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Diabetic peripheral neuropathy and its evaluation in a clinical scenario: A review

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:: Abstract

Diabetes mellitus is not only a clinical syndrome characterizing hyperglycemia, but is also a cause of debilitating problem known as peripheral neuropathy (PN). This review addresses the importance of diagnosing PN in a clinical setting as PN causes pain and discomfort in lower extremities, loss or absence of protective sensations in the lower extremities leading to balance problems, risk of foot ulcerations, and a reduced quality of life in adults with type 2 diabetes. A variety of modalities or methods are available to evaluate both subjective and objective measures of peripheral nerve functions, and have been discussed in detail in this review. It is of utmost importance to understand that evaluating PN as a routine practice in a simple way may also play a vitally important role in preventing foot ulcers or fall-related morbidity and mortality in adults with type 2 diabetes.

Keywords: Diabetes, postural control, prevalence, quality of life, risk scores

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:: Diabetes Mellitus

Definition

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia caused by relative or absolute deficiency of insulin in the body. [1]

Long standing metabolic derangement is associated with functional and structural changes in many organs, particularly those of vascular system, which leads to clinical 'complications' of diabetes. These characteristics may affect eye, kidneys, and the nervous system. [1],[2]

:: Prevalence of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus a global epidemic

Studies estimate that 250 million people will have diabetes by the year 2020; most of them will have Type 2 diabetes mellitus. [3] It is found that a person having impaired glucose tolerance (126-200 mg/dl) testing is 10 times at the risk of developing diabetes than the person with normoglycemia. [4] Various studies conducted all over the world, have found an increase in the prevalence of Type 2 diabetes and have concluded that there is an increase in the incidence, prevalence, and mortality due to diabetes in the elderly population. [5],[6],[7]

In a survey done in 1995 by the World Health Organization (WHO), it was estimated that there were 135 million diabetics in 1995, which is all set to increase to 300 million by 2025. [8] Another estimate of the problem by Shaw *et al*., found that the highest regional prevalence was reported for North America (10.2%) followed by south Asia (6.7%). [9]

Studies on diabetes in various parts of India found high trends of prevalence of diabetes and its risk factors among Indian population, [10],[11],[12] with an alarming increase in diabetes and its complications. [13]

It is well-known that Asian Indians develop diabetes 1 or 2 decades earlier than Europeans. [14] In an analysis of preventive measures by Narayan *et al*., the authors laid emphasis on early recognition of prediabetes and undetected diabetes and implementing effective measures on a single stage. [15]

Prevalence of diabetic peripheral neuropathy (DPN)

The International Association for the Study of Pain (IASP) has defined neuropathic pain as "*pain initiated or caused by a primary lesion or dysfunction in the nervous system*". [16] The most frequently occurring complication in Type 2 diabetes is DPN or distal symmetrical polyneuropathy (DSP). DPN affects up to 50% of the population with diabetes. Complications of PN include severe pain, loss of ambulation, and increased risk of foot ulceration and amputation. [17]

Studies conducted in United States of America have reported that neuropathic pain syndromes have affected up to 70% of the American population with diabetes. [18] In an observational study in patients with Type 2 diabetes it was found that painful symptoms had an occurrence of 26% in patients without neuropathy and 60% of patients with severe neuropathy. [19] DPN is one of the commonest causes of foot complications like amputation and disability in ambulation and it is also the most common cause of nontraumatic amputation. [20],[21]

In India there had been a small number of trials to screen the current status for DPN, among them a study estimated an overall prevalence of neuropathy as 19.1% in south Indian Type 2 diabetic patients. [22] Another study by Dixit *et al*., found poor awareness levels among Indian diabetic population and authors asserted the need to bridge the discrepancies in self-management of foot problems. [23] A study by Vishwanath *et al*., reported primary intervention like education to be superior to secondary management of DPN. [24]

A prospective study reported that older people with severe bunion, toe deformity, ulcer, and deformed nails have a two-

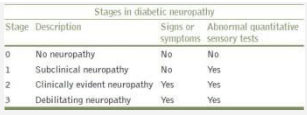
fold increased risk of falling when compared with the healthy counterparts. Approximately 10-20% of falls result in fractures, [25] thereby DPN contributes to age-related frailty, restricted mobility and pain, increased probability of fall in elderly, and reduced quality of life. Hence, there appears a need to understand the nature of neuropathy, which requires early and frequent reassessment due to its progressive etiology.

