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Ultrasonographic evaluation of tibial nerve in diabetic peripheral neuropathy

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Abstract
One of the major complications of diabetes mellitus is peripheral neuropathy with reported prevalence of approximately 25%. The pathophysiology of DPN is multifactorial and involves genetic, metabolic and vascular factors. Diabetes induced endothelial dysfunction with a resultant decrease in nerve blood flow (vasa nervorum) plays a key role in axonal degeneration, demyelination of nerve fibre. Hyperglycemia includes increased metabolic flux through the polyol pathway with consequent sorbitol and fructose accumulation in DPN. High-resolution ultrasound is the most commonly used imaging modality because it is inexpensive, provides high resolution, is readily available and allows for dynamic imaging. Most studies suggest that the key ultrasonographic finding is enlargement of the tibial nerve in diabetic peripheral neuropathy. Hence the present study was planned with aims of study was to evaluate the cross sectional area and maximum thickness of nerve fascicles of the tibial nerve in patients of diabetic peripheral neuropathy by using high resolution ultrasound.
Total 30 cases of the diabetic peripheral neuropathy (DPN) were enrolled as cases in Group A and in Group B 20 cases of the control patients without any indications of diabetes and peripheral neuropathy. The patients were examined in supine position with lateral rotation of foot. The transducer was placed 3cm above the medial malleolus to locate the tibial nerve in the transverse (short axis) and in the longitudinal (long axis) axis by using GE LOGIQ P5 ultrasound machine. The cross sectional area of tibial nerve was taken by manual tracing was used for tibial nerve scanning.
From the findings of present study it can be concluded that the cross sectional areas and maximum thickness of nerve fascicles of the tibial nerve is larger in type 2 diabetic patients with peripheral neuropathy than those of healthy control cases and sonographic examinations are very useful for the early diagnosis of diabetic neuropathy. Early detection of nerve dysfunction is important to provide appropriate care for patients with diabetic polyneuropathy.

Keywords: tibial nerve, diabetic peripheral neuropathy, diabetes, high resolution ultrasonography, etc

Introduction
The tibial nerve is a branch of the sciatic nerve. The tibial nerve passes through the popliteal fossa to pass below the arch of soleus. Tibia nerve is the larger terminal branch of the sciatic nerve with root values of L4, L5, S1, S2, and S3. It lies superficial (or posterior) to the popliteal vessels, extending from the superior angle to the inferior angle of the popliteal fossa, crossing the popliteal vessels from lateral to medial side.
Diabetic neuropathies are nerve damaging disorders associated with diabetes mellitus. These conditions are thought to result from a diabetic microvascular injury involving small blood vessels that supply nerves (vasa nervorum) in addition to macrovascular conditions that can accumulate in diabetic neuropathy. Relatively common conditions which may be associated with diabetic neuropathy include third, fourth, or sixth cranial nerve palsy [1]; mononeuropathy; mononeuropathy multiplex; diabetic amyotrophy; a painful polyneuropathy; autonomic neuropathy; and thoracoabdominal neuropathy.
Diabetic neuropathy affects all peripheral nerves including sensory neurons, motor neurons, but rarely affects the autonomic nervous system. Therefore, diabetic neuropathy can affect all organs and systems, as all are innervated. There are several distinct syndromes based on the organ systems and members affected, but these are by no means exclusive. A patient can have sensorimotor and autonomic neuropathy or any other combination. Signs and symptoms vary depending on the nerve (s) affected and may include symptoms other than those listed. Symptoms usually develop gradually over years.
Vascular and neural diseases are closely related and intertwined. Blood vessels depend on normal nerve function, and nerves depend on adequate blood flow. The first pathological change in the small blood vessels is narrowing of the blood vessels. As the disease progresses, neuronal dysfunction correlates closely with the development of blood vessel abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia, which contribute to diminished oxygen tension and hypoxia. Neuronal ischemia is a well-established characteristic of diabetic neuropathy. Blood vessel opening agents (e.g., ACE inhibitors, α1-antagonists) can lead to substantial improvements in neuronal blood flow, with corresponding improvements in nerve conduction velocities. Thus, small blood vessel dysfunction occurs early in diabetes, parallels the progression of neural dysfunction, and may be sufficient to support the severity of structural, functional, and clinical changes observed in diabetic neuropathy. Elevated levels of glucose within cells cause a

non-enzymatic covalent bonding with proteins, which alters their structure and inhibits their function. Some of these glycated proteins have been implicated in the pathology of diabetic neuropathy and other long-term complications of diabetes.

