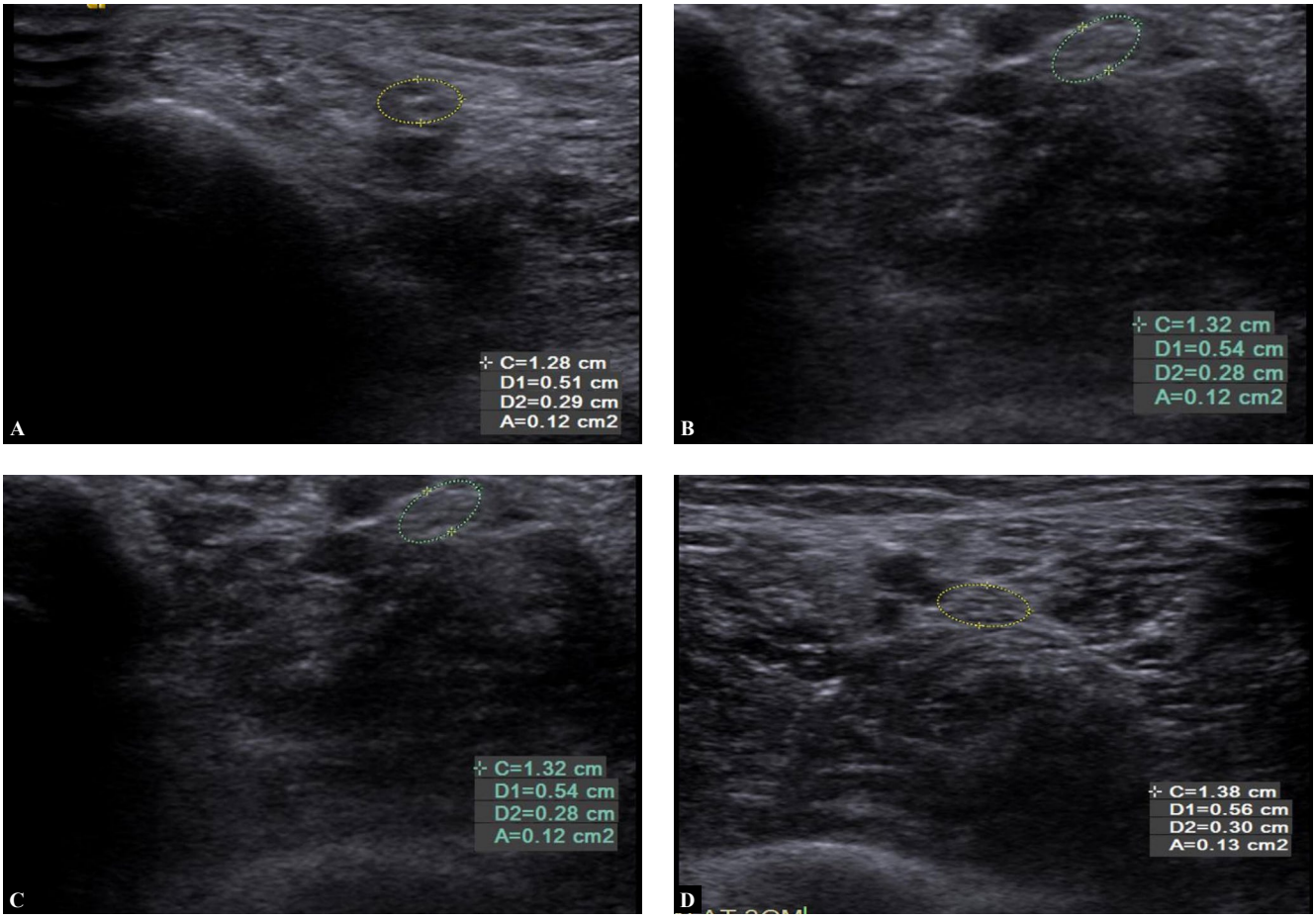

Fig. 2. *Transverse grey-scale ultrasound showing:* **A.** *Median nerve in a 45-year-old female patient diagnosed with T2DM 3 years previously. The patient did not have any neuropathic symptoms. Her HbA_{1c} was 7.9% and her random blood sugar value was 250 mg/dl. It showed mean cross-sectional area of 8 mm², meaning median nerve did not show any thickening. On monofilament examination, she was given a total score of 6 and her tactile sensations were intact.* **B.** *Thickening of tibial nerve (in the same patient) at 1 cm proximal to medial malleolus.* **C.** *Thickening of tibial nerve (in the same patient) at 3 cm proximal to medial malleolus.* **D.** *Thickening of tibial nerve (in the same patient) at 5 cm proximal to medial malleolus*

Sundaram *et al.*[16] reported similar findings in their study comparing nerve thickness with the duration of diabetes. Increased nerve thickness correlated positively with the duration of diabetes.

In our study, we calculated the monofilament score, where a score of less than 3 out of 8 was considered negative, i.e. tactile sensations were absent and indicative of neuropathy, and similarly a score of more than 3 out of 8 was considered positive, i.e. tactile sensations were present in these cases[17]. It was noted that as the nerve thickness increased, the monofilament score decreased. Monofilament examination was found positive in 63.5% and negative in 37.5% of the study subjects. The mean CSA of MN 5 cm, TN 1 cm, TN 3 cm, and TN 5 cm were 10.90, 12.80, 13.02, and 12.90 mm² in cases where the monofilament examination was negative, while the mean CSA of MN 5 cm, TN 1 cm, TN 3 cm, and TN 5 cm thickness was 7.30, 7.78, 7.91, and 7.87 mm² in patients with positive monofilament examination. A score of less than 3 was considered negative and indicative of diabetic neuropathy. A systematic review done to evaluate the Semmes-Weinstein monofilament (SWME) used for diagnosing DPN showed that SWME had a specificity of 75–100% and a positive predictive value of 84–100%[18].