:: Definition, Stages and Classification of Diabetic Neuropathy

Definition

American Diabetes Association (ADA) published a statement on diabetic neuropathies as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes". [26]

Confirmed clinical neuropathy is defined as clinical neuropathy plus confirmation by abnormal quantitative neurological function tests (e.g., electrophysiological test, quantitative sensory testing, or autonomic function tests). Whereas, subclinical neuropathy is defined as presence of an abnormal quantitative sensory neurological testing with little or no evidence of clinical neuropathy on examination. [26] Stages as defined by the criteria given by Mayo clinic of diabetic neuropathy are depicted in [Table 1]. [26]



Stages in diabetic neuropathy

Stage	Description	Signs or symptoms	Abnormal quantitative sensory tests
0	No neuropathy	No	No
1	Subclinical neuropathy	No	Yes
2	Clinically evident neuropathy	Yes	Yes
3	Debilitating neuropathy	Yes	Yes

Table 1: Stages as defined by the criteria given by Mayo

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Classification of diabetic peripheral neuropathy

A symmetrical distal neuropathy is the most common presentation of diabetic neuropathy. It can be symptomatic in patients complaining of numbness, tingling, and burning in the feet and lower shins or it can be asymptomatic. [27]

Classification of diabetic neuropathy:

I. Symmetrical distal neuropathy

II. Symmetrical proximal neuropathy

III. Asymmetrical proximal neuropathy

IV. Asymmetrical neuropathy and symmetrical distal neuropathy

:: Clinical Presentation

Symptoms of DPN vary from patients-to-patients, but common complaints are numbness, tingling, and pain beginning in the toes and soles of the feet, ankles, and lower shins. Patients often enlist another description of pain as given in [Table 2]. [26] Sensory symptoms are usually worse at night when the patient is trying to sleep. Often, patients with diabetic neuropathy state that movement, walking, or standing lessens the pain. Balance problem is also increasingly common among people with neuropathy. [26],[28],[29]

Dysesthesia	Paresthesia	Muscular pain
Burning sensation	Pins and needles	Dull ache
Skin tingles	Electric like	Night cramps
Painful sensation when bed sheet and stockings touches me	Numb but achy	Band like sensation
	Knife like shooting Pain, lancinating pain	Deep aches, spasms

Table 2: Descriptors of different kinds of neuropathic pain©

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Types of pain

Dysesthetic pain is associated with increased firing of cutaneous and subcutaneous distribution of damaged nociceptive fibers, particularly sprouting regenerating fibers. Paraesthetic pain is thought to occur from various possible etiologies: (I) Spontaneous activity and increased mechanosenstivity near the cell body of damaged afferent axons in the dorsal root ganglion; (II) loss of segmental inhibition of large myelinated fibers on small unmyelinated fibers; and (III) ectopic impulses generated from demyelination patches of myelinated axons.

The third type of pain is muscular pain. These are ectopic neural impulses to the muscles might be generated from the demyelinating patches in motor nerves. Muscular pain descriptors includes "dull-ache", " night cramps", " band like sensation", " drawing sensation", "toothache-like". [26]

Motor signs and symptoms

Imbalance of walking is a commonly elicited complaint even if not volunteered by the patient initially. Patients may have gait ataxia while walking in the dark yet no ataxia during the day. This relates to loss of joint position sense of feet. Leg weakness is usually a late feature of diabetic neuropathy, as patients usually do not complain of toe weakness, the first body region to be affected by weakness in most people with diabetic neuropathy.

Symptoms of autonomic neuropathy

Autonomic neuropathy in diabetes affects many organs systems, including the skin, the conduction system of the heart, gastric bowel motility, urinary bladder, and sexual functions. Patients complain of a range of symptoms from dry, cracked and mottled skin, dizziness, syncope, and abdominal bloating after eating, diarrhea or constipation, urinary retention or incontinence, and penile erection and ejaculation impairment. It is well-known that resting tachycardia and silent myocardial infarction is common in diabetic patients. [26],[29]

Neurologic examination

The physical examination begins with vital signs and need for checking the pulse and blood pressure measurements in several positions (supine, sitting, and standing) to assess orthostasis and pulse changes. Patients with symptoms that are suggestive of orthostatic hypotension the measurements should be delayed for 1 min after position change. Patients with normal cardiac function should have a rise of pulse of 20-30 beats when patient changes position. Patients having dry, cracked skin, and changes in nails and skin discoloration may have underlying autonomic neuropathy. [26]Even an algorithm has been devised to asses DPN at an early stage [Figure 1].

