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A Review on Diabetic Neuropathy

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ABSTRACT

Diabetic neuropathy (DN) is the most common and multifactor complication of diabetes mellitus. It is late finding in type I diabetes and can be an early finding in type II diabetes. It is characterized by hyper responsiveness to pain typically originating in the extremities, progressive loss of neuronal function. The exact etiopathogenesis of diabetic neuropathy is dependent on many factors such as hyperglycemia, neuronal loss, alteration in neurotransmitters and growth factors. Other mechanisms include insulin deficiency, oxidative stress, nitrosative stress, ischemia, osmolytic accumulation, neurotropic factor deficiency, autoimmune nerve destruction, alteration in cellular signaling pathways and gene expression of proteins. The main risk factor for diabetic neuropathy is hyperglycemia. Good control of hyperglycemia, blood pressure and dyslipidemia is important for prevention and reducing progression of neuropathy. Although current treatment focusses on pain management, attention should be paid to potential risk factors for neuropathy. For eg. glycemic control, hyperlipidemia, and hypertension should be managed with diet, exercise, and medication.

Keywords: *Diabetic Neuropathy, Hyperglycemia, Type 1 Diabetes, Type 2 Diabetes, Pain.*

1. INTRODUCTION

Diabetic neuropathy (DN) is a chronic complication of both type I DM (beta cell destruction – absolute lack of insulin) and type II DM (insulin resistance and/or decreased secretion of insulin). Patients with long-term diabetes may develop complications affecting the eyes, kidneys or nerves (micro vascular complications) or major arteries. Diabetic neuropathy is nerve damaging disorders associated with diabetes mellitus. These conditions are thought to result from a diabetic micro vascular injury involving small blood vessels that supply blood to nerves (vasa nervorum) and macro vascular conditions that culminate in diabetic neuropathy. The most common form of diabetes mellitus, type 2 diabetes mellitus, is projected to affect an estimated 366 million people worldwide by 2030. The life time incidence of neuropathy is approximately 45% for patients with type II diabetes mellitus and 54% to 59% for patients with type I diabetes mellitus.

Diabetic neuropathy is a very common complication of diabetes. There are many forms of diabetic neuropathy but most common form is a peripheral sensorimotor neuropathy that affects the feet first, poorly controlled hyperglycemia, uncontrolled hypertension and progression of neuropathy. Peripheral nerve injury is associated with neuropathic pain and is characterized by the sensory abnormalities such as unpleasant abnormal sensation (dysesthesia), an increased response to painful stimuli (hyperalgesia), and pain in response to stimulus that does not normally provoke pain (allodynia). The various proposed mechanisms which lead to pathogenesis of diabetic neuropathy are activated polyol pathway, AGE's (Advanced Glycation Endproducts) formation PKC (Protein Kinase C) activation and Hexosamine pathway. Hyperglycemia is the primary cause for diabetic neuropathy. There have been major advances in the control of hyperglycemia (diabetes), through dietary changes, hypoglycemic agents, insulin and islet transplantation, even though the long-term complication of diabetes, such as neuropathy remains a serious problem.[(1)]

Oxidative stress, is a major determinant in diabetic complication including diabetic neuropathy which is a result of cross-links between above pathways, as proposed by several studies. Therefore, agents or compounds that exerts multiple actions, such as antioxidants, antidiabetic/ hypoglycemic AR inhibitory and antiglycation properties could be more effective than agents with a single action. Significant neuropathic pain occurs in 7.5% to 24% of all patients with diabetic mellitus. Neuropathic pain is also one of the most common presentation in impaired glucose. Interestingly, although pain specific medication are required to treat the discomfort, therapies that ameliorate the underlying neuropathy also reduce the severity of the neuropathic pain. Several micro vascular and macro vascular complications arise as a result of the onset and progression of diabetes.[(2)] These complications affect the eyes (retinopathy), kidneys (nephropathy), nerves (neuropathy), or heart (cardiovascular diseases) and are mainly responsible

for the increase in morbidity and mortality of diabetics worldwide.[3] DN results from peripheral nerve dysfunctions involving different parts of the somatic and autonomic nervous systems which are the basis for many classifications of the disease.[4] Diabetic peripheral neuropathy (DPN) generally encompasses polyneuropathies and some rare varieties which can be further subdivided based on differences in onset, duration, clinical manifestations, and pathophysiology.[5,6]

Neuropathies Associated with Diabetic Mellitus: [7, 8]

- Distal symmetric sensorimotor polyneuropathy
- Small fiber neuropathy
- Acute severe distal sensory polyneuropathy
- Autonomic neuropathy
- Diabetic neuropathic cachexia
- Hypoglycemic neuropathy
- Treatment-induced neuropathy (insulin neuritis)
- Polyradiculopathy
- Diabetic radiculoplexopathy
- Mononeuropathies
- Cranial neuropathies (in particular, oculomotor)

Pathogenesis of Diabetic Neuropathy

The pathogenesis of diabetic neuropathies in general is complex. Several trials have been conducted to clear the relationship between impaired glycemic control, neuropathy and retinopathy. It is clear from the trial that increased glucose level above normal, result in increased risk of organ injury, including neuropathy. In addition to hyperglycemia, hyperlipidemia play an important role in pathogenesis of diabetic neuropathy. There are some biochemical pathways which are involved in the pathogenesis of diabetic neuropathy. [10, 11]

