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Ultrasonogram morphology of tibial nerve in type 2 diabetes mellitus patients and its association with HbA1c

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Abstract
Background: In the recent years High-resolution ultrasonography (HRUS) has geared up as a new diagnostic tool in the work-up of peripheral nerve diseases. As most of the peripheral nerves run a superficial course over a long tract, especially in the arms and legs which could be easily visualised using ultrasonogram.
Aim: To assess the morphology of tibial nerve using ultrasonogram and correlate it with the glycemic score among the diabetes mellitus patients
Methodology: A cross-sectional study was conducted for a period of 6 months in the radiology department. A non-random quota sampling was followed to select the sample size and based on that 50 subjects were taken as our study sample. All known type II diabetes patients with a history of peripheral neuropathy were included as our study subjects. Ultrasonography was performed for all study subjects with USG Samsung Accuvix XG Linear probe 5-12 MHz. The maximum thickness of the nerve fascicle was calculated by the largest antero-posterior dimension and the lateral dimension of the largest hypoechoic area in the short axis view of the tibial nerve.
Results: Correlation between the HbA1C levels and the maximum thickness of nerve fascicles measurements shows that there was statistically significant positive correlation exist between the two parameters, as the levels of HbA1c increases the thickness of nerve fascicles also increases and similarly a statistical significant association was observed between the duration of diabetes and maximum thickness of nerve fascicles.
Conclusion: Ultrasonography is an excellent diagnostic tool for detecting morphological changes in the tibial nerves in diabetic patients.

Keywords: peripheral neuropathy, diabetes, HbA1C, ultrasonogram

Introduction

World Health Organisation in its report on non-communicable diseases published in the year 2015 had quoted that more than 69 million people in India are living with diabetes and more than 50% of the cases still being undiagnosed [1]. Of the various complications reported in diabetes mellitus peripheral neuropathy is one the most common complication with a prevalence of 30% and it is found to be one of the earliest complication to occur. The major risk factor for the development of peripheral neuropathy among diabetes patients is poor glycemic control [2]. The pathogenesis behind this is constant increase in blood glucose levels leads to osmotic swelling of the nerves which would injure the axons and myelin sheath invariably triggers the onset of peripheral neuropathy. The most common presentation is the patients come with the complaints of tingling, numbness, or prickling sensations in the feet which presents most often bilaterally and sometime even asymmetrical presentation. The most common sign is the absence of ankle reflexes [3]. Most of the time the clinicians treat the conditions based on the symptoms presented but today the practice of medicine is insisting more on evidence based medicine and so merely relying on the symptoms of the patients certain investigation can be made to exactly identify the peripheral neuropathy. Nerve conduction study being considered as the gold standard for diagnosing peripheral neuropathy but it is mostly used by neurologist with a sophisticated set up and presence of at least one abnormal parameter such as amplitude, latency and conduction velocity of the nerve is required for diagnosing peripheral neuropathy [4]. In the recent years High-resolution ultrasonography (HRUS) has geared up as a new diagnostic tool in the work-up of peripheral nerve diseases [5].

As most of the peripheral nerves run a superficial course over a long tract, especially in the arms and legs which could be easily visualised using ultrasonogram. This is a major advantage when compared to Magnetic Resonance Imaging (MRI) when we need multiple nerves to be studied, as MRI is expensive, time consuming and not readily available everywhere [6, 7]. Using HRUS different aspects of nerve morphology can be studied, such as the nerve cross sectional area (CSA) which can be determined at multiple sites along the nerve both at the nerve entrapment and non-entrapment sites. Apart from nerve CSA vascularization, echogenicity, fascicular pattern and endoneurial thickness can also be assessed using ultrasonogram. All these measurements would yield a critical insight in the origin and development of various peripheral neuropathies. More recent studies had shown that HRUS use in determining the diagnosis and cause of different types of mononeuropathy, like carpal tunnel syndrome and ulnar neuropathy at the elbow [8-10]. In recent years research into applications of HRUS in assessing polyneuropathies has vastly expanded as well. As such only very few studies had been done on usage of ultasonogram in diagnosing peripheral neuropathy diseases and those studies were also mostly done in western countries and so the present study was conducted to assess the morphology of tibial nerve using ultrasonogram and correlate it with the glycemic score among the diabetes mellitus patients.

