**Diabetic Neuropathy: Part 1**

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**Introduction**

Diabetic neuropathy (DN) is a descriptive term meaning a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. It is the most common and troublesome complication accounting for more hospitalizations than all the other diabetic complications combined, and is responsible for 50% to 75% of non-traumatic amputations.\(^1\)

In this review, we have summarized the epidemiology, clinical features, pathogenesis, classification and diagnosis of diabetic neuropathy. The management will be reviewed in Part 2.

**Prevalence**

The true prevalence is not known and depends on the criteria and methods used to define neuropathy. Of patients attending a diabetes clinic, 25% volunteered symptoms, but 50% were found to have neuropathy after a simple clinical test such as eliciting the ankle reflex or vibration perception test. Almost 90% tested positive on sophisticated tests of autonomic function or peripheral sensation.\(^2\)

Diabetes is the most common cause of neuropathy worldwide. Diabetic neuropathy occurs in approximately 60% of individuals with long-standing type 1 and type 2 DM.\(^3\) A recent cross sectional hospital based study in Lahore done on 113 newly diagnosed T2DM patients found a prevalence of 68.5% in those with poor glycaemic control (HbA1c ≥ 6.5%) and 50% in those with good glycemic control (HbA1c < 6.5%).\(^4\)

Diabetic autonomic neuropathy is also very common. Definitive Cardiac autonomic neuropathy has been reported in 30% of patients with T2DM in a study from Hyderabad, Pakistan (disease duration > 10 years).\(^5\)

**Classification**

Diabetic neuropathy can be broadly divided into symmetric and asymmetric types (Figure).

Symmetric neuropathies usually present as chronic neuropathies and include distal sensorimotor polyneuropathies; small fibre; autonomic/large fibre predominant neuropathies and chronic inflammatory demyelinating polyradiculopathies (CIDP). DSPN is the most common form of diabetic neuropathy.\(^3\)

The acute onset symmetric neuropathies include diabetic neuropathic cachexia which is an uncommon painful sensory neuropathy occurring in type 1 diabetes in the setting of poor glucose control and weight loss. Insulin neuritis, which is again a painful neuropathy is seen with initiation of insulin treatment.

The asymmetric neuropathies can also be divided into those with acute onset and those with gradual onset. Diabetic truncal radiculoneuropathy, radiculoplexopathy or diabetic amyotrophy, cranial neuropathies (third or sixth nerves) and mononeuritis multiplex constitute the acute onset group. Limb mononeuropathies due to compression/entrapment are of more gradual onset.

An easy and practical way to approach this conundrum of classifications is to classify diabetic neuropathy as typical and atypical. Typical DSPN is chronic, distal, symmetric, sensory predominant, and often painful. Any variation (eg, acute, asymmetric, proximal, or motor involvement) suggests an atypical neuropathy.\(^6\)

**Clinical Features**

Diabetic neuropathy has a wide spectrum of clinical manifestations, the most common being distal symmetrical sensorimotor loss in the classical ‘stocking-glove’ distribution (DSPN).

Diabetic sensorimotor polyneuropathy (DSPN) is a mixed neuropathy with small and large fibre sensory, motor and autonomic involvement in various combinations. Sensory and autonomic symptoms are more prominent. The symptoms start as numbness, tingling, burning or pricking sensation in the feet and spread proximally in a length dependent fashion (stocking-glove pattern). Over time gait disturbance and mild distal weakness occur. Associated autonomic symptoms may be present. Examination shows distal loss of pinprick, temperature, touch and vibration sense. with reduced or absent Ankle jerks and weakness of toe flexors and extensors may be

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present. It predisposes the patients to falls, development of foot ulcers and Charcot joints. The most disabling symptom in these patients is pain which is difficult to treat and substantially affects the quality of life.\(^7\)

**Diabetic small fibre neuropathy (DSFN):** Small fibre predominant neuropathy in diabetes is being increasingly recognised and is an early manifestation of peripheral nerve involvement. It presents with pain and dyesthesias in the feet and is difficult to diagnose, as the clinical examination and nerve conduction studies may be normal. It often progresses to the typical DSPN.