Following pathways are involved in pathogenesis of DN

Pathogenetic Mechanisms of Neuropathy

- Oxidative stress with nitric oxide depletion
- Advanced glycosylated end products
- Activation of the polyol pathway
- Activation of the hexosamine pathway
- Excessive protein kinase C activity
- Activation of poly(ADP-ribose) polymerase
- Diminished neurotrophic peptide factors

a) Oxidative stress- There is a high evidence of diabetic neuropathy with oxidative stress. Oxidative stress results from over production of oxygen free radical as compared to body's ability to eliminate it by antioxidant activity. Hyperglycaemia-induced oxidative and nitrosative stress has been singled out as one of the major links between diabetes and diabetic complications. [12] Hyperglycaemia leads to generation of free radicals due to autoxidation of glucose and glycosylation of proteins. [13] The persistent increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) accompanied by a decrease in antioxidant activity leads to the occurrence of oxidative and nitrosative stress which can cause endothelial dysfunction, insulin resistance, and alterations in number and functions of pancreatic cells and eventually leads to diabetic microvascular and macro vascular complications.[14] Once ROS and RNS are produced in excess, they cause the structural deterioration of macromolecules (carbohydrates, proteins, lipids, and DNA) leading to their instability and consequently loss of function. [15] Thus there is formation of superoxide in the body, which is when in higher concentration combines with nitric oxide to form peroxynitrate, which is implicated in diabetes associated motor and sensory nerve conduction deficits and peripheral nerve energy deficiency. ROS and RNS have also been reported to induce several cellular signaling cascades that ultimately lead to the transcription of stress-related genes which promote the development of diabetic complications.[16] These complications affect the eyes (retinopathy), kidneys (nephropathy), nerves (neuropathy), or heart (cardiovascular diseases) and are mainly responsible for the increase in morbidity and mortality of diabetics worldwide. [17]

b) Advanced glycosylated end products – Advanced glycosylated end products (AGEs) from chronic hyperglycemia play an important role in diabetic neuropathy and micro vascular complication. Excess glucose combines with amino acids on circulating or tissue proteins to form AGEs. [18] These AGEs peptides crosslink strongly with collgen invitro, damaging nerve fibres. AGEs also bind to and activate the cell surface receptor called RAGE (Receptor for Advanced Glycation Endproducts). RAGE proteins are proinflammatory and expressed on endothelial cells, fibroblasts, mesangial cells, and macrophages. Endothelial cells with RAGE internalized AGEs into the subepithelium enhancing permeability and endothelium dependent coagulant activity which can contribute to the vascular injury and endoneural hypoxia. These advanced glycation end products are formed due to glycation of intracellular and extracellular proteins which is responsible for inadequate activation of protein kinase C and increased protein kinase C lead to damage to vasanervum. [19]

c) 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. [20, 21]

d) Hexosamine pathway- Fructose-6-phosphate is an intermediate of the glycolytic pathway which is formed from glucose-6-phosphate by the enzyme phosphoglucoisomerase. However, in the presence of high glucose, fructose-6-phosphate can accumulate, and it is utilized by the hexosamine pathway. Here, fructose-6-phosphate is converted to glucosamine-6-phosphate by catalytic action of the enzyme glutamine-fructose-6-phosphate aminotransferase (GFAT). Glucosamine is well documented to increase oxidative stress in cells via the production of H_2O_2. [22] This H_2O_2 undergo Fenton reaction to form OH which is responsible for increase in intracellular calcium ion, increased intracellular calcium ion lead to rapid beta cell destruction. While, Glucosamine-6-phosphate is further processed via conjugation reactions with uridine triphosphate (UTP) to yield uridine diphosphate-N-acetylglucosamine (UDPGlcNAc). UDPGlcNAc thus formed can attach to the amino group of serine and threonine residues of proteins relevant to the elevation of transcription factor SpI which in turn activates the transcription of growth factors like TGF and TGF1 and plasminogen activator inhibitor-1 (PAI-1). [23]

These proteins are involved in the pathogenesis of diabetes-induced vascular complications especially in the nerve [24, 25] Similarly, GFAT enzyme has been implicated in insulin resistance and hyperinsulinaemia in type 2 diabetes mellitus. [26]
e) Protein kinase C activity- Protein kinase C (PKC) is involved in controlling the function of proteins through the phosphorylation of hydroxyl groups of serine and threonine amino acid residue on these proteins. PKC is responsible for activation of essential proteins and lipids in cells that are needed for survival. [27] Nevertheless, excessive PKC can be harmful to the nervous system. Its contribution to the diabetic neuropathy is likely through the effect on vascular blood flow and micro vascular diseases rather than directly on neuronal cells. Glucose is converted into diacylglycerol which activates PKC. PKC then activates mitogen-activated protein kinase which is responsible for apoptosis and vascular atherosclerosis. [28] The inhibition of PKC reduces oxidative stress and normalizes blood flow and nerve conduction deficits in diabetic rats. [29]

f) Poly (ADP-ribose) polymerase- When there is hyperglycemia, then poly (ADP-ribose) polymerase (PARP) get activated. Thus the over-activation of PARP results in formation of free radical, increased protein kinase C activity and AGE formation and all these promotes nerve damage through metabolic pathway. [30]

g) Neurotrophic peptide factors- Neurotrophic peptide factors consist of endogenous proteins essential to the health and survival of neurons. These peptide includes nerve growth factor, brain-derived neurotrophic factors, neurotrophin-3 and insulin-like growth factors (IGF) and vascular endothelial growth factors. These factors are important for maintenance of nerve structure and function as well as repair of nerves after injury. Impaired peripheral nerve repair in diabetes may be due to diabetes-induced loss of these peptides. Insulin also function as neurotrophic factor to the peripheral neurons, and thus loss of insulin in diabetes may compromise nerve viability and repair. [31]

- **Classification of Diabetic Neuropathy**

A. Diffuse

- Distal symmetric sensori-motor polyneuropathy
- Autonomic neuropathy

a. Sudomotor

b. Cardiovascular

c. Gastrointestinal

d. Genitourinary

- 3. Symmetric proximal lower limb motor neuropathy (amyotrophy)