Methodology

A cross-sectional study was conducted for a period of 6 months in the radiology department of Annapoorna Medical College and Hospital. The study was started after getting approval from the institutional ethics committee and the informed consent was obtained from all the patients involved in the study. A non-random quota sampling was followed to select the sample size and based on that 50 subjects were taken as our study sample. All known type II diabetes patients with a history of peripheral neuropathy whom were referred from medicine department were included as our study subjects. Patients with history of varicose veins, cellulitis, Vitamin B12 deficiency, toxic or uremic neuropathy and with metabolic or inflammatory causes were excluded from study. A semi-structured questionnaire was prepared to obtain the details related to demographic information, BMI, blood pressure, clinical history, symptoms, diabetes duration and glycemic status. HbA1c was measured for all the patients involved in the study. Ultrasonography was performed with USG Samsung Accuvix XG Linear probe 5-12 MHz. The examination was performed with the patient lying in a lateral position for an easy assessment of the medial aspect of the ankle and distal leg. The cross sectional area and maximum thickness of nerve fascicles of bilateral tibial nerves were recorded 3 cm above the medial malleolus. The cross sectional area was calculated by manual tracing. The maximum thickness of the nerve fascicle was calculated by the largest antero-posterior dimension and the lateral dimension of the largest hypoechoic area in the short axis view of the tibial nerve. The radiologist who was performing the ultrasonogram was blinded to HbA1c levels, the duration of the disease and the pain symptom for peripheral neuropathy. The maximum thickness of nerve fascicles (MTNF) were statistically correlated with HbA1c and duration of diabetes. Pearson's correlation co-efficient and chi-square test were used to derive the statistical inference.

Results

The age and gender wise distribution of our study subjects shows that majority of them were in the age group between 50 and 70 years with a mean age of 57.5 years among males and 56.7 years among females. Males were comparatively larger in number than the females with a male: female ratio of 1.97: 1 (table 1). Among our study population only 14% of them had a strict diabetes control with HbA1c <7gms% and 50% of them had the HBA1C levels between 8 and 10 gms% with a mean level of 8.2 ± 1.3 gms% (table 2). Based on the history derived more than 80% of the study subjects had the duration of diabetes for more than 5 years with 6% of subjects having it for more than 20 years and the mean duration was 9.5 years (table 3). The common symptoms presented among the patients were pain, swelling, numbness and loss of sensation with more than 50% complains of pain (table 4). The mean and standard deviation of maximum thickness of nerve fascicles of antero-posterior and lateral dimensions of both the right and left leg was tabulated in table no. 5. Correlation was made between the HbA1C levels and the maximum thickness of nerve fascicles measurements and it was shown that there was statistically significant positive correlation exist between these two parameters, as the levels of HbA1c increases the thickness of nerve fascicles increases (table 6). Similarly a qualitative analysis was done between the duration of diabetes and the nerve thickness measurements using chi-square test and it was shown that there is a statistical significant association between the duration of diabetes and the maximum thickness of nerve fascicles, as the duration of diabetes increases the thickness of nerve increases (table 7).

Table 1: Age and gender wise distribution of the study subjects

Age group	Male	Female
20 – 30	1 (3%)	2 (11.7%)
31 – 40	2 (6%)	2 (11.7%)
41 – 50	4 (12%)	1 (5.8%)
51 – 60	12 (36.3%)	6 (35.2%)
61 – 70	13 (39.3%)	3 (17.6%)
>70	1 (3%)	3 (17.6%)
Total	33 (100%)	17 (100%)
Mean ± SD	57.5 ± 10.9	56.7 ± 14.3

Table 2: Distribution of the study subjects based on HbA1C levels

HbA1C (gms %)	Frequency	Percentage	Mean ± SD
<7	7	14%	8.2 ± 1.3
7 – 8	18	36%	
8.1 – 9	13	26%	
9.1 – 10	12	24%	
>10	1	2%	
Total	50	100%	

Table 3: Distribution of the study subjects based on the duration of diabetes

Duration of diabetes (in years)	Frequency	Percentage	Mean ± SD
<5	9	18%	9.5 ± 5.9
5 – 10	31	62%	
10.1 – 15	5	10%	
15.1 – 20	2	4%	
>20	3	6%	
Total	50	100%	

Table 4: Distribution of the study subjects based on the symptoms of peripheral neuropathy

Symptoms of peripheral neuropathy	Frequency	Percentage
Pain	27	54%
Swelling	24	48%
Numbness	20	40%
Loss of sensation	15	30%

Table 5: Mean and SD of the measurements on tibial nerve made by the ultrasonogram

Measurements	Mean	SD
Right leg antero-posterior	0.55	0.10
Right leg lateral	0.62	0.11
Left leg antero-posterior	0.55	0.11
Left leg lateral	0.61	0.11

Table 6: Correlation between HbA1C levels and the tibial nerve measurements

	Tibial nerve measurements	r value (Pearson's co-efficient)	P value
HbA1C	Right leg antero-posterior	0.687	<.001
	Right leg lateral	0.649	<.001
	Left leg antero-posterior	0.650	<.001
	Left leg lateral	0.607	<.001