We also studied the association between the nerve CSA and HbA_{1c} levels. The study found that the mean CSA of the right median nerve 5 cm proximal to the wrist (MN 5 cm), and the tibial nerve 1 cm (TN 1 cm), 3 cm (TN 3 cm) and 5 cm (TN 5 cm) proximal to the medial malleolus were 9.59 ± 2.44, 10.97 ± 3.355, 11.16 ± 3.313, and 11.06 ± 3.296 mm², respectively. All the nerve parameters showed a positive correlation with HbA_{1c}, i.e. as HbA_{1c} levels rose, the nerve thickness also increased. Based on these findings, we conclude that there was a significant thickening of the nerves in patients who had poor glycaemic control. Consequently, the patients who had HbA_{1c} levels of more than 8% showed a significant thickening of the nerves. All the nerve parameters showed a positive correlation with RBS as well i.e., as the RBS levels increased, the nerve thickness increased as well.

Afsal *et al.*[19] identified a generalised thickness of the peripheral nerve in individuals with DPN on high-resolution

sonography, and the mean CSA of the MN and ulnar nerves was considerably higher in subjects with DPN than in normal matched controls. The patients with DPN had a median nerve CSA of 10.5 mm^2, whereas the controls had a median nerve CSA of 7.1 mm^2. According to Watanabe *et al*.[20], patients with DPN showed a considerable rise in the CSA of the MN (median nerve) when compared to the controls. The aim of the authors was to find an association between the NCS and size of nerves on HRU. They selected 40 patients (20 diabetics and 20 healthy subjects), and by studying them, they found a significant increase in the size of the nerve (increased CSA) in patients with diabetic neuropathy. They reported that the mean CSA of MN 5 cm proximal to the wrist crease in individuals with DPN was 11.61 ± 2.87 mm^2, which was substantially greater than the value of 7.09 ± 1.49 mm^2 reported in healthy volunteers.

Pitarokoili *et al*.[21] also discovered that the patients had a higher median nerve CSA (in mm^2) than the controls. In our case, tibial nerve 1 cm (TN 1 cm), 3 cm (TN 3 cm) and 5 cm (TN 5 cm) proximal to the medial malleolus were 9.59 ± 2.44, 10.97 ± 3.355, 11.16 ± 3.313, and 11.06 ± 3.296 mm^2, respectively. Kumar *et al*.[22] conducted a study among 50 adult diabetes patients with DPN and 50 without DPN (diabetic neuropathy). HRU was performed on the medial, ulnar and common peroneal nerves. At 5 cm proximal to the wrist, the diabetics without DPN had a significantly smaller median nerve thickness (7.34 ± 1.24 vs 11.12 ± 1.56, $p < 0.0001$). The tibial nerve was significantly thickened in patients with DPN compared to those without DPN and control participants in a study by Dikici *et al*.[23]. Grey-scale ultrasonography and shear wave elastography (SWE) were used to investigate the tibial nerve 4 cm proximal to the medial malleolus in their study. Ishibashi *et al*.[24] also found that the mean CSA of TN was significantly higher when compared with controls. Patients with DPN had a substantially greater mean CSA (22.63 ± 2.66 mm^2) and maximum thickness of the nerve fascicles (0.70 mm) of the TN than the control groups. Singh *et al*.[1] in their study showed that the peripheral nerves can be reliably visualised by HRU in both healthy volunteers and diabetic patients. HRU demonstrates an increase in the CSA of all peripheral nerves examined in a patient with DPN as compared to normal healthy volunteers. The observed difference was statistically significant.

All the above-mentioned studies showed that the CSA of the nerves in patients with DPN increased compared to the control groups, so the findings were consistent with our study. However, there was not a single study which compared all the factors at the same time, that is the duration of diabetes, HbA_{1c} levels, random blood sugar (RBS) levels and the monofilament examination, with the CSA of the peripheral nerves on HRU, as we did in our study. Hence our study was unique as compared to all the previous studies which only considered one or more of the above parameters, but never all the parameters investigated in our study.

Limitations & future prospects

A major limitation of our study was that we were unable to perform nerve conduction tests in all the patients included in the study due to logistic and other reasons. Further studies should be performed with the inclusion of the gold standard nerve conduction tests in order to accurately validate the results.

Another limitation was that the RBS level is an unreliable marker of glycaemic control because of its variability with quality and quantity of food consumed. Since HbA_{1c} levels are only indicative of glycaemic control over a period of three months, follow-up HbA_{1c} levels would be required. In addition, we could not measure interobserver variability since a single observer measured the CSA of the nerves in all the patients. However, since the examination is a relatively simple one for a radiologist with more than 10 years of experience, we hoped that this would not have much effect on the results.

Based on the findings, we believe that more research should be done in the near future to validate HRU as an easier strategy for screening and diagnosis of early cases of DPN, which can aid in improving patient management and thus improve the overall quality of life.

Conclusion

In our study, the cross-sectional area of the tibial and median nerves was found to correlate strongly with HbA_{1c} levels, RBS levels, duration of diabetes, and monofilament examination. In our opinion, HRU in combination with HbA_{1c} levels and monofilament examination can be regarded as an easily available, inexpensive, and effective technique for detecting changes secondary to peripheral neuropathy.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contributions

Original concept of study: TR, SC, JH. Writing of manuscript: TR, S.C. Analysis and interpretation of data: TR, S.C. Final approval of manuscript: TR, S.C. Collection, recording and/or compilation of data: TR, SC, AM, AA, DS. Critical review of manuscript: TR, JH SC, AM, AA.

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