Diabetes mellitus is a chronic metabolic disease with acute and chronic complications. Neuropathy is Microvascular complication, which leads to distressing neurological complaints and ultimately diabetic foot which may require amputation. Thorough clinical examination and investigations are required. Tight blood glucose control is sheet anchor of prevention and management.

**SHORT COMMUNICATION**

**Introduction**

The clinical features of diabetes mellitus have been recognized over a thousand years ago. Both Type1 and Type 2 diabetes are associated with micro and macro vascular complications [1-4]. Microvascular complications include retinopathy, nephropathy and neuropathy. Diabetic neuropathy (DN) by causing an insensitive neuropathic foot causes considerable morbidity [5-6].

**Definition**

The first description of diabetic neuropathy was by Rollo in 1798 when he described pain and paraesthesias in the legs of a diabetic patient. Pavy described “pain of a burning and unremitting nature” in 1887. Diabetic neuropathy (DN) is a non-inflammatory disease process associated with diabetes mellitus and characterized by sensory and/or motor disturbances in the peripheral nervous system [7-8]. The presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.

Diabetic neuropathy is a demonstrable disorder that can affect both peripheral and autonomic nervous systems. Neuropathy is the most common chronic complication of DM affecting up to 50% of patients with type1 and Type 2diabetes [8-11]. But the time of presentation differs. In Type1 Diabetes becomes symptomatic after several years of diagnosis; in contrast, Type 2 diabetes patients may have neuropathy at the time of diagnosis [12-14].
Diabetic neuropathy encompasses a series of different neuropathic syndromes which can be schematized in the following way:

**Classification of Diabetic Neuropathy**

- **Focal and multifocal neuropathies:**
  - Mononeuropathy
  - Amyotrophy, radiculopathy
  - Multiple lesions "mononeuritis multiplex"
  - Entrapment neuropathy (e.g. median, ulnar, peroneal) [15]

- **Symmetrical neuropathies:**
  - Acute sensory
  - Autonomic
  - Distal symmetrical polyneuropathy (DSPN), also known as diabetic peripheral neuropathy (DPN) (most common presentation) [16]

**Pathophysiology**

Recent studies in patients with debilitated glucose resilience give critical bits of knowledge into the part of the level of glucose dysmetabolism in the improvement of neuropathy. The deleterious effect of hyperglycemia is affirmed by the occurrence of neuropathy connected with impaired glucose resilience [17-21]. In this setting, the neuropathy is milder than it is in recently analyzed diabetes, and small nerve-fiber involvement is the soonest noticeable indication of the neuropathy. Factors leading to the development of diabetic neuropathy [22-24].

**Factors associated with neuropathy**

Important biochemical mechanisms are polyol pathway, advanced glycation and oxidative stress. The pathogenesis of DN is multifactorial. The various pathogenic factors are inter related and together contribute to the development and progression of the syndrome [25-30].

The actual process of neuropathic progression is dynamic, with nerve degeneration and regeneration occurring spontaneously and simultaneously [31]. The net balance between these processes determines whether the neuropathy progresses, regresses or stabilizes. The Sorbitol pathway appears to be involved in diabetic complications, particularly in microvascular harm to the retina, kidney, and nerves [32]. Sorbitol pathway can't cross cell membranes, and, when it gathers, it creates osmotic stresses on cells by drawing water into the insulin-free tissues [33-39].

![Figure 1: Sorbitol pathway](image-url)
Diabetic neuropathy influences every fringe nerve including pain fibers, motor neurons and the autonomic nervous system. It consequently can influence all organs and systems, as all are innervated. There are a few distinct disorders based upon the organ systems and individuals influenced, however these are in no way, shape or form select [40-46]. A patient can have sensorimotor and autonomic neuropathy or some other combination. Signs and side effects change contingent upon the nerve(s) influenced and may incorporate indications other than those recorded. Side effects typically grow slowly over years [47-51].

Figure 2: Current view of pathogenesis of diabetic neuropathy

The chief mechanisms involved in the pathogenesis of DN

- Mitochondrial dysfunction (cellular level)
- Hyperglycemia (metabolic)
- Local nerve ischemia (vascular)
- Neuropathic factor deficiency (nutritional) [52]
- Immune mechanisms (immunological)
- Genetic susceptibility to hyperglycemic complications (genetic) [53]

Reversible and Irreversible Neuropathies

Neuropathy may be reversible, or at least controllable. There are 3 proposed stages of neuropathy:

**Functional neuropathy**

This stage is without pathology but with biochemical alteration in nerve function. It is reversible.