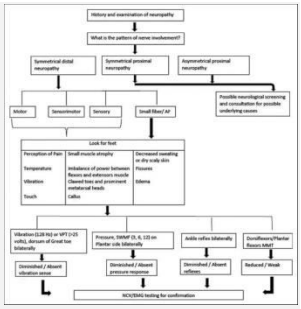

Figure 1: Algorithm for examination of neuropathy in Type 2 diabetes for early diagnosis of DPN

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In mild diabetic distal neuropathy, the two most prominent changes on neurological examination will be reduced or lost ankle reflexes and a distal gradient loss of large and small sensory fiber modalities or "stocking-and-gloves" sensory loss. Examination of vibration senses using 128 Hz tuning fork is the most practical way to check the presence or absence of vibratory senses at the feet. [26]

Monofilament testing

Performing monofilament testing of the plantar surface of great toe and pulp of the index finger bilaterally can assess sense of touch. The current available device is known as Semmes-Weinstein monofilaments (SWM). They are usually made of fine nylon and are designed in a way that the amount of pressure on the plantar surface is the function of instrument not the examiner. They are calibrated, single-fiber nylon threads, identified by values ranging from 1.65 to 6.65, that generate a reproducible buckling stress [Figure 2]. [30] Each monofilament is marked with a number that represents the decimal log of 10 times the force in milligrams ranging from 1.65 (000.45 g) to 6.65 (447 g) of linear force.[26]

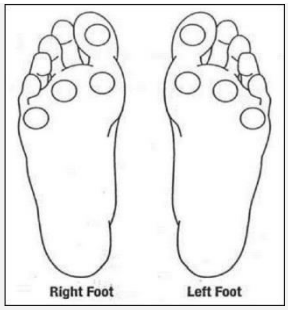

Figure 2: Sites in foot for monofilament testing

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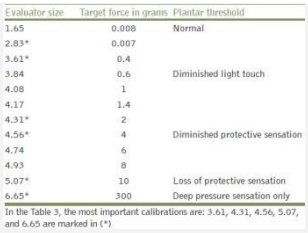
In examining the feet, a series of monofilaments that range in sizes from 2.83 to 6.65 are typically used. The tip of the monofilament is gently placed perpendicularly on the surface until the monofilament buckles. The approach, the skin

contact, and the departure of the monofilament should be 1.5 s approximately. [26] Lists of monofilament with their target force and evaluator size are enlisted in [Table 3]. [26]



Evaluator size	Target force in grams	Plantar threshold
1.65	0.008	Normal
2.83*	0.007	
3.61*	0.4	
3.84	0.6	Diminished light touch
4.08	1	
4.17	1.4	
4.31*	2	
4.56*	4	Diminished protective sensation
4.74	6	
4.93	8	
5.07*	10	Loss of protective sensation
6.65*	300	Deep pressure sensation only

In the Table 3, the most important calibrations are: 3.61, 4.31, 4.56, 5.07, and 6.65 are marked in (*)

Table 3: Monofilament table

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Sensitivity of monofilament ranges from 0.41 to 0.93 and specificity varies from 0.68 to 1. Though this difference usually seems to be because of variability in the number of sites being tested. [28] The examiner should also be sure to avoid callus area. Patients without neuropathy should be able to sense 3.61 monofilament (equivalent to 0.4 g of linear force). The inability to sense 4.17 (equivalent to 1 g of linear pressure) or higher is considered consistent with neuropathy. Inability to sense 5.07 is consistent with loss of protective sensation. [30]

In the [Table 3], the most important calibrations are: 3.61, 4.31, 4.56, 5.07, and 6.65 are marked $(*)$. The patients unable to sense 3.61 size are presumed not to have small fiber neuropathy.