Table 7: Association between duration of diabetes and tibial nerve measurements

Duration of diabetes	Tibial nerve measurements			
	Right leg antero-posterior	Right leg lateral	Left leg antero-posterior	Left leg lateral
<7	0.52	0.61	0.51	0.57
7 – 10	0.56	0.61	0.55	0.62
10.1 – 15	0.62	0.66	0.63	0.70
>15	0.68	0.68	0.62	0.69
P value	<.05	0.03	<.05	0.024

Discussion

In the earlier days peripheral nerve disorders was diagnosed only based on clinical history and neurological examination then later on diagnostic technique like nerve conduction study and electromyography were introduced but both these methods had some limitations such as either being invasive procedure, high cost and time consuming [11]. Nerve imaging technique had gained its popularity by overcoming these limitations by providing information on nerve morphology, its anatomical location and evaluation of areas which were not accessible with electro diagnostic tests [12]. Among these nerve imaging techniques High resolution ultrasound (HRUS) and magnetic resonance imaging (MRI) are the most commonly used methods. An important break-through occurred in the ultrasound diagnostics of peripheral nerves when the ultrasound probes with high frequencies (greater than 12-15 MHz) were introduced [13]. Peripheral nerves visualised through ultrasound have a typical pattern; hypoechoic areas being separated by hyperechoic bands. The hypoechoic areas correspond to neuronal fascicles [14, 15].

In patients with diabetic neuropathy sural nerve and tibial nerve were the earliest nerves to be affected. Due to high spatial resolution of ultrasound and the tibial nerve getting visualised at the level of medial malleolous examining tibial nerve has become a good choice for investigation. The vessels accompanying the nerves are taken as anatomical reference points, at the level of the medial malleolus, it is accompanied by the posterior tibial artery and veins, proximally on its anterior side, and distally along its medial aspect [16]. The symptoms of diabetic peripheral neuropathy usually first felt either on the side of greater toe or the soles of the feet and so we used the tibial nerve as the studied structure in our study [17]. In our study we measured the cross-sectional area of the tibial nerve at 1, 3, and 5 cm proximal to the level of the medial malleolus, as previously conducted studies had concluded that the sensitivity and specificity of diagnosing diabetic peripheral neuropathy was 70% and 77% respectively when the cross sectional area was measured at 3 cm above the medial malleolus [10].

In a study conducted in Japan hypoechoic area and MTNF (maximum thickness of nerve fascicles) of the median and posterior tibial nerves measured by direct tracing and concluded that the morphological changes in peripheral nerves of type 2 diabetic patients were seen much earlier to the clinical onset of neuropathy [18]. In our study we were not able to assess whether the tibial nerve morphological changes had occurred much earlier to the clinical manifestations as our study subjects were only diabetic patients and majority of them had the symptoms of peripheral neuropathy when they were subjected to ultrasonogram. All the study subjects involved in our study were having either one or multiple symptom of peripheral neuropathy like pain, swelling, numbness or loss of sensation.

The mean MTNF of anterio posterior and transverse diameter of the patients in our study was more than 0.5 mm in both the legs which is found to be much higher than the normal (0.3 mm), as mentioned by the previous studies. There was no statistically significant difference in the MTNF measurement of the tibial nerves between right and left lower limbs and similarly no statistical significant difference was observed in MTNF measurement between males and females. Whereas in a study conducted by Fukashi Ishibashi *et al. and* Kunwarpal Singh *et al*. had showed a higher reading in males compared to females and the difference was found to be statistically significant [18, 19]. HbA1c is an index of the average blood glucose level over the preceding weeks to months. HbA1c determination is an important measure of glycemic control of the patient which is most often done at every quarter. Poor glycaemic control can result in the onset as well as progression of diabetic peripheral neuropathy. In the present study we found a statistically significant positive correlation between HbA1c levels and the MTNF antero posterior and transverse diameter but our results were contradicting to the observations made by Watanabe *et al., in his study he found there was no statistical significant correlation between the two parameters, whereas in the study done by* Kunwarpal Singh *et al*. the results were almost similar to our study highlighting a positive statistically significant correlation between HBA1c and MTNF measurements [9, 19]. A similar type of association was also seen between the duration of diabetes and measurements of maximum thickness of nerve fascicles. Studies done earlier had shown that the size of the nerve fascicles is one of the determinants of the hypoechoic area in cross-sectional area of peripheral nerves and the MTNF measurements in non-neuropathic diabetic patients was larger compared to non-diabetic patients [20, 21]. This shows that the nerve pathology can be identified much earlier even before the symptoms of neuropathy occur among the diabetes patients. In our study as we did not use a

control group (non-diabetic group) and so we were not able to prove this result.

Conclusion

Our study confirms that the maximum thickness of nerve fascicles of the tibial nerve correlates with HbA1c levels and the duration of diabetes. Ultrasonography is an excellent diagnostic tool for detecting morphological changes in the tibial nerves in diabetic patients much earlier than the clinical presentation of peripheral neuropathy

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