Diabetic autonomic neuropathy affects various organs of the body resulting in cardiovascular, gastrointestinal, urinary, sweating, pupils, and metabolic disturbances. Orthostatic hypotension, resting tachycardia, and heart rate unresponsiveness to respiration are a hallmark of diabetic autonomic neuropathy.

**Diabetic lumbar radiculoplexopathy:** Also known as Diabetic amyotrophy or proximal diabetic neuropathy, it

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Figure: Classification of Diabetic neuropathy.
presents with abrupt onset, often unilateral severe pain in
the anterior thigh, buttock or lower back followed by
weakness and wasting in the thigh. Sensory phenomena
are minimal and knee jerk is absent. The symptoms after
progression over few weeks, stabilise and then gradually
improve. Pathological assessment reveals evidence of
ischaemic injury and microvasculitis and prognosis is
favourable.

**Diabetic truncal radiculoneuropathy:** It presents with
abrupt onset severe pain (burning, stabbing or belt like)
with contact hyperesthesia in the thoracic spine, flank, rib
cage or upper abdomen. Bulging of abdominal wall may
occur because of muscle weakness. It may be confused
with intra-abdominal or thoracic disease or herpes zoster.

**Cranial neuropathy:** The oculomotor nerves are most
often affected (third, sixth, rarely fourth). Diabetic third
nerve palsy presents with abrupt onset retro-orbital pain,
followed by double vision, unilateral ptosis, restriction of
medial and upgaze and sparing of the pupil. Aneurysm
must be excluded by neuroimaging in atypical cases
(pupillary involvement or absence of pain). It improves
spontaneously in 3-6 months without any treatment.

Patients with diabetes can also present with mononeuritis
multiplex without an underlying rheumatological cause
and are at increased risk of entrapment mononeuropathy.

**Pathogenesis**

Chronic hyperglycaemia is an important contributing
factor leading to diabetic complications. A possible
unifying mechanism is that hyperglycaemia leads to
increased production of reactive oxygen species or
superoxide in the mitochondria; these compounds may
activate all four pathways (formation of advanced
glycosylation end products, sorbitol pathway, protein
kinase C pathway and hexosamine pathway), leading to
chronic complication of diabetic neuropathy.⁸

The other prominent factors implicated in diabetic
neuropathy are dyslipidaemia⁹ and impaired insulin
signalling.¹⁰

Additionally, factors such as visceral obesity and
hypertension are associated with DPN.¹¹ Microvascular
dysfunction in the nerve and decreased endo-neural
perfusion are also thought to contribute to neuropathy.¹²

**Advances in Diagnosis**

It is generally agreed that diabetic neuropathy should not
be diagnosed on the basis of one symptom, sign, or test
alone. A minimum of two abnormalities (from symptoms,
signs, nerve conduction abnormalities, quantitative
sensory tests, or quantitative autonomic tests) is
recommended.¹³

**Diagnostic modalities**

**Nerve conduction studies**

Traditionally, nerve conduction studies (NCSs) have been
the most frequently used diagnostic tool for DSPN. As
with most other axonal neuropathies, the central feature
of DSPN is reduced distal lower extremity sensory nerve
action potential amplitudes.¹⁴ But over the years it has
been realised that diagnosis of DSFN (Aδ-fibres and C
fibres) is challenging as the clinical picture can be difficult
to interpret and results from nerve conduction studies are
often normal. In cases of suspected DSFN, measurement
of intraepidermal nerve fibre density (IENFD) and/or
analysis of quantitative sensory testing can enable
diagnosis. New diagnostic techniques (including
measurement of nerve fibre density using corneal
confocal microscopy, and nociceptive evoked potentials)
may contribute to the diagnostic work-up.¹⁵