A prospective multicenter trial done by Pham *et al.,* on 248 patients found that foot ulcers developed in 95 feet (19%) or 73 patients (29%) during the study. They stated that the combination of the NDS and the inability to feel a 5.07 SWM reached a sensitivity of 99%. [31]

Deep tendon reflexes

Deep tendon or muscle stretch reflexes are absent in a length dependent pattern such that the ankle reflexes are typically lost first followed by knee reflex. Upper limb reflexes are usually preserved in early diabetic neuropathy. [26]

Motor function

Loss of motor function most commonly follows the changes in sensation and reflexes. Typically weakness will be first detected in the toe extensors followed by the toe flexors, a pattern that follows the length dependent nature of diabetic neuropathy. Proximal muscles of the legs are often spared unless the diabetic neuropathy is unusually long-standing approximately 25-30 years. [26]

Once diabetic neuropathy advances to the level of the knee, patients begin to complain of hand weakness. Usually weakness will start in the lower limbs in dorsal and ventral interossei muscles and abductor digiti minimi.

Electrophysiological testing

Electrophysiological testing plays a major role in evaluation of patients with DSP using motor and sensory nerve conduction studies. [32]

DPN is a major cause that initiates the pathophysiological pathway to foot ulceration and amputation. [33]Electrophysiological testing not only defines the fibers that are affected in DPN (motor and sensory), but also renders a gross estimate of the duration of the neuropathy, and even gives an insight into the prognosis.

Routine nerve conduction studies include evaluation of motor function of the median, ulnar, peroneal, and tibial nerves, and sensory function of median, ulnar, radial, and sural nerves. Velocities are in meters per second, motor amplitudes in millivolts, and sensory amplitudes in microvolts. These measurements of upper and lower limb motor and sensory nerve function show the presence, distribution, and severity of peripheral nerve disease.

Nerve conduction studies (NCS) have always been considered the gold standard for the diagnosis of neuropathy. NCS correlate with clinical scores, nerve amplitude reflects the degree of nerve fiber loss. Usually in NCS abnormalities are detected in 45-60% of patients with type 2 diabetes. Severity of abnormality in NCS reflects a correlation with the glycemic levels and usually abnormal NCS increases with the duration of diabetes. [32] A study by Resnick *et al*., demonstrated reductions in walking speed, static balance, dynamic balance, and coordination in a population of aged people with diabetes as compared to those without diabetes on abnormal electrophysiological test in neuropathy. [34]

In a 6 years follow-up of diabetic patients it was found that motor nerve conduction study (MNCV) is an independent predictor for the development of new foot ulcers in people with diabetes. [35] Clinical studies have used MNCV as a "benchmark" for the assessment of distal symmetrical diabetic polyneuropathy, as it is a very reproducible and objective method of assessment. [36]

Common peroneal nerve conduction

The most frequently occurring lesion is axonal degeneration regardless of etiology of common peroneal neuropathy. A neurophysiological study suggested axonal involvement in 64 patients, conduction block in 23. The peroneal MNCV recording from tibialis anterior is reported to be the single most important electrophysiological finding in any electrodiagnostic study (Misra and Kalita). [36]

The reported values for common peroneal nerve conduction velocity of below knee segment in Indian population for NCS below knee segment is 46.54 ± 4.4 m/s and that across the fibular neck is 49.67 ± 8.77 m/s. The latency at ankle is 4.55 ± 0.59 ms and the distal CMAP amplitude is 4.23 ± 1.61 mV (Misra and Kalita). [36]

Tibial nerve conduction

Damage to the tibial nerve in the popliteal fossa is uncommon; however, in DPN tibial nerve frequently gets affected in conjunction with peroneal nerve. Tibial neuropathy may result in the weakness of plantar flexors, invertors, and the intrinsic foot muscles. For tibial nerve conduction study, the active surface recording electrode is placed on abductor halluces, slightly below and anterior to navicular tuberosity. Surface stimulation is given behind and proximal to the medial malleolus and in the popliteal fossa. The normal conduction velocity of tibial nerve in Indian population is 48.3 ± 4.5 μ/s. [36]