B. Focal

- Cranial neuropathy
- Radiculopathy/plexopathy
- Entrapment neuropathy
- Asymmetric lower limb motor neuropathy (amyotrophy) [34]

i. Distal Symmetric Sensori-Motor Polyneuropathy

This is the commonest neuropathic syndrome. There is a "length-related" pattern of sensory loss, with sensory symptoms starting in the toes and then extending to involve the feet and legs in a stocking distribution. In more severe cases, there is often upper limb involvement, with a similar progression proximally starting in the fingers. Although the nerve damage can extend over the entire body including the head and face, this is exceptional. As the disease advances, overt motor manifestations such as wasting of the small muscles of the hands and limb weakness become apparent. However, subclinical motor involvement detected by magnetic

resonance imaging appears to be common, and thus motor disturbance is clearly part of the functional impairment caused by distal symmetrical neuropathy. [35] The main clinical presentation of distal symmetrical neuropathy is a sensory loss which the patient may not be aware of, or may be described as "numbness" or "dead feeling." However, some may experience a progressive buildup of unpleasant sensory symptoms [36] including tingling (paraesthesia); burning pain; shooting pains down the legs; lancinating pains; contact pain often with daytime clothes and bedclothes (allodynia); pain on walking often described as "walking barefoot on marbles," or "walking barefoot on hot sand"; sensations of heat or cold in the feet; and persistent achy feeling in the feet and cramp-like sensations in the legs.

Differential diagnosis of distal symmetrical neuropathy- Absence of other complications of diabetes, rapid weight loss, excessive alcohol intake, and other atypical features in either the history or clinical examination should alert the physician to search for other causes of neuropathy.

ii. Autonomic Neuropathy

Diabetic autonomic neuropathy (DAN) is a common and serious complication of diabetes. The prevalence of DAN varies from 1% to 90% in patients with type 1 diabetes and from 20% to 73% in patients with type 2 diabetes.[37] Risk factors for autonomic neuropathy are age, duration of diabetes, glycemic control, microvascular complications (polyneuropathy, retinopathy, nephro pathy) and other factors such as hypertension, dyslipidemia, smoking, obesity and alcohol con- sumption. The main factor among the listed is glycemic control. [38]

Clinical presentation (symptoms and signs)

The symptoms and signs of DAN vary widely and depend on the affected organ [37, 39, 40, and 41].

Cardiovascular autonomic neuropathy (CAN)

- Loss of circadian rhythm of blood pressure ('nondipping')
- Resting tachycardia
- Exercise intolerance
- 'Silent ischemia' and 'painless' myocardial infarction
- Diabetic cardiomyopathy
- Arrhythmias, cardiac arrest
- Orthostatic hypotension

Gastrointestinal system

- Dysfunction of the esophagus
- Gastro paresis
- Change in gut motility (constipation, diarrhea)
- Anorectic dysfunction (fecal incontinence)

Genitourinary system

- Bladder dysfunction
- Sexual dysfunction in both sexes

Respiratory system

- Central deregulation of breathing
- Reduced bronchial reactivity

Neurovascular system

- Sweating abnormalities
- Changes in skin blood flow (warm skin, varicose veins, peripheral edema)

Neuroendocrine system

- Decrease or loss of signs of hypoglycemia
- Impaired counter-regulation mechanism of hypoglycemia
- Change in the formation of renin

Pupillomotor

- Pupil dysfunction

iii. Proximal Motor Neuropathy

It typically affects the elderly males (> 50 years) suffering from type 2 diabetes mellitus but it can also occur in females and type 1 diabetes mellitus. It may be symmetrical or asymmetrical, and with or without sensory loss. The patient usually presents with difficulty in getting up from squatting position, pain in climbing stairs and marked weight loss (sometimes up to 40% of original weight). It predominantly affects anterior (quadriceps) and adductor compartments of the thigh. Wasting and weakness of quadriceps is so severe that the knee often gives way, and patient may fall. This has been labelled as diabetic amyotrophy also. The cause of diabetic amyotrophy is unknown but neurological deficit and anatomical distribution suggest nerve root involvement presumably due to occlusion of the vasa nervosum and infarction. Examination shows wasting and weakness of the anterior and adductor compartments of thigh. The knee jerk is absent, while the ankle jerk may be intact. Sometimes, other muscles, especially the anterior tibial and peroneal muscles may also be involved. [(42)]

iv. Focal Neuropathies or Mono-Neuropathies

The diabetic patients are also susceptible to a variety of asymmetric and focal neuropathies.

a. Cranial Neuropathy: The third, fourth, and sixth cranial nerves are commonly involved. Elderly patients are the most affected. The third cranial nerve palsy presents with eye pain, diplopia, and ptosis but pupillary response to light is usually spared. The pupillary sparing favours vascular aetiology of III rd nerve palsy. Exclusion of other causes of III rd nerve palsy is necessary before labeling diabetes as a cause. Spontaneous recovery generally occurs within 6-12 weeks, although recurrent or bilateral lesion may also occur. [(43)]

b. Truncal Neuropathy : Symptomatic truncal polyneuropathy though less common, tends to occur in the setting of long-standing diabetes with other microvascular complications, especially peripheral neuropathy. Most of the affected individuals are in the 5th or 6th decade of life, with a variable duration of diabetes. [(44)] It usually presents with gradual onset of pain and dysaesthesia in the lower anterior chest or upper abdomen with nocturnal intensification. On examination, hypo aesthesia or hyper aesthesia may be present in the appropriate thoracic segment and abdominal muscle weakness leading to abdominal swelling. [(45)] A careful sensory examination of abdomen and thorax is mandatory in a diabetic person presenting with unexplained thoracoabdominal pain. It resolves, spontaneously within 2 to 6 months.

c. Entrapment neuropathy: Also known as pressure palsy, this is relatively uncommon. The median nerve is mostly affected and is secondary to soft tissue changes associated with limited joint mobility. Occasionally ulnar or lateral cutaneous nerve of the thigh may also be affected.