**Quantitative sensory testing (QST)**

QST is an objective index of neurologic functional status.
For the evaluation of small nerve fibre dysfunction, only
temperature thresholds are measured. The other common
parameter measured by QST in clinical practice, reflecting
large fiber involvement is vibration sensation. For reliable
results, QST requires the patient to be alert and
cooperative.¹⁵

**Skin biopsy and measurement of IENFD**

Pathologically, DSFN is characterized by degeneration of
distal terminations of small-diameter sensory fibres,
observed as low IENF density (IENFD) on histological
analysis of tissue from patients with the condition. For
diagnostic purposes in cases of suspected DSFN
presenting with length-dependent symptoms and signs, a
punch skin biopsy can be taken from the distal part of the
leg, within a region 10cm above the lateral malleolus.¹⁶
After anti-PGP 9.5 staining, bright-field immuno-
histochemistry or immuno-fluorescence, either with or
without confocal microscopy, are used to assess IENF
loss.¹⁵ IENFs are counted under the optical microscope and
the number is divided by the length of the epidermal
surface to obtain a linear density per millimetre; the
density reported is the mean of the values calculated from
at least three sections from the same biopsy.¹⁵ The
diagnostic value of skin biopsy in patients with DSFN has
been established.¹⁶ An IENFD below the fifth percentile is
usually considered confirmatory for a diagnosis of SFN.

**New diagnostic modalities**

**Corneal confocal microscopy**

Over the past decade, the non-invasive technique of in
vivo confocal microscopy of the cornea has been developed, mainly for use in patients with diabetic neuropathy. Confocal microscopy in healthy individuals has confirmed that the cornea is innervated by both A\(\delta\) fibres and C fibres of trigeminal origin.\(^{17}\) The technique allows observation of the living eye in situ, at the cellular level.\(^{18}\) A correlation between low corneal nerve fibre density and severity of the somatic neuropathy and IENF loss in the distal leg has been described.\(^{19}\)

### Nociceptive evoked potentials

They are used to selectively activate A\(\delta\) and C fibres. A relationship between poor nociceptive evoked potential response and severity of IENF loss has been described.\(^{20}\)

### Microneurography

Microneurography has made recording of single A\(\delta\)-fibre and C fibre activity possible, and provides a direct method for measuring sympathetic activity. However the routine use of this technique is limited as it is invasive, time consuming and requires an expert investigator.\(^{21}\)

Other diagnostic tools include nerve axon reflex/flare response. In the nerve axon reflex, C nociceptive fibres are stimulated by acetylcholine iontophoresis producing vasodilatation which can be quantitatively measured and serves as a measure of small fibre function.\(^{22}\) The laser Doppler imaging flare test evaluates 44°C heat-induced vasodilatation and is reduced in subjects with IGT and type 2 diabetic patients with and without neuropathy. These tests still require validation by further studies.\(^{23}\)

Based on signs/symptoms and diagnostic modalities, neuropathy in diabetes has been defined as in Table.\(^{6}\)

Various clinical composite scores have been developed to screen for and quantify the severity of neuropathy.\(^{24-28}\) Out of these, Michigan neuropathy screening instrument (MNSI) is a good screening tool for diabetic neuropathy.\(^{27}\) It has been widely used to assess distal symmetrical peripheral neuropathy in clinical practice and in large clinical trials, including the DCCT/EDIC\(^{29}\) and the Action to Control Cardiovascular Disease in Diabetes (ACCORD).\(^{30}\)

### Summary

To conclude, diabetes is associated with a variety of chronic and acute neuropathies, the commonest form being distal symmetric polyneuropathy. Performing an annual screening through a good neurological history and clinical examination and using a sensitive screening tool can facilitate an early diagnosis. More sensitive and quantitative measures of detecting early peripheral nerve injury including skin biopsy for intra-epidermal and dermal nerve fiber density and confocal corneal microscopy, hold promise to identify neuropathy patients early in their disease course.

### References