Longer nerve fibers are affected to a greater degree than shorter ones because nerve conduction velocity is slowed in proportion to a nerve's length. In this syndrome, decreased sensation and loss of reflexes occurs first in the toes on each foot, then extends upward. It is usually described as a glove-stocking distribution of numbness, sensory loss, dysesthesia and night time pain. The pain can feel like burning, pricking sensation, achy or dull. A pins and needles sensation is common. Loss of proprioception, the sense of where a limb is in space, is affected early. These patients cannot feel when they are stepping on a foreign body, like a splinter, or when they are developing a callous from an ill-fitting shoe. Consequently, they are at risk of developing ulcers and infections on the feet and legs, which can lead to amputation. Similarly, these patients can get multiple fractures of the knee, ankle or foot, and develop a Charcot joint. Loss of motor function results in dorsiflexion, contractures of the toes, loss of the interosseous muscle function that leads to contraction of the digits, so-called hammer toes. These contractures occur not only in the foot but also in the hand where the loss of the musculature makes the hand appear gaunt and skeletal. The loss of muscular function is progressive.

The autonomic nervous system is composed of nerves serving the heart, lungs, blood vessels, bone, adipose tissue, sweat glands, gastrointestinal system and genitourinary system. Autonomic neuropathy can affect any of these organ systems. The most commonly recognized autonomic dysfunction in diabetics is orthostatic hypotension, or becoming dizzy and possibly fainting when standing up due to a sudden drop in blood pressure. In the case of diabetic autonomic neuropathy, it is due to the failure of the heart and arteries to appropriately adjust heart rate and vascular tone to keep blood continually and fully flowing to the brain. This symptom is usually accompanied by a loss of respiratory sinus arrhythmia – the usual change in heart rate seen with normal breathing. These two findings suggest autonomic neuropathy.

GI tract manifestations include gastroparesis, nausea, bloating, and diarrhea. Because many diabetics take oral medication for their diabetes, absorption of these medicines is greatly affected by the delayed gastric emptying. This can lead to hypoglycemia when an oral diabetic agent is taken before a meal and does not get absorbed until hours, or sometimes days later when there is normal or low blood sugar already. Sluggish movement of the small intestine can cause bacterial overgrowth, made worse by the presence of hyperglycemia. This leads to bloating, gas and diarrhea. Urinary symptoms include urinary frequency, urgency, incontinence and retention. Again, because of the retention of urine, urinary tract infections are frequent. Urinary retention can lead to bladder diverticula, stones, reflux nephropathy.

When cranial nerves are affected, neuropathies of the oculomotor nerve (cranial nerve #3 or CNIII) are most common. The oculomotor nerve controls all the muscles that move the eye except for the lateral rectus and superior oblique muscles. It also serves to constrict the pupil and open the eyelid. The onset of a diabetic third nerve palsy is usually abrupt, beginning with frontal or pain around the eye and then double vision. All the oculomotor muscles innervated by the third nerve may be affected, but those that control pupil size are usually well-preserved early on. This is because the parasympathetic nerve fibers within CNIII that influence pupillary size are found on the periphery of the nerve (in terms of a cross-sectional view), which makes them less susceptible to ischemic damage (as they are closer to the vascular supply). The sixth nerve, the abducens nerve, which innervates the lateral rectus muscle of the eye (moves the eye laterally), is also commonly affected but fourth nerve, the trochlear nerve, (innervates the superior oblique muscle, which moves the eye downward) involvement is unusual. Damage to a specific nerve of the thoracic or lumbar spinal nerves can occur and may lead to painful syndromes that mimic a heart attack, gallbladder inflammation, or appendicitis. Diabetics have a higher incidence of entrapment neuropathies, such as carpal tunnel syndrome.

Diabetes is the leading known cause of neuropathy in developed countries, and neuropathy is the most common complication and greatest source of morbidity and mortality in diabetes. It is estimated that neuropathy affects 25% of people with diabetes [2]. Diabetic neuropathy is implicated in 50–75% of nontraumatic amputations. The main risk factor for diabetic neuropathy is hyperglycemia. In the DCCT (Diabetes Control and Complications Trial, 1995) study, the annual incidence of neuropathy was 2% per year but dropped to 0.56% with intensive treatment of Type 1 diabetics. The progression of neuropathy is dependent on the degree of glycemic control in both Type 1 and Type 2 diabetes. Duration of diabetes, age, cigarette smoking, hypertension, height, and hyperlipidemia are also risk factors for diabetic neuropathy.