2. RISK FACTORS

There are several risk factors for the development of diabetic nephropathy. They can be divided into those that cannot be altered (genetic factors, age, and race) and those that can and must be changed (hyperglycemia, hypertension, dyslipidemia, and GFR). [(46)]

- Genetic predisposition
- Race
- Age
- Increased blood pressure
- Glomerular filtration rate
- Glycemic regulation
- Smoking
- Oral contraceptives
- Overweight

Signs and Symptoms of Diabetic Neuropathy

Depending on the type(s) of nerves involved, one or more signs and symptoms may be present in diabetic peripheral neuropathy.

For sensory neuropathy:

• Numbness or tingling in the feet

• Pain or discomfort in the feet or legs—including prickly, sharp pain or burning feet

For motor neuropathy:

• Muscle weakness and loss of muscle tone in the feet and lower legs

• Loss of balance

• Changes in foot shape that can lead to areas of increased pressure

For autonomic neuropathy:

• Dry feet

• Cracked skin

- Some mimickers of diabetic neuropathy

Distal axonal neuropathies-

-Vitamin B12 deficiency

-Monoclonal gammopathies

-Vasculitis Infectious causes Lymphoproliferative disorders

-Paraneoplastic diseases

Small fiber neuropathies (many of these diseases can also cause large fiber neuropathies)-

- Alcoholism

-HIV

-Monoclonal gammopathy

-Pharmacologic or environmental toxins

-Sjo ¨gren syndrome

-Systemic or familial amyloidosis Sarcoidosis

-Hereditary sensory neuropathy

-Other inherited neuropathies

Demyelinating neuropathy

-Chronic inflammatory demyelinating polyradiculoneuropathy and other demyelinating neuropathies

Multifocal neuropathy

-Other causes of mononeuropathy multiplex

Radiculopathy and plexopathies

-Sarcoidosis

-Amyloidosis

-Vasculitis

- Neoplastic and paraneoplastic causes [32, 33]

Diagnosis of Diabetic Neuropathy

Current screening for diabetic neuropathy is typically performed during a patient's routine examination. Recommendations for screening and management are included in the International Guidelines for Diagnosis and Outpatient Management of Diabetic Peripheral Neuropathy and they are as follows: [47]

Patient history	Age, diabetes, physical factors, lifestyle, social circumstances, symptoms, other possible etiological factors.
Examination of both feet	Skin status, sweating, infections, ulcerations, deformity, muscle wasting, arches, palpitation for temperature, pulses, joint mobility, examination of gait/ shoes.
Vascular examination	Check foot pulses
Other	Thyroid function to exclude other etiologies for neuropathy.

According to American Diabetes Association's recommendations, people with diabetes should have an annual foot examination to identify high-risk conditions. [48]

Test for Neuropathy

Several different methods are commonly used to screen and assess diabetic neuropathy. This includes the reflex testing, superficial pain testing, light touch perception, vibration testing, sympathetic skin response, and quantitative sensory testing and nerve conduction studies.

a) Reflex testing- It is most common to test only the ankle reflexes as these are the most sensitive to early diabetic peripheral neuropathy. This test is performed on both the ankles. While the patient is sitting or kneeling, the examiner dorsiflexes the foot and gently strikes the Achilles tendon with the reflex hammer. If no reflex occurs the test can be repeated with reinforcement. Reflexes are typically scored as 0 (absent), 1(present but decreased), 2 (normal), 3 (increased) or 4 (increased with clonus). [49] Ankle reflex has better reproducibility if evaluated as normal or abnormal. However, the test is poor a predictor of ulceration. [50]

b) Superficial pain testing- Pain sensation can be tested with a sterile safety pin. The site of testing varies with the specific algorithm but may include the dorsum of the great toe or the plantar aspect of the distal first, third, and fifth toe of each foot. Mostly the stimulus is applied once per site, and patients are asked to identify the sensation as to whether they feel it at all, and whether it is sharp or dull. Results are scored accordingly. As a means of screening for neuropathy, pinprick is highly subjective and thus, poorly reproducible. [49.51]

c) Light touch perception- It can be evaluated using a number of methods from a finger, to cotton, to specifically calibrated devices. The best known of the calibrated devices is the Semmes- Weinstein 10-g monofilament, a nylon filament embedded in a plastic handle. Gentle pressure is applied to the handle to bow the nylon filament. The initial study in patients with a neuropathic ulcer could sense the 10- g monofilament. [52]

d) Vibration testing- vibration testing is another measure used to evaluate nerve function. Traditionally, vibration perception has been measured with a 128-Hz tuning fork, or less commonly a 64- or 256-Hz tuning fork. There are several methods for testing vibration. Although vibration testing can be a highly subjective measure of severity of neuropathy and may be poorly reproducible, the absence of vibration sensation at the great toe is significantly associated with the development of foot ulcers. [49, 50] vibration perception threshold can also be measured using a graduated tuning fork. Testing with the graduated tuning fork was rapid and showed high inter and intrarater reliability, as well as utility in monitoring changes in sensory function over time. [53] The plots of the vibration perception threshold were comparable, indicating that the turning fork had a high sensitivity and positive predictive valve for the diagnosis of abnormal bedside tests and symptomatic neuropathy. [54]

e) Sympathetic skin response- The sympathetic skin response is a reflex that occurs in response to a change in the electrical potential of the skin. [55] Measurement requires special equipment that is not typically available in most physicians' offices.