**Mononeuropathies**

Femoral, Cranial nerve palsies (III, IV, VI) and Truncal radiculopathies, Pressure palsies, Median, Ulnar and Lateral popletial

**Structural neuropathy**

This stage involves the loss of structural change in nerve fibers. It may be reversible.
**Nerve death**

There is critical decrease in nerve fiber density and neuronal death in this stage. It is irreversible [54-57].

- Chronic sensory motor neuropathy
- Autonomic neuropathy

**Clinical features**

- There is a wide range of symptoms associated with diabetic neuropathy, and they depend on which nerves and parts of the body are affected and also on the type of neuropathy present.
- Some patients have mild symptoms, while others are severely disabled.
- In severe diabetic neuropathy loss of sensation can lead to injuries that are unnoticed, progressing to infections, ulceration and possibly amputation.

**Acute Sensory Neuropathy**

Acute sensory neuropathy which tends to follow periods of poor metabolic control e.g. sudden change in glycemic control leading to painful neuritis [58]. Patients may report that they cannot tolerate the sensation of sheets or clothing touching their feet. The acute, often focal onset suggests an immune-mediated or vascular process at the level of the posterior root or dorsal root ganglion [59].

A common staging scales is given below

| N0 |
| : |
| N1a |
| : |
| N2a |
| : |
| N2b |
| : |
| N3 |
| : |

| : |

| No Neuropathy |
| : |
| Signs but no symptoms of neuropathy |
| : |
| Symptomatic mild diabetic polyneuropathy |
| : |
| Severe symptomatic diabetic polyneuropathy |
| : |
| Disabling diabetic polyneuropathy |

**Common symptoms of diffuse peripheral neuropathy**

- Numbness and feeling of tingling or burning
- Insensitivity to pain
- Needle-prick like pain
- Extreme sensitivity to touch
- Loss of balance and coordination

**Common symptoms of diffuse autonomic neuropathy**

- Nausea, vomiting and bloating
- Dizziness, lightheadedness, and fainting spells
- Loss of appetite Impaired urination and sexual function
- Stomach disorders, due to the impaired ability of the stomach to empty (gastric stasis)

**Common symptoms of focal neuropathy**

- Pain in the front of a thigh
- Severe pain in the lower back
- Ache behind an eye
- Double vision
- Paralysis of one side of face
Chronic Sensory Motor Neuropathy

- It is predominant sensory neuropathy rather than motor. Earliest manifestations are loss of pain and temperature sensation due to small fiber affliction. Most patients with distal symmetric polyneuropathy will develop diabetic foot problems, like neuropathic ulceration, neuropathic edema and Charcot’s arthropathy. These may ultimately lead to refractory infections, gangrene and sepsis with loss of foot [60-62].

Proximal Motor Neuropathies And Diabetic Amyotrophy

- The onset may be acute or gradual. Usually men above 50 years with poor glycemic control are affected. The cardinal feature is wasting of the thigh with or without pain. On examination there is readily demonstrable weakness of the iliopsoas, obturator and adductor magnus with relative preservation of power in the gluteus maximus and the hamstrings [64-65].

Diagnostic Procedures

Diagnosis of Pre-Diabetes and Diabetes Mellitus

It has been previously demonstrated that pre-diabetes can also be connected with neuropathy. Based on the recent ADA rules, diabetes can be analyzed on the consequences of HgbA1c, fasting plasma glucose or 2-hour postprandial glucose levels. This announcement suggested the utilization of the A1c test to analyze diabetes, with an threshold of ≥6.5%. The established glucose criteria for the diagnosis of diabetes (fasting plasma glucose ≥7 mmol/l or 2-hour postprandial glucose ≥11.1 mmol/l) remained valid as well [9, 66-69].

Diagnosis of Sensorimotor Neuropathy

Quantitative sensory testing (QST) assess patient’s ability to detect a number of sensory stimuli and offer the advantage of determining the degree of sensory loss [70].