Neuropathies are the most common complication of diabetes mellitus (DM), affecting up to 50% of patients with type 1 and type 2 DM. In type 1 diabetes mellitus, distal polyneuropathy typically becomes symptomatic after many years of chronic prolonged hyperglycemia. Conversely, patients with type 2 diabetes mellitus may present with distal polyneuropathy after only a few years of known poor glycemic control; sometimes, these patients already have neuropathy at the time of diagnosis. Neuropathies severely decrease patients' quality of life (QOL). Furthermore, while the primary symptoms of neuropathy can be highly unpleasant, the secondary complications (eg, falls, foot ulcers, cardiac arrhythmias, and ileus) are even more serious and can lead to fractures, amputations, and even death in patients with DM.

Since diabetic neuropathy can manifest with a wide variety of sensory, motor, and autonomic symptoms, a structured list of symptoms can be used to help screen all diabetic patients for possible neuropathy. Physical examination of patients with suspected distal sensory motor or focal (i.e, entrapment or noncompressive) neuropathies should include assessments for both peripheral and autonomic neuropathy. Multiple consensus panels recommend the inclusion of electrophysiologic testing in the evaluation of diabetic neuropathy. An appropriate array of electrodiagnostic tests includes both nerve conduction testing and needle EMG of the most distal muscles usually affected.

Management of diabetic neuropathy should begin at the initial diagnosis of diabetes. The primary care physician needs to be alert for the development of neuropathy—or

even its presence at the time of initial diabetes diagnosis—because failure to diagnose diabetic polyneuropathy can lead to serious consequences, including disability and amputation. In addition, the primary care physician is responsible for educating patients about the acute and chronic complications of diabetes (see Patient Education). Patients with diabetic peripheral neuropathy require more frequent follow-up, with particular attention to foot inspection to reinforce the need for regular self-care.

Management of diabetic neuropathy includes 2 approaches: therapies for symptomatic relief and those that may slow the progression of neuropathy. Of all treatments, tight and stable glycemic control is probably the most important for slowing the progression of neuropathy. Many medications are available for the treatment of diabetic neuropathic pain, although most of them are not specifically approved by the United States Food and Drug Administration for this use. Nonpharmacologic treatment includes rehabilitation, which may comprise physical, occupational, speech, and recreational therapy.

High-resolution ultrasonography (HRUS) is a diagnostic tool that is increasingly used in the work-up of peripheral nerve disease. As many peripheral nerves run a superficial course, they can be studied over a long tract, especially in the arms. This is a big advantage over Magnetic Resonance Imaging (MRI) when multiple nerves have to be studied, as MRI is relatively expensive, time consuming and not readily available everywhere. Different aspects of nerve morphology can be studied with HRUS. Nerve cross-sectional area (CSA) can be determined at multiple sites along the nerve. CSA can be measured at entrapment sites (e.g. the carpal tunnel, cubital tunnel, Guyon's canal and the fibular head), but also at nonentrapment sites. Apart from nerve CSA vascularization, echogenicity, fascicular pattern and endoneurial thickness can be investigated as well. All those modalities can give critical insight in the origin and development of various peripheral neuropathies. The additional value of HRUS in determining diagnosis and cause of different types of mononeuropathy, like carpal tunnel syndrome and ulnar neuropathy at the elbow, has been established in the past years [3-5]. In recent years research into applications of HRUS in assessing polyneuropathies has vastly expanded as well. This lecture summarizes the most important findings of those studies.

The pathophysiology of DPN is multifactorial and involves genetic, metabolic and vascular factors. Diabetes induced endothelial dysfunction with a resultant decrease in nerve blood flow (vasa nervorum) plays a key role in axonal degeneration, demyelination of nerve fibre. Hyperglycemia includes increased metabolic flux through the polyol pathway with consequent sorbitol and fructose accumulation in DPN [6]. High-resolution ultrasound is the most commonly used imaging modality because it is inexpensive, provides high resolution, is readily available and allows for dynamic imaging. Most studies suggest that the key ultrasonographic finding is enlargement of the tibial nerve in diabetic peripheral neuropathy. Hence the present study was planned to evaluate the cross sectional area and maximum thickness of nerve fascicles of the tibial nerve in patients of diabetic peripheral neuropathy by using high resolution ultrasound.

Evaluate the tibial nerve in patients with diabetic peripheral neuropathy by using high resolution ultrasound.