f) Quantitative sensory testing- It is an extension of the sensory portion of the neurological evaluation. It determines the absolute sensory threshold [56] which is useful in assessing the integrity of the axons that form the peripheral nervous system and their distal receptors. It is well accepted because it is simple, noninvasive. Quantitative sensory testing system has been developed to measure the threshold of various stimuli that pertain to distinct neuroanatomical pathways. There are typically 2 types of devices: those that generate specified vibratory or thermal stimuli, and those that generate specified vibratory or thermal stimuli, and those that deliver electrical impulses at certain frequencies. [57]

g) Nerve conduction studies- It is frequently used to assess the presence and severity of peripheral nerve involvement in the patients with diabetes. They are sensitive, specific, reproducible, and easily standardized. Studies typically are performed on upper and lower limbs on the motor and sensory nerve. Most clinicians reserve the use of nerve conduction studies including electromyography to these with symptomatic, confusing, unusual, or severe neuropathy. These studies can be performed with surface or needle electrodes, surface techniques are more widely used, technically easier to perform, more comfortable, and produce results that are easier to measure.[56] Results of nerve conduction studies show amplitudes, distal latency of compound muscle action and sensory potentials, the conduction velocity of fastest conducting fibers, and minimum F- wave latencies. Nerve conduction studies do not always correlate well with symptoms and signs. [57]

Physical Examination in Diabetic Neuropathy

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 are-

- Inspection of the feet for evidence of dry skin, hair or nail abnormalities, callus or infection or any deformity of foot.
- Examination of vibratory sensation at the dorsum of toe with a 128 Hz tuning fork.
- 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 preoperative 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 trial) have suggested that manifestations of neuropathy may be stabilized or improved by improved glucose control. [58]

Staging

Different clinical neurological scales can be used to assess the severity of diabetic polyneuropathy. A common staging scales is given below. [59]

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

Treatment for Diabetic Neuropathy [60]

The treatment of diabetic neuropathy can be broadly divided into two major groups:
(i) Symptomatic treatment
(ii) Treatment design to modify the course of diabetic neuropathy.

i) Symptomatic treatment

Pain is the most common symptom, which could be superficial, deep, or aching. The management of pain is often difficult and disappointing. There is no single correct approach to the management of any given patient with peripheral neuropathy. Sometimes simple reassurance that the pain is not permanent does produce great relief from pain, pain-related anxiety or depression. However, following measures can be taken in order of preference for pain relief:

Symptomatic Therapy

1. Treatment of neuropathic pain.
2. Treatment of symptomatic autonomic neuropathy.
3. Treatment of mononeuropathies.
4. Treatment of diabetic foot.

Disease-modifying therapy

1. Measures of established clinical value: Optimized Glycemic control.
2. Measures approaching clinical usefulness:
   a. Aldose reductase inhibitors.
   b. Essential fatty acids.
   c. Vasodilator drugs.
3. Measures under experimental investigation
   a. Inhibitors of glycation.
   b. Antioxidants.
   c. Agents promoting nerve growth and repair.

Symptomatic Therapy

- Treatment of neuropathic pain-

Neuropathic pain in diabetic patients is commonly seen in clinical practice. Many drugs are available for treatment of diabetic neuropathic pain. Antidepressant and anticonvulsants play an important role in pain.
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. [61, 62] The drug has been proven effective and can improve quality of life. Gabapentin and Sodium Valproate are also considered for diabetic neuropathic pain management. They are reasonably tolerated. Tricyclic antidepressants (Imipramine and Amitryptilin) are also effective in pain management with some anticholinergic like side effects. [61, 62] Anticonvulsants like Gabapentin 300-1, 200 mg t.i.d. Its efficacy for painful diabetic neuropathy is comparable to Amitriptyline. The mechanism of action is postulated to be a central voltage dependent 1-type Ca++ channel. The older anticonvulsant drugs have been largely replaced by the newer ones which are better tolerated and safe like Oxcarbamazepine, Toporamate, Pregabalin, and Tamotrigine. But different anticonvulsant drugs of choice for different painful states have not yet been determined.

Treatment of Symptomatic Autonomic Neuropathy-[63]

The first step in the management of autonomic neuropathy is to identify correctly those patients who are affected because once the autonomic nervous system is involved, the mortality rate may be as high as 50% within five years, pointing to the serious consequences of this complication. Diagnosis depends upon the correct interpretation and recognition of often disguised and ambiguous problems like dizzy turns, blackouts (postural hypotension), recurrent urinary tract infections (bladder dysfunction), impotency (organic or functional).
a) Diabetes gastro paresis- It may require hospital admission fluids and occasional parenteral nutrition and nasogastric drainage or sometimes percutaneous intrajejunal tube feeding. Metoclopramide, domperidone, cisapride, and erythromycin are the best options for enhancing gut motility.
b) Problems with lower GIT- These include constipation, the most common problem, diabetic diarrhea (usually paroxysmal with nocturnal exacerbation), and fecal incontinence (because of internal anal sphincter dysfunction). Constipation usually responds to stimulant laxatives (e.g. senna, codanthrustate) at night and diarrhea to codeine or loperamide or if due to bacterial overgrowth of small bowel to short course (5-7 days) of antibiotics (tetracycline or erythromycin).

c) Postural hypotension- Mild symptoms may respond to raising the head end of the bed by 10 centimeters, which helps to maintain the postural vascular tone. Fludrocortisone is the drug of choice that increases the peripheral vascular tone and extracellular blood and fluid volume, but it can cause hypokalemia and hypertension.
d) Bladder dysfunction- For poor bladder emptying, mechanical measures like manual suprapubic pressure or intermittent self-catheterization are usually sufficient. Long-term cyclical antibiotic therapy may be needed for recurrent urinary tract infection.
e) Abnormal sweating- Excessive and inappropriate sweating especially gustatory sweating is a very distressing problem and no satisfactory treatment for this is yet available. Clonidine has been used with some success.
Other drug available is polidine but it is not well tolerated because of its anticholinergic side effects like tachycardia, dryness of mouth, urinary retention etc.
f) Impotence-Impotence is extremely common in men with diabetes and is a major source of frustration. Once non-organic causes are excluded, treatment can be mechanical (vacuum device, rubber bands, semirigid and malleable or the inflatable penile prosthesis) or pharmacological. Unquestionably, the pharmacological agent receiving the greatest fanfare and publicity for the treatment of impotence has been sildenafil. Sildenafil is contraindicated in those on nitrate therapy for coronary heart disease.