Sural nerve conduction

Compression injury to sural nerve can occur due to baker cyst, resting leg against hard objects. It is often involved distally in DPN. Nerve conduction velocity might get slowed down in metabolic neuropathy. The surface electrodes are kept between the lateral malleolus and tendo-achilles junction that records nerve conduction of the sural nerve. The nerve is stimulated antidromically 10-16 cm proximal to the recording electrodes, distal to the lower border of gastrocnemius at the junction of middle and lower third of leg. Sural nerve conduction velocity among healthy Indians was found to be approximately 50.9 ± 5.4 m/s with an amplitude (SNAP) of 18 ± 10.5 mV. [36]

Quantitative sensory testing

Quantitative sensory testing is an essential method for quantifying sensory function in patients with polyneuropathies and specifically in DPN [Figure 3]. The different modalities of QST have measurement errors as high as, or higher than the 30% associated with amplitude measures in NCS. [37] Though precision can reduce the error significantly if standardized methods of assessments are used, but still it cannot achieve the precision of motor and sensory conduction velocity measures of NCS. [32] The precision of QST devices are quite variable, as are the correlations with NCS. Vibration perception threshold (VPT) can be obtained with a simple, relatively inexpensive device, which is comparable to those obtained using more elaborate equipment and testing methods. [37] Thermal threshold testing is generally considered to be less reliable than VPT testing, which reflects the complexity in the objective measurement of small fiber function. Variances of 50% and higher in thermal thresholds are common limiting diagnostic value and the utility of this end point in clinical trials. [38]

Figure 3: Quantitative sensory testing device

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The major limitation of QST is the psychophysical nature of the examination, since the test relies on subjective responses by the patient. [37] Unlike NCS a practical limitation observed in QST is the absence of any standardized procedures which can translate VPT observations into a more clinically relevant outcome. Usually the findings with VPT measurements are reported with 'volts' as the unit, some researchers have used 'micron' of detectable displacement. Usually values from 20 to 25 volts are described as impaired vibratory perception, values equal to or greater than 25 as presence of neuropathy and the values above 30 volts are identified as the presence of severe neuropathy.

Clinical scoring scales

Usually clinical scores are developed to provide wider information regarding the neurological assessment in diabetic neuropathy. Neuropathy impairment scales were developed over time for assessment of diabetic neuropathy which includes NCS, vibration perception thresholds (VPT), and autonomic function (heart rate with deep breathing) in percentile of the abnormalities reported which was then converted to a point system. Drawbacks of such scales are that its time consuming, overtly detailed and very difficult to inculcate in day-day practice in a clinical scenario. [26]

In an effort to devise a scoring system that is feasible in a clinical scenario Michigan Neuropathy Screening Instrument (MNSI) was developed. This instrument includes a 15-item questionnaire and a simple clinical examination of the feet. Even the algorithm mentioned [Figure 1] for the examination of neuropathy in type 2 diabetes can also be followed which will ensure identification of the problem in a systematic way.

Michigan diabetic neuropathy score (MDNS) is a 46 point clinical score was developed by Feldman *et al*. The MDNS consists of two parts, each of which is easily conducted in routine clinical practice: A clinical neurological examination followed by

routine nerve conduction measurements. [39]

Cross-sectional study by Feldman *et al*., for early diagnosis of distal polyneuropathy had compared to clinical scores MNSI and MDNS and found MNSI to be a good screening instrument and MDNS coupled with NCS provides an easy way to confirm the diagnosis. [39]

Clinical utility of posturography

Despite of various clinical tools available in practice to assess balance issues in various conditions, still there remains a disparity to the naked eyes to differentiate between causes (i.e., specific abnormalities in postural control) and effects (i.e., the consequential imbalance). [40]

The current management of patients with postural instability is hampered by the intricate assessment of balance disorders. The current standard in clinical practice is a combination of history taking and physical examination, but neither approach is infallible.

Postural stability can be evaluated in terms of sway velocity, velocity moment, and sway length under four conditions in quiet static standing: Eyes open (EO), eyes closed (EC), eyes open on foam (EOF), and eyes closed on foam (ECF). It is an electric medical instrument with electromagnetic compatibility. It has a force plate which is in regular triangle shape with a side length of approximately 800 mm and a height of 90 mm [Figure 4]a-c. The system measures the postural sway of a subject by sensing the vertical force on platform and analyzing the excursion of the center of pressure (COP), while the individual maintains a quiet standing position on the platform. Information about vertical force pressure on the plate was obtained by three-channel direct current amplification and was then transmitted to a computer via a standard bluetooth wireless link. The inbuilt software is used for the analysis of the transmitted information from the force plate.

