Diabetic Neuropathy is a demonstrable disorder, either subclinical or clinically evident, that occurs in both peripheral and the autonomic nervous systems. Neuropathies are the most common complication of diabetes mellitus (DM) affecting up to 50% of patients with Type 1 and Type 2 diabetes. In type 1 diabetes, distal polyneuropathy becomes symptomatic after several years of diagnosis; in contrast, type 2 diabetes patients may have neuropathy at the time of diagnosis.¹

Peripheral neurons can be categorized broadly as motor, sensory, or autonomic.

Motor neurons originate in the central nervous system (CNS) and extend to the anterior horn of the spinal cord. From the anterior horn, they exit the spinal cord (via ventral roots) and combine with other fibers in the brachial or lumbar plexuses and innervate their target organs through peripheral nerves.

Sensory neurons originate at the dorsal root ganglia (which lie outside the spinal cord) and follow a similar course with motor neurons. Sensory neurons are subdivided into categories according to the sensory modality they convey (Table 1).

Autonomic neurons consist of sympathetic and parasympathetic types. In the periphery, preganglionic fibers leave the CNS and synapse on postganglionic neurons in the sympathetic chain or in sympathetic ganglia.

The smaller fibers are affected first in DM. With continued exposure to hyperglycemia, the larger fibers become affected. Fibers of different size mediate different types of sensation, as shown in the Table 1.

Peripheral Neuropathies in diabetes include:

1. Polyneuropathies e.g. distal sensorimotor neuropathy and proximal motor neuropathy
2. Focal neuropathies e.g. mononeuropathies (including cranial) and entrapment neuropathies
3. Multifocal neuropathies

Autonomic Neuropathies may involve the cardiovascular, gastrointestinal, genitourinary and sudomotor systems.

The most common form of neuropathy is distal symmetrical sensorimotor polyneuropathy which can be divided into 3 stages; early, symptomatic and severe.

Early distal sensorimotor neuropathy is usually asymptomatic, but sensory loss may be detectable; neurophysiological abnormalities are demonstrable at this stage.

<table>
<thead>
<tr>
<th>Fiber Type</th>
<th>Size</th>
<th>Modality</th>
<th>Myelination</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-alpha (I)</td>
<td>13-20 micrometers</td>
<td>Limb proprioception</td>
<td>Yes</td>
</tr>
<tr>
<td>A-beta (II)</td>
<td>6-12 micrometers</td>
<td>Limb proprioception, vibration, pressure</td>
<td>Yes</td>
</tr>
<tr>
<td>A-delta(III)</td>
<td>1-5 micrometers</td>
<td>Mechanical sharp pain</td>
<td>Yes</td>
</tr>
<tr>
<td>C (IV)</td>
<td>0.2-1.5 micrometers</td>
<td>Thermal pain, mechanical burning pain</td>
<td>No</td>
</tr>
</tbody>
</table>
Diabetic Neuropathy

Symptomatic distal sensorimotor neuropathy is manifested by sensory loss, often with frank numbness, and may be accompanied by paresthesia and/or pain. Severe distal sensorimotor neuropathy is manifested by motor involvement, and may be accompanied by disabling symptoms and the potential risk for ulceration which can lead to infection, necrosis, gangrene and amputation (Table 2).

PATHOPHYSIOLOGY

Factors leading to the development of diabetic neuropathy are not understood completely; multiple hypotheses have been advanced (Table 3).

Important biochemical mechanisms are polyol pathway, advanced glycation and oxidative stress. Development of symptoms depends though on many factors, such as total hyperglycemia exposure, elevated lipids, blood pressure, smoking, increased height and exposure to neurotoxic agents such as ethanol.\(^1\)\(^,\)\(^2\) Polyol Pathway: Hyperglycemia causes increased level of intracellular glucose in nerves, leading saturation of normal glycolytic pathway. Extra glucose shunted to polyol pathway and converted to sorbitol and fructose by the enzyme aldose reductase and sorbitol dehydrogenase. Accumulation of sorbitol and fructose lead to reduced myoinositol, decreased membrane Na\(^+\)/K\(^+\)-ATPase activity, impaired axonal transport and structural breakdown of nerves. This is the rationale for using aldose-reductase inhibitors as treatment to improve nerve function.

Advanced glycation end products (AGE): Excess glucose in hyperglycemia can lead to nonenzymatic glycation of proteins, nucleotides and lipids resulting in production of advanced glycation end products (AGE) that may have role in disrupting neuronal integrity and repair mechanisms.

Oxidative Stress: The increased production of free radicals in diabetes may be detrimental via several mechanisms. They may directly damage small blood vessels, supplying nerves, leading to nerve ischemia. Use of antioxidant alpha-lipoic acids may hold promise for improving neuropathic symptoms.

PHYSICAL EXAMINATION

The most important physical examination in diabetic neuropathy is examination of foot. All diabetic patient’s feet should be examined in each visit at the clinic.