Methodology

The present study was planned in Department of Radio-Diagnosis, DMCH, Bihar from April 2015 to March 2016. Total 30 cases of the diabetic peripheral neuropathy (DPN) were enrolled as cases in Group A and in Group B 20 cases of the control patients without any indications of diabetes and peripheral neuropathy were enrolled. The patients were examined in supine position with lateral roatation of foot. The transducer was placed 3 cm above the medial malleolus to locate the tibial nerve in the transverse (short axis) and in the longitudinal (long axis) views. The cross sectional area of Tibial nerve was taken by manual tracing. The maximum thickness of nerve fascicles was taken by antero-posterior diameter of tibial nerve in short axis view. Ultrasound of tibial nerve was done on GE LOGIQ P5 machine and 3.5 - 10.8 MHz multi frequency linear array 11 L transducer was used.

All the patients were informed and written consent were taken from them. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Cases of the diabetic peripheral neuropathy (DPN), Age ranging from Age 40 – 75 years.

Exclusion Criteria: Non diabetic cases of neuropathy.

Results & Discussion

High resolution sonographic examination can be performed to assess the peripheral nerves with less discomfort of patients. Moreover it is painless, noninvasive, less expensive and to screen extensive length of nerves quickly with good resolution and has already been used for the evaluation of disorders of the peripheral nerves. Thus, this would be a beneficial tool for the doctor to assess and make quick decision about patient with DPN and to follow up the patients [7, 8].

The clinical and US characteristics of groups are presented in Tab. 1 and Tab. 2. Male predominance is observed. The mean CSA of the tibial nerve is significantly larger in patients with diabetic peripheral neuropathy compared with control group. The maximum thickness of nerve fascicles of tibial nerve in patients with diabetic peripheral neuropathy is 7.0 mm which is significantly larger than control group.

Table 1: Demographic Details

Group	**Group A**	**Group B**
Cases of	**Diabetic peripheral neuropathy**	**Control**
Number of Cases	30	20
Age	40-75	35 – 64
Sex		
Males	28	12
Females	12	8

Table 2: Comparison of mean CSA and MTNF of tibial nerve

Group	**Group A**	**Group B**
Cases of	**Diabetic peripheral neuropathy**	**Control**
Number of Cases	30	20

Level of examination	Cross sectional area in mm^2	Cross sectional area in mm^2
3 cm proximal to medial malleolus	19.4 – 30	9.8 – 13.6
(mean)	22.8	12.6
MTNF	0.3- 0.7	0.1-0.3

The diagnosis of diabetic neuropathy is based primarily on the characteristic symptoms and is confirmed with a nerve conduction study (NCS), however NCS is time-consuming and invasive, and is not feasible for repeated evaluations. With the use of ultrasound (US), imaging of peripheral nerves has become feasible and, can be performed with little or no discomfort to the patient, and has already been used for evaluating peripheral neural pathologies. Nerve imaging has also provide information about lesion morphology, anatomical location, relationship of the lesions to the adjacent structures, and evaluation of areas not accessible with electrodiagnostic tests. The nerve consists of multiple hypoechoic bands corresponding to neuronal fascicles, which are separated by hyperechoic lines that correspond to the epineurium and perineurium. The cross section of the tibial nerve appears as a hypoechoic oval to round structure, which is surrounded by hyperechoic rim of epineurium and perineurium. It is slightly hyperechoic in comparison to muscle [9].

The sural nerve is affected earliest in diabetic neuropathy, and is detected on nerve conduction studies. The tibial nerve at the level of the medial malleolus may be similarly affected in this disease (10- 11). Due to high spatial resolution of US, the modality is useful for studying the morphology of the peripheral nerves, with the tibial nerve being a good choice for this investigation. The vessels accompanying the nerves are taken as anatomical reference points during US examination. The tibial nerve is the thicker terminal branch of the sciatic nerve. 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 [12]. The diagnosis of diabetic neuropathy can be confirmed with NCS, however it is time-consuming and invasive, and is not feasible for repeated evaluations. US, on the other hand, can be performed at the patient's little or no discomfort, and has already been used for evaluating peripheral neural pathologies [13, 14]. The symptoms of DPN usually first appear in the toes or the soles of the feet [15, 16].

Sheila Riazi *et al*. studied 98 diabetic patients classified by NCS. The severity of neuropathy was determined using TCNS. The cross-sectional area of the tibial nerve was measured at 1, 3, and 5 cm proximal to the level of the medial malleolus. They concluded that CSA measured at 3 cm above the medial malleolus had an optimal threshold value for diagnosing diabetic peripheral neuropathy, with a sensitivity and specificity of 0.69 and 0.77 respectively [17]. In our study, we measured CSA at the level of 3cm proximal to the medial malleolus, with a cutoff value of 18.5 mm^2 in dabetic patients with symptoms of peripheral neuropathy and 14 mm^2 in control subjects.