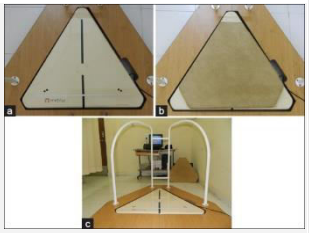

Figure 4: (a) Posturography for evaluating balance without foam, a superior view (b) Posturography for evaluating balance with foam, a superior view (c) Complete set up of posturography with analyzer and display unit

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Postural stability is usually defined as the ability to modify postural strategies in response to changing surface and environmental demands. This response is impaired in DPN leading to higher risks of fall. [41]

A study that evaluated individuals with diabetes on deformable surfaces (foam) by Lord *et al*., in which degree of postural stability measures were evaluated using a sway meter attached at the level of waist, [42] reported that participants with diabetes had a greater sway amplitude as compared to healthy controls. [42]

Another study by Ahmmed *et al*., concluded that participants with DPN had a far greater postural sway as compared to participants with diabetes mellitus and healthy controls. [43] To add further to the current evidence a study by Lafond *et al*., reported that even with vision ankle strategies were impaired in static stance in DPN. [44] Helene *et al*., in a study found that center of pressure-center of mass variable displacement were significantly larger in AP and ML direction for DPN population as compared to healthy controls. [45]

In conclusion there are various data on postural instability suggests that due to diabetes and its complications postural strategies are compromised on even or uneven surfaces. There appears a need for early assessment and identification of individuals at risk of fall and fall-related injuries in DPN. Moreover, there is also a need to conduct a well-designed trial to address the issue of balance impairments in the diabetic population.

Quality of life in diabetic peripheral neuropathy

WHO defines quality of life as "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns". [46] Studies have stated a correlation between the mortality rate and health-related quality of life (HRQOL) in Type 2 diabetes. Quality of life as reported by patients is the patient's perspective on health and disease, which is easily missed in a clinical scenario. In Type 2 diabetes a comprehensive assessment which includes HRQOL and health assessment should be undertaken rather than just emphasizing on strict glycemic control regimes.

A study by Kleefstra *et al*., found that HRQOL is an independent marker of mortality and further suggested to look beyond clinical parameters in Type 2 diabetes. [47] Another study by Landman *et al*., on HRQOL and mortality in general and elderly population with Type 2 diabetes revealed that lower physical and mental HRQOL was associated with higher rates of total mortality and cardiovascular mortality in Type 2 diabetes. [48]

DPN is the single leading cause for amputations in diabetes. It also causes pain, disrupted sleep, and may be a cause for depression leading to a reduced quality of life in diabetes. Usually there is a poor quality of life reported in patients with diabetic foot ulcers on comparison with general population and patients with diabetes. [49]

A study done by Nabuurs-Franssen *et al*., in 2005 revealed that patients with healed ulcers had a better quality of life than patients with persisting ulcers. Moreover, it also appears to be an emotional burden on the patient's caregiver, hence revealing the seriousness of the situation in DPN. [50]

Vileikyte *et al*., designed a scale specific to the neuropathy population in Type 2 diabetes with an objective to measure patient's perception of foot problems and impact of DPN on quality of life. The results in the study revealed a good reliability (alpha = 0.86-0.95) of the scale. Hence, neuropathy quality of life (NeuroQoL) was more strongly associated with measures of neuropathic severity than SF-12; they found NeuroQoL addresses the key dimensions of the patients' experience of DPN and is a valid tool for studying the impact of neuropathy and foot ulceration on quality of life. [47]

In conclusion, measurement of peripheral nerve functions are usually done through clinical measures with evaluation of associated risk factors to stratify the risks of foot ulcers or amputations in an individual with type 2 diabetes. At present there is a need for a trial to address the current situation of DPN in India, where the quality of life of patients with DPN in/or response to a therapy remains to be evaluated. Hence, it is of vital importance to evaluate DPN as a routine part of assessment in a clinical setting as neuropathy is progressive in nature which if ignored can be a sole cause for an amputations and amputation related mortalities in type 2 diabetes.

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