Diagnosis of Autonomic Neuropathy

Cardio vascular autonomic dysfunction can be evaluated in detail by employing Ewing and Clarke’s battery of 5 tests

- The average inspiratory- expiratory heart rate difference with its deep breaths
- The Valsalva ratio
- The 30:50 ratios
- The diastolic blood pressure response to isometric exercise; and
- The systolic blood pressure fall to standing [71-74]

Electrocardiography

Electrocardiography may reveal prolongation of the QT interval. This is secondary to imbalance between right and left heart sympathetic innervation [75].

Peripheral nerve imaging

Eaton et al suggested that the endoneural edema reflected magnetic resonance imaging of peripheral nerves may initiate the deterioration that is later detected in Electro physiologic testing and neurologic examination [76].
Several highly sensitive methods are being developed for early detection of diabetes [77] and intervention can be done

- Skin punch biopsy
- Immunohistochemical staining
- Nerve biopsy

Management

- Strict glycemic control is the cornerstone of management
- Symptomatic management
- Physiotherapy
- Diabetic foot care and surgical measures

The drugs which have a role in alleviating neuropathy in different ways [78]

- Aldose reductase inhibitors: Reduce the flux of glucose through the polyol pathway, inhibiting tissue accumulation of sorbitol & fructose. Eg Alrestatin, Tolrestat
- Human Intra Venous Immuno Globulin: works as immunomodulator
- Gamma linolenic acid: It preserves prostaglandin E2 and is believed to increase the nerve blood flow
- Amlnoguanidine: It is an inhibitor of AGE formation (used in animal trials)
- Alpha Lipoic Acid: It acts as a thiol replenishing and redox-modulating agent and has to be used parenterally
- Capsacin: Best used for localized pain syndromes
- Protein kinase C inhibitor: Protein kinase C is implicated in the pathogenesis of microvascular complications. Methyl cobalamin and vitamin B12 act as neurotrophics

Drugs which appear to prevent or block the development of diabetic neuropathy [79]

- Myoinositol
- Gangliosides
- Nerve Growth Factors
- Calcium channel blockers
- Continuous insulin infusion
- N- acetyl L-carnitine
- ACE inhibitors

Symptomatic relief may be achieved by

- Tricyclic antidepressants: Amitriptyline 25-150mg, Imipramine 25-150mg
- SSRIs: Paroxetine 40mg, Citalopram 40mg/day
- Anticonvulsants: Gabapentin 900-1800mg/day, Pregabalin 150-600mg/day, topiramate 50-400mg/day
- Opiates: Tramadol 50-400mg/day

Treatment of Diabetic Neuropathy

In diabetic patients the risk of DPN and autonomic neuropathy can be reduced with improved blood glucose control, and the improvement of lipid and blood pressure indexes and the avoidance of cigarette
smoking and excess alcohol consumption are already recommended for the prevention of other complications of diabetes [17].

In diabetic patients the risk of DPN and autonomic neuropathy can be decreased with enhanced blood glucose control, and the change of lipid and blood pressure indexes and the avoidance cigarette smoking and overabundance alcohol utilization are now suggested for the avoidance of different complications of diabetes [80].

- Postural hypotension – Pressure stockings, Head end elevation, fludrocortisones
- Gastro paresis – Frequent small meals, Prokinetic drugs e.g. domperidone
- Constipation- Senna / dulcolax
- Diarrhea – loperamide, codeine, tetracycline
- Neuropathic bladder—Manual pressure, crede’s method
- Erectile dysfunction – Psychotherapy drugs like sildenafil, papaverine
- Vaginal dryness – Vaginal lubricants
- Sudomotor dysfunction- Emoliants, skin lubricants

Physiotherapy
- Appropriate physical manipulations go a long way

Management of Entrapment neuropathy
- Rest
- Placement of a splint
- Anti-inflammatory medication
- Surgical treatment is indicated when conservative methods fail
- Sectioning of the volar carpal ligament of carpal tunnel syndrome.

Conclusion

Diabetic neuropathy is a distressing condition which requires tight blood sugar control, besides early recognition and appropriate management measures. It should be addressed in multidisciplinary approach. Sensorimotor and cardiovascular neuropathies are common in diabetic patients. Aside from strict glycaemic control, no further remedial methodology exists in the prevention of this phenomenon. The reasons that just a few patients with nerve lesions develop neuropathic torment are still obscure. Risk factors, for example, age, sexual orientation, pain intensity before and after the lesion, and emotional and cognitive features indicate that there are multiple factors other than the nerve lesion itself that contribute to the manifestation of chronic pain.

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