



Diabetic Neuropathy: A Review

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ABSTRACT

Neuropathy is one of the most common complications of diabetes, with patients often suffering from severe and unremitting pain. The pain can be acute in onset, resolving within around six months, or more chronic with symptoms lasting for many years. About 60 to 70 % of people with diabetes have some form of neuropathy. People with diabetes can develop nerve problems at any time, but risk increase with age and longer duration of diabetes. The highest rates of neuropathy are among people who have had diabetes for at least 25 years. However there is no particular or specific drug available for the diabetic neuropathic condition till date. The traditional analgesic ladder described by the World Health Organization (WHO) is of limited usefulness in the treatment of neuropathic pain. This is because simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are often less effective in neuropathic pain (although, as mentioned above, they may have a role in the treatment of inflammatory ‘flare-ups’) Several medicinal plants have been used as dietary adjunct and in the treatment of numerous diseases without proper knowledge of their function. So there is always search for new drugs which can combat the neuropathic pain and which improves the quality of lifestyle of patients. In recent years the model of STZ-induced diabetes in the rat has been increasingly used in an attempt to provide information on underlying processes, and to evaluate potential therapies.

Key words: Diabetic Neuropathy, NSAIDs, Ketoacidosis

INTRODUCTION

*Diabetic Neuropathy*¹⁻⁶

Patients with diabetes mellitus may suffer from both acute and chronic complications. Acute complications concerned with ketoacidosis and ketoacidotic coma. Chronic complications can be classified into macrovascular and microvascular complications. Macrovascular diseases, predominantly myocardial infarction, CHF, and stroke. More than 75% of diabetic mortality due to these complications. Microvascular abnormalities include diabetic neuropathy, diabetic nephropathy, and diabetic retinopathy¹. Diabetic neuropathy is the most common of diabetic complications up to 50% of patients with type 1 or 2 disease have some form of neuropathy. Diabetic neuropathy is associated with progressive nerve fiber loss and both positive and negative clinical signs and symptoms such as pain, paresthesia, and loss of sensation.

Causes of Diabetic Neuropathy

The causes are probably different for different types of diabetic neuropathy. Researchers are studying how prolonged exposure to high blood glucose causes nerve damage. Nerve damage is likely due to a combination of factors:

- Metabolic factors, such as high blood glucose, long duration of diabetes, abnormal blood fat levels, and possibly low levels of insulin.
- Neurovascular factors, leading to damage to the blood vessels that carry oxygen and nutrients to nerves.
- Autoimmune factors that cause inflammation in nerves.
- Mechanical injury to nerves, such as carpal tunnel syndrome.
- Inherited traits that increase susceptibility to nerve disease.
- Lifestyle factors, such as smoking or alcohol use.

Types and Classification

Diabetic neuropathy can be classified as peripheral, autonomic, proximal, or focal. Each affects different parts of the body in various ways.

- a) Peripheral neuropathy, the most common type of diabetic neuropathy, causes pain or loss of feeling in the toes, feet, legs, hands, and arms.
- b) Autonomic neuropathy causes changes in digestion, bowel and bladder function, sexual response, and perspiration. It can also affect the nerves that serve the heart and control blood pressure, as well as nerves in the lungs and eyes. Autonomic neuropathy can also cause hypoglycemia unawareness, a condition in which people no longer experience the warning symptoms of low blood glucose levels.
- c) Proximal neuropathy causes pain in the thighs, hips, or buttocks and leads to weakness in the legs.
- d) Focal neuropathy results in the sudden weakness of one nerve or a group of nerves, causing muscle weakness or pain. Any nerve in the body can be affected.

a) Peripheral Neuropathy

Peripheral neuropathy, also called distal symmetric neuropathy or sensorimotor neuropathy is nerve damage in the arms and legs. Feet and legs are likely to be affected before hands and arms. Many people with diabetes have signs of neuropathy that a doctor could note but feel no symptoms themselves. Symptoms of peripheral neuropathy may include

- numbness or insensitivity to pain or temperature
- a tingling burning or prickling sensation
- sharp pains or cramps
- extreme sensitivity to touch, even light touch
- loss of balance and coordination

These symptoms are often worse at night. Peripheral neuropathy may also cause muscle weakness and loss of reflexes, especially at the ankle, leading to changes in the way a person walks. Foot deformities such as hammertoes and the collapse of the mid foot may occur. Blisters and sores may appear on numb areas of the foot because pressure or injury goes unnoticed. If an infection occurs and is not treated promptly the infection may spread to the bone, and the foot may then have to be amputated. Many amputations are preventable if minor problems are caught and treated in time.

b) Autonomic Neuropathy

Autonomic neuropathy affects the nerves that control the heart, regulate blood pressure, and control blood glucose levels. Autonomic neuropathy also affects other internal organs, causing problems with digestion, respiratory function, urination, sexual response, and vision. In addition, the system that restores blood glucose levels to normal after a hypoglycemic episode may be affected,

resulting in loss of the warning symptoms of hypoglycemia.

c) Proximal neuropathy

Proximal neuropathy, sometimes called Lumbosacral plexus neuropathy, femoral neuropathy, or diabetic amyotrophic starts with pain in the thighs, hips, buttocks, or legs, usually on one side of the body. This type of neuropathy is most common in those with type 2 diabetes and in older adults with diabetes. Proximal neuropathy causes weakness in the legs and the inability to go from a sitting to a standing position without help. Treatment for weakness or pain is usually needed. The length of the recovery period varies, depending on the type of nerve damage.

d) Focal neuropathy

Focal neuropathy appears suddenly and affects specific nerves, most often in the head, torso or leg. Focal neuropathy may cause.

- inability to focus the eye
- double vision
- aching behind one eye
- paralysis on one side of the face, called Bell's palsy
- severe pain in the lower back or pelvis
- pain in the front of a thigh
- pain in the chest, stomach, or side
- pain on the outside of the shin or inside of the foot
- chest or abdominal pain that is sometimes mistaken for heart disease, a heart attack, or appendicitis.

Focal neuropathy is painful and unpredictable and occurs most often in older adults with diabetes. However it tends to improve by itself over weeks or months and does not cause long-term damage.

Signs and Symptoms

In humans

Symptoms of nerve damage may include

- numbness, tingling, or pain in the toes, feet, legs, hands, arms, and fingers
- wasting of the muscles of the feet or hands
- indigestion, nausea, or vomiting
- diarrhea or constipation
- dizziness or faintness