The bare foot should be routinely examined. Unfortunately, many clinics and OPD’s in busy hospitals don’t have the arrangements for foot examination.

A simple procedure for the examination of diabetic neuropathy is given below-.

1. Inspection of the feet for evidence of dry skin, hair or nail abnormalities, callus or infection or any deformity of foot.
2. Examination of vibratory sensation at the dorsum of toe with a 128 Hz tuning fork
3. Examination of Ankle reflex

After this simple screening, patient with abnormalities should undergo a more complete neurological examination including assessment of autonomic neuropathy. Cardiovascular autonomic neuropathy may be detected by testing heart rate control in response to breathing or after standing from lying down position and/or circulatory response to the Valsalva maneuver. These are important tests before general anesthesia since those with cardiovascular autonomic neuropathy have an increased mortality risk during the perioperative period.

The frequency, severity and progression of neuropathy are related to the degree and duration of hyperglycemia. Several studies (including DCCT- diabetes control and complication

Table 2: Symptoms of autonomic neuropathy

<table>
<thead>
<tr>
<th>I- Gastrointestinal</th>
<th>II- Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia</td>
<td>Persistent sinus tachycardia</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Upper abdominal fullness /nausea</td>
<td>Decreased heart rate variability in deep breathing</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Near syncope upon changing posture</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Factors associated with Neuropathy

- Poor Glycemic control;
- Advanced age;
- Hypertension;
- Long duration of diabetes;
- Dyslipidemia;
- Smoking;
- Heavy alcohol intake;
- HLA DR3/4 phenotype;
- Tall Height;

The auditory system is innervated by cranial N VII (facial nerve) which is the motor nerve for facial muscles and also by cranial N VIII (vestibulocochlear nerve) which is the sensory nerve for hearing and balance. Hearing impairment is common in diabetes mellitus and may be caused by a variety of factors including noise exposure, smoking, medications, infections and metabolic abnormalities such as hyperglycemia. The frequency of hearing loss increases with age, duration of diabetes, and presence of microvascular complications. The most common cause of hearing loss in diabetes mellitus is high frequency sensorineural hearing loss. This type of hearing loss typically affects the high frequencies and is more common in older adults. It is important to screen for hearing loss in patients with diabetes mellitus as early detection and intervention can help prevent further hearing loss.
trial) have suggested that manifestations of neuropathy may be stabilized or improved by improved glucose control.\(^5\)

**Staging**

Different clinical neurological scales can be used to assess the severity of diabetic polyneuropathy.

A common staging scales is given below.\(^6\)

- **NO**— No neuropathy
- **N1a**— Signs but no symptoms of neuropathy
- **N2a**— Symptomatic mild diabetic polyneuropathy
- **N2b**— Severe symptomatic diabetic polyneuropathy (as in N2a but patient unable to heel walk)
- **N3**— Disabling diabetic polyneuropathy

**Investigation in a case of diabetic neuropathy**

Fasting blood sugar (FBS) and glycated hemoglobin (HbA1c) test are very important to assess the glycemic status in a case of diabetic neuropathy. FBS should remain below 110mg/dl and Hba1c should remain below 7%. If these targets are not reached; efforts should be made to improve glycemic status and its impact on diabetic neuropathy.

Imaging rarely helps the physician diagnoses and management diabetic neuropathy. However, in the appropriate clinical setting MRI of the cervical, thoracic or lumbar region may help exclude another cause for symptoms mimicking diabetic neuropathy.

Multiple consensus panels recommend the electrophysiologic testing in the evaluation of diabetic neuropathy. They include both nerve conduction testing and needle EMG of the most distal muscles usually affected. It can document the characteristics of neuropathy (e.g axonal, demyelinating) and the localization (mononeuropathy Vs radiculopathy). Findings on nerve conduction studies depend on the pattern of nerve damage. Patients with distal symmetrical sensorimotor polyneuropathy from predominantly axonal loss have reduced or absent sensory nerve action potentials, especially in the legs. With progression of neuropathy, compound motor action potentials amplitudes may also be reduced and abnormalities may also be observed in hands. In patients with diabetes, nerve conduction study abnormalities may be found even in the absence of clinical symptoms of polyneuropathy.

All patients with diabetic neuropathy should be screened for dyslipidemia and other long term complications (such as fundoscopy for retinopathy, urine examination to detect microalbuminuria for nephropathy and ECG for coronary artery disease).

Quantitative sensory testing (QST): QST assess patients ability to detect a number of sensory stimuli and offer the advantage that they directly assess the degree of sensory loss at the most vulnerable site, the foot. However these tests are complex and rely on patients cooperation and concentration.

**Semmes Weinstein Monofilaments**

These monofilaments consist of sets of nylon filaments that buckle at a predefined force when applied to the testing site. They are used widely in clinical practice and are particularly helpful in the identification of subjects who are at risk for neuropathic foot ulceration. Inability to perceive of a 10gm monofilament has been shown to predict risk for neuropathic ulceration.