- Treatment of mononeuropathies-

Mononeuropathies can be of two types: compressive and non-compressive. Noncompressive mononeuropathies include diabetic amyotrophy (proximal motor neuropathy of lower extremities more common in type 2 diabetes), cranial mononeuropathies (involving the third, fourth, sixth and seventh cranial nerves), truncal or thoracoabdominal neuropathy or radiculopathy. These usually affect diabetic individuals above age 50 and resolve spontaneously. General measures including pain relief, psychological support and physiotherapy are often sufficient. Compressive mononeuropathies, especially carpal tunnel syndrome, often require surgical relief of pressure, but the outcome of surgery may be less favourable than in non-diabetic subjects. Also, this is to be carried out before irreversible damage occurs.

Treatment of diabetic foot- The foot examination can be accomplished in a primary care setting and should include the use of a monofilament, tuning fork, palpation, and a visual examination. Patients with diabetes and high-risk foot conditions should be educated regarding their risk factors and appropriate management. Patients at risk should understand the implications of the loss of protection sensation and the importance of foot monitoring on a daily basis. The following measures can prevent many amputations:
The patient's knowledge of foot care practices should be assessed.
Essential guidelines for preventive foot care should be advised. Advice should be given to consult the doctor in case of swelling of foot, the color change of toe / nail, pain or throbbing, thick hard skin or corns, breaks in skin, cracks, blisters or sores.
Foot at risk (low and high risk) should be identified and measures taken to prevent foot ulceration in them.
Assess at each visit for protective sensation (touch, pain, and vibrations), foot structure, biomechanics, vascular status and skin integrity.
Evaluate for additional risk factors and plan strategies accordingly.

- Disease-modifying therapy-

1) Glycemic control- Of all the treatments, tight and stable glycemic control is probably the only one that may provide symptomatic relief as well as slow down the relentless progression of the neuropathic state. Even very badly damaged nerves have been found to show some improvement with the maintenance of normoglycemia. Since it has been suggested that rapid surges in blood glucose level from hypo to hyperglycemia can aggravate and induce neuropathic pain, the stability rather than the actual level of glycemic control may be more important in relieving neuropathic pain.
2) Measures approaching clinical usefulness-
a) Aldose reductase inhibitors (ARI) - These agents prevent and reverse nerve conduction defects and biochemical abnormalities in diabetic animals is firmly established, but the results of clinical trials in human have not been very convincing. Sorbinil and tolerant are the two ARIs most studied in humans. Tolerastat has also been found to improve autonomic nervous system function in patients with diabetic autonomic neuropathy. (63)
b) Essential fatty acids- In diabetes, the metabolism of essential fatty acids is impaired and this defect can be overcome by administration of GLA. This may be a rate limiting step for the synthesis of many biologically important eicosanoids like PGE1, PGE2, and prostacyclins. Several studies have confirmed clinical and electrophysiolgical improvement in peripheral nerve function when GLA is administered to neuropathic patients. (63)
c) Vasodilators- . Many vasodilator drugs are reported to improve nerve functions and correct endoneurial capillary abnormalities in diabetic animals. The most promising agents include alpha 1- adrenergic antagonists, ACE inhibitors, and vasodilator prostanoids. Recently EFAs and electrical stimulation have shown beneficial vasodilator effect in diabetic neuropathic subjects. (63)
3) Measures under experimental investigation-
a) Inhibitors of glycation- Advanced glycation products may play an important role in chronic diabetic complications. Aminoguanidine inhibits non-enzymatic glycation and has a beneficial effect in experimental diabetic neuropathy.
b) Antioxidants- Oxidative stress, as reflected by increased peroxidation of nerve lipids in experimental diabetes, may comprise of numerous neuronal and endoneurial vascular functions. But the role of antioxidants in inhibiting oxidative damage is not yet established.
c) Agents promoting nerve growth and repair- Neuronal sprouting and growth are stimulated by nerve growth factor (NGF) and insulin-like growth factor – 1 (IGF-1). NGF administration has been shown to protect against experimental diabetic neuropathy.

The corticotrophin (ACTH) analog, ORG2766, and gangliosides (which are normal components of the neuronal membrane) are known to promote neuronal regeneration and growth. (63)

Biomarkers of Diabetic Neuropathy

Albuminuria remains the only biomarker acceptable for diagnostic purposes, although some growth factors are expected to replace albuminuria in future. It is known that values of TGF beta, vascular endothelial growth factor (VEGF), and CTGF are increased in the plasma and urine of patients with diabetic nephropathy. [64-67]