Fukashi Ishibashi *et al*. studied CSA, hypoechoic area and MTNF of the median and posterior tibial nerves in patients with or without diabetic neuropathy. CSA was measured by direct tracing. They concluded that the morphological changes in peripheral nerves of type 2 diabetic patients were seen even prior to the clinical onset of neuropathy, and were closely correlated with the severity of the disease. Moreover, CSA and MTNF in patients with neuropathy were larger than those in the controls, with significant p-values (18). The findings were similar in our study, where CSA and MTNF were larger in diabetic peripheral neuropathy group than control group (Fig 1, 2)

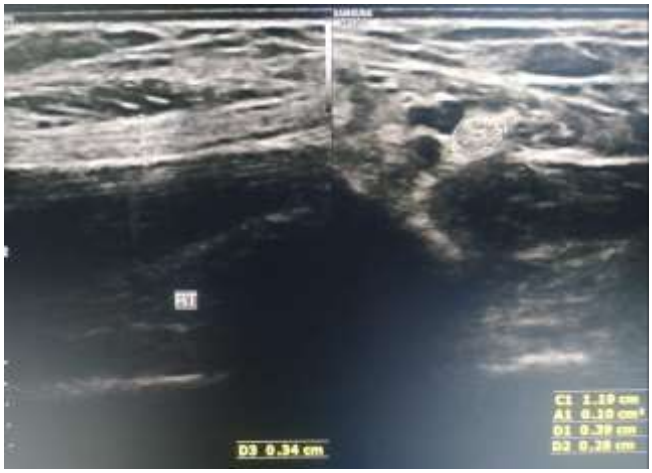

Fig 1: High resolution ultrasound (longitudinal and short axis view) of 36 yrs old patient in control group shows normal appearance of tibial nerve with CSA of 10 mm^2 (circle in image) and MTNF of 0.28mm.

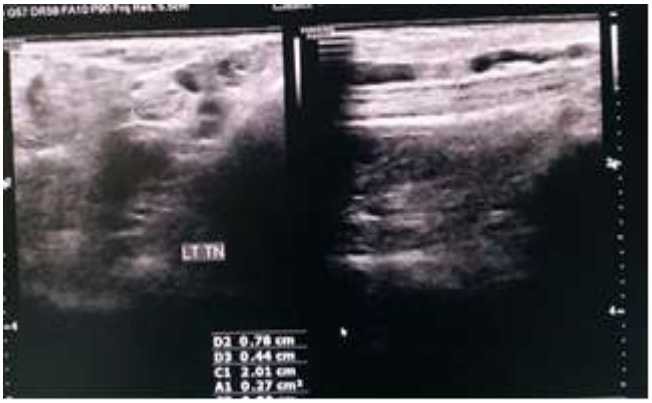

Fig 2: High resolution ultrasound (longitudinal and short axis view) of 65 yrs old patient with diabetic peripheral neuropathy shows thickened tibial nerve with CSA of 27 mm^2 (circle in image) and MTNF of 0.44mm.

Our finding that the mean CSA of the posterior tibial nerve in patients with DPN was significantly larger than the mean CSA in healthy volunteers was concordant with the findings of Watanabe *et al*. [19]. So, the result of present study coincides with those of the previous studies. The mean cross sectional area of tibial nerve of diabetic patients with peripheral neuropathy is significantly higher than that found in control group. Similar findings were reported by Riazi S *et al*. [20], Pitarokoili *et al*, [21] that the mean CSA of the posterior tibial nerve (P TN) was larger in patients with DPN than in control subjects. Singh also found that the CSA and the maximum thickness of nerve fascicles of the tibial nerve are larger in patients with DPN than in healthy subjects or in diabetic patients with no signs of neuropathy [22].

Furthermore most studies had relatively small sample size

and/or a retrospective design, and most studies were performed in a single center, on a single device, and by only one or a limited amount of investigators. Large prospective studies investigating the diagnostic and prognostic value of HRUS in polyneuropathies in a multi center setting are therefore needed.

Conclusion

Ultrasonography is an excellent diagnostic tool for detecting morphological changes in the tibial nerves in diabetic patients, even before the clinical onset of peripheral neuropathy. From the findings of present study it can be concluded that the cross sectional areas and maximum thickness of nerve fascicles of the tibial nerve is larger in type 2 diabetic patients with peripheral neuropathy than those of healthy control cases and sonographic examinations are very useful for the early diagnosis of diabetic neuropathy. Early detection of nerve dysfunction is important to provide appropriate care for patients with diabetic polyneuropathy.

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