**Vibration perception**

Several devices designed specifically to assess vibration perception thresholds (VPTs) are used to test large myelinated fibre function. VPT increases with age in normal individuals and tends to be higher in the lower extremities. It is useful in practice, as well as in epidemiological studies — abnormal reading greater than 25V has been associated with high risk for foot ulceration

**Computer assisted sensory examination**

This complex method, currently regarded as state of the art for clinical trials, uses a computerized device that can measure touch-pressure, vibration and warm-cold thresholds using a forced choice algorithm. It is being used in several long term trials of new therapeutic interventions.\(^7\)

**Autonomic Function Testing**

Cardiovascular autonomic dysfunction can be evaluated in detail by employing Ewing and Clarke’s battery of 5 tests \(^7\)

1. The average inspiratory-expiratory heart rate difference with its deep breaths;
2. The Valsalva ratio;
3. The 30:50 ratios;
4. The diastolic blood pressure response to isometric exercise; and
5. The systolic blood pressure fall to standing.

**Corneal Confocal Microscopy (CCM)**

Corneal confocal microscopy represents a novel reiterative in vivo clinical examination technique that is capable of imaging corneal nerve fibres. It has been shown to accurately define the extent of corneal nerve damage, which has been related to the somatic diabetic neuropathy. CCM demonstrates the capacity to detect early nerve fibre repair following therapy.\(^8\)

**Management**

Diabetic neuropathy has an adverse effect on quality of life. Main objective of treatment of diabetes is to prevent long term complications. Neuropathy is one and most common of them. The presence of neuropathy is associated with
significant morbidity, including recurrent foot infection; impotence in diabetic men, and sudden death in individuals with cardiovascular autonomic neuropathy. More hospital beds are occupied by diabetic patients with foot problems than by those with all other consequences of diabetes.

Management of diabetic neuropathy should begin at the initial diagnosis of diabetes. Patient should be educated and trained for good glycemic control from the beginning to prevent diabetic neuropathy. Physicians should be trained for inspection of feet in each visit and thereby early detection of neuropathy. The goals are early detection, halting disease progress and minimizing further deterioration. To consider any patient with clinical evidence of diabetic neuropathy to be at risk for foot ulceration and to provide education on foot care.

**Diabetic neuropathic pain management:**

Neuropathic pain in diabetic patients is commonly encountered in clinical practice. Many medications are available for the treatment of diabetic neuropathic pain. Oral agents include antidepressants and anticonvulsant drugs. According to the 2011 guidelines issued by the American Academy of Neurology (AAN)—Pregabalin is recommended for treatment of diabetic neuropathic pain, the dose recommended is 75mg to 150mg per day. The drug has been proven effective and can improve quality of life. Gabapentin and Sodium Valproate are also considered for diabetic neuropathy pain management. They are reasonably tolerated. Tricyclic antidepressants (Imipramine and Amitryptilin) are also effective in pain management with some anticholinergic like side effects.10,11

Topical therapy with capsaicin or transdermal lidocaine may be useful in some patients, especially those with more localized pain or those in whom adverse effect with existing oral medication are of concern.

**Experimental therapies**

Aldose reductase inhibitors: Aldose reductase inhibitors block the rate-limiting enzyme in the polyol pathway that is activated by chronic hyperglycemia. Epralrestat is available in India, reduces intracellular sorbitol accumulation, which has been implicated in the pathogenesis of diabetic neuropathy. Epralrestat 150mg/day for 12 wks improved motor and sensory nerve conduction velocity and vibration threshold in patients with diabetic neuropathy. Subjective symptoms, including pain, numbness, hyperesthesia coldness in extremities, muscular weakness and orthostatic fainting were also improved.12

**Alpha lipoic acid:** Alpha-lipoic acid has shown to improve symptomatic relief of neuropathy symptoms in type 2 diabetes with neuropathy,

**CONCLUSION**

Arealisticobjective must be chosen for any programmedesigned to prevent the onset or progression of diabetic neuropathy. In the early stage of distal sensorimotor neuropathy, the goals are early detection, halting disease progress and minimizing further deterioration. In the symptomatic stage, they include symptom assessment, halting disease progression, allowing nerve repair and regeneration, relief of symptoms and preventing further deterioration. In the severe stage, they include management of clinical symptoms, helping patients to overcome disability and to learn to have a limited expectation of full return of function and preventing further deterioration and ulceration.

Far all patients good glycemic control, blood pressure control, lipid management, maintaining healthy lifestyle and monitoring of all parameters of diabetes management as advised by the physicians are of paramount importance for a patient with diabetic neuropathy.

**REFERENCES**

1. Maji D &. Maji T Neuropathy is the commonest long term complication of Type 2 diabetic individuals at diagnosis. Diabet & Metab 2003; 2373.