3. REFERENCES

[1] Vrhovac B, Jacksik B, Reiner Z, Vucelic B. Interna Medicina Zgreb Naklada L jevak. 2008; 1258-1259.
[2] Kiritoshi S, Nishikawa T, et al., "Reactive oxygen species from mitochondria induce cyclooxygenase-2 gene expression in human mesangial cells: potential role in diabetic nephropathy," Diabetes. 2003; 52 (10), 2570–2577.
[3] Fernyhough P, Roy Chowdhury S. K., and Schmidt R. E. "Mitochondrial stress and the pathogenesis of diabetic neuropathy." Expert Review of Endocrinology and Metabolism. 2010; 5 (1), 39–49.
[4] Casellini C. M. and Vinik A. I., "Recent advances in the treatment of diabetic neuropathy," Current Opinion in Endocrinology and Diabetes, 2006;13 (2), 147–153.
[5] Boulton A. J. M., Vinik A. I., Arezzo J. C. et al., "Diabetic neuropathies: a statement by the American Diabetes Association," Diabetes Care. 2005; 28 (4), 956–962.
[6] Hosseini A. and Abdollahi M., "Diabetic neuropathy and oxidative stress: therapeutic perspectives," Oxidative Medicine and Cellular Longevity, 2013; 16 (8), 15-19.
[7] Dyck PJ, Albers JW, Andersen H, et al., "Toronto Expert Panelon Diabetic Neuropathy. Diabetic polyneuropathies: update on research definition, diagnostic criteria, and estimation of severity" Diabetes Metab Res Rev. 2011; 1226 -1228.
[8] Tesfaye S, Boulton AJ, Dyck PJ, et al. "Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments." Diabetes Care. 2010; 33(10):2285-2293.
[9] Mogensen CE, "Microalbuminuria, blood presure and diabetic renal disease: origin and development of ideas". Diabetologia.1999; 42:263-285.
[10] Russell JW, Smith AG, Singleton JR. "Impaired glucose regulation and neuropathy." In: Gilman S, ed. Neurobiology of diseases. San Diego: Elsevier. 2006; 849-869.
[11] Callaghan BC, Cheng HT, Stables CL, et al. "Diabetic neuropathy: clinical manifestations and current treatments." Lancet Neurol. 2012; 11(6), 521-534.
[12] Negi G., Kumar A, et al. "Oxidative stress and diabetic neuropathy: current status of antioxidants," Institute of Integrative Omics and Applied Biotechnology Journal. 2011; 2 (6), 71–78.
[13] Al-Faris N. A., Al-sawadi A. D., and Alokail M. S., "Effect of samh seeds supplementation (Mesembryanthemum forsskalei Hochst) on liver enzymes and lipid profiles of streptozotocin (STZ)-induced diabetic Wistar rats," Saudi Journal of Biological Sciences. 2010; 17 (1), 23–28.
[14] Bandeira S. D. M., Fonseca L. J. S, et al. "Oxidative stress as an underlying contributor in the development of chronic complications in diabetes mellitus," International Journal of Molecular Sciences. 2013; 14 (2), 3265–3284.
[15] Negre-Salvayre A, Coatrieux C, et al. "Advanced lipid peroxidation end products in oxidative damage to proteins. Potential role in diseases and therapeutic prospects for the inhibitors," British Journal of Pharmacology. 2008; 153(1), 6-20.
[16] Ayepola O. R., Chegou N. N, et al. "Kolaviron, a Garcinia biflavonoid complex ameliorates hyperglycemia-mediated hepatic injury in rats via suppression of inflammatory responses," BMC Complementary and Alternative Medicine. 2013; 13, 363.
[17] Fernyhough P, Roy Chowdhury S.R, and Schmidt R. E., "Mitochondrial stress and the pathogenesis of diabetic neuropathy," Expert Review of Endocrinology and Metabolism. 2010; 5 (1), 39–49.
[18]Thornalley P "Glycation in diabetic neuropthy: characteristics, consequences, causes, and therapeutic options." Int Rev Neurobiol. 2010; 50: 37-57.
[19] Singh R, Barden A, Mori T et al. Advanced glycation end products: a review. Diabetologia. 2001, 44: 129-146.
[20] Dyck PL, Davies JC, Micleon DM "Risk factors for severity of diabetic polyneuropathy intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study cohort." Diabetes Case. 1999; 22:1470-1476.
[21] Endorinology: 6th edition: Larry Jameson, Leslie J De Groot: Neuropathy 2010; 984- 998.
[22] Evans J. L., Goldfine I. D, et al. "Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes," Endocrine Reviews. 2002; 23 (5), 599-622.
[23] Buse M. G., "Hexosamines, insulin resistance, and the complications of diabetes: current status," The American Journal of Physiology—Endocrinology and Metabolism. 2006; 290 (1), 1-8.
[24] Hosseini A and Abdollahi M, "Diabetic neuropathy and oxidative stress: therapeutic perspectives," Oxidative Medicine and Cellular Longevity. vol. 2013; 16 (8), 15-19.
[25] Leinninger G. M., Vincent A. M., and Feldman E. L, "The role of growth factors in diabetic peripheral neuropathy," Journal of the Peripheral Nervous System. 2004; 9 (1), 26–53.
[26] Feldman E. L, Vincent A, "The prevalence, impact, and multifactorial pathogenesis of diabetic peripheral neuropathy," Advanced Studies in Medicine. 2004; 4 (8), 5642–5649.
[27] Vincent A, Russell J, Low P et al. "Oxidative stress in the pathogenesis of diabetic neuropathy." Endocr 2004, 3 (25) 612-628.
[28] Tormlinson D "Mitogen activated protein kinase C as glucose transducers for diabetic complications." Diabetologia. 1994; 42, 1271- 1281.
[29] Ishii H, Koya D, King G "Protein kinase C activation and its role in the development of vascular complications in diabetes mellitus." J Mol Med (Berl). 1998; 76: 21-31.
[30] Pacher P, Obrosova I, Mabley J, et al. "Role of nitrosative strees and peroxinitrite in the pathogenesis of diabetic complications. Emerging new therapeutic strategies." Curr Med Chem. 2005; 12: 267- 275.

[31] Kennedy J, Zochodne D. "The regenerative deficit of peripheral nerves in experimental diabetes: its extent, timing and possible mechanisms." Brain. 2000; 123, 2118-2129.
[32] Russell JW, Smith AG, Singleton JR. "Impaired glucose regulation and neuropathy. In: Gilman S, ed. Neurobiology of diseases." San Diego: Elsevier. 2006; 849-869.
[33] Callaghan BC, Cheng HT, Stables CL, et al. "Diabetic neuropathy: clinical manifestations and current treatments." Lancet Neurol. 2012; 11(6), 521-534.
[34] Thomas PK. "Metabolic neuropathy." Jr Coll Physicians Lond. 1973; 7, 154-60.
[35] Andersen H, Jakobsen J. "Motor function in diabetes." Diabetes Rev. 1999; 7, 326–341.
[36] Witte DR, Tesfaye S, Chaturvedi N, et al. "Risk factors for cardiac autonomic neuropathy in type 1 diabetes mellitus." Diabetologia. 2005; 48:164–171
[37] Dimitropoulos G, Tahrani AA, Stevens MJ. "Cardiac autonomic neuropathy in patients with diabetes mellitus." World J Diabetes. 2014; 5(1), 1739.
[38] Martin CL, Albers JW, Pop-Busui R. "Neuropathy and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study." Diabetes Care. 2014; 37, 31-38.
[39] Vinik AI, Erbas T, Casellini CM. "Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease." J Diabetes Investig. 2013; 4, 4-18.
[40] Pop-Busui R. "Cardiac autonomic neuropathy in diabetes: a clinical perspective." Diabetes Care. 2010; 33,434-441.
[41] Deli G, Bosnyak E, et al. "Diabetic neuropathies: diagnosis and management." Neuroendocrinology. 2013; 98,267-280.
[42] Barohn RJ, Sahenk Z, Warmolts JR et al. The BrunsGarland syndrome (diabetic amyotrophy). Arch Neuro. 1990; 48, 1130.
[43] Harati Y. Diabetes and the nervous system. Endo Metab Clin North Am. 1996; 25, 325-59.
[44] Pourmand R. "Diabetic neuropathy." Neurol Clin.1997; 15, 569-76.
[45] Boulton AJM, Augur E, et al. "Diabetic thoracic polyradiculopathy presenting as an abdominal swelling." BMJ. 1984; 289, 798-9.
[46] Tap RJ, Shaw JW, and et al. "Albuminuria is evident in the early stages of diabetes onset: results from the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab)." Am. j. kidney dis. 2004; 44, 792-798.
[47] Medicine Group (Education) Ltd. "International guidelines on the Out- Patient Management of Diabetic Peripheral Neuropathy." oxford shine: m1998.
[48] American Diabetes Association. Standards of medical care in diabetes. Diabetes care. 2004; 27 (1), 515-535.
[49] Smieja M, Hunt DL, et al. "Clinical examination for the detection of protective sensation in the feet of diabetic patients, International Cooperative Group of Clinical Examination Research." J Gen Intern Med. 1999; 14(7), 418-424.
[50] Boyko E, Ahroni JH. Et al. "A prospective study of risk factors for diabetic foot ulcer: The Seattle Diabetic Foot Study." Diabetes Care. 1999; 22(7), 1036-1042.
[51] Maser RE, Nielsen VK, Bass EB, et al, Measuring Diabetic neuropathy. Assessment and comparison of clinical examination and quantitative sensory testing. Diabetes Care. 1989; 12(4), 20-275.
[52] Birke JA, Sims DS. "Plantar sensory threshold in the ulcerative foot." Lepr Rev. 1986; 57(3), 261- 267.
[53] Pestronk A, Florence PT, Levine T, et al. "Sensory exam with a quantitative tuning fork: rapid, sensitive, and predictive of SNAP amplitude." Neurology. 2004; 62(3), 461-464.
[54] Kastenbauer T, Sauseng S. et al. "The value of the Rydel-Seiffer tunuing fork as a ppredictor of diabetic polyneuropathy compared with a neurothesiometer." Diabet Med. 2004; 21(6), 563-567.
[55] Bril V, Nyunt M, Ngo M. "Limits of the sympathetic ski response in patients with diabetic polyneuropathy." Muscle Nerve. 2000; 23(9), 1427- 1430.
[56] American Diabetes Association. Standardized measures in diabetic neuropathy. Diabetes Care. 1996; 19(15), 725-925.
[57] Shy EM, Frohman EM, So YT, et al. "Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology." Neurology. 2003; 60(6), 898-904.
[58] Diabetes control of complications trial research group: "The effect of intensive diabetes therapy on the development and progression of neuropathy." Ann of Intern Med. 1995; 122, 561-568.
[59] Wwlyn JG, Tomlinson DR et al. "End point assessed longitudinally for change and monotonicity." Diabetes Care. 2007; 30, 2619-2625.
[60] Afzaal S, Singh M, Sallem I, "Aetiopathogenesis and Management of Diabetic Neuropathy." JAPI. 2002; 50, 707-11.
[61] Iton AJM, Malik RA, and Arezzo JC. "Diabetic somatic neuropathy, technical review" Diabetes care. 2004; 27, 1458-1487.
[62] lton AJM, Grics FA, Tevel JA. "Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy." Diab Med. 1998; 15, 508-514
[63] Peter D. Donofrio. "Diabetic Neuropathy. In: Medical Management of Diabetes Mellitus." New York: Ed. Leahy JL, Clark NG, Cefalu WT. New York, 2000; 479-97.
[64] K/DOQI "clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease" Am. j. kidney dis. 2007; 49, 512.
[65] Nguyen TQ, Tarnow L, Jorsal A, Oliver N, Roestenberg P, Ito Y et al. "Plasma connective tissue growth factor is an independent predictor of end-stage renal disease and mortalityin type 1 diabetic nephropathy." Diabetes care. 2008; 31, 1177-1182.
[66] Nguyen TQ, Tarnow L. et al. "Urinary connective tissue growth factor excretion correlates with clinical markers of renal disease in a large population of type 1 diabetic patients with diabetic nephropathy." Diabetes care. 2006; 29, 83-88.
[67] Pfeiffer A, Middelberg-Bisping K, Drewes C, Shatz H "Elevated plasma levels of transforming growth factor-beta 1 in NIDDM." Diabetes care. 1996; 19, 1113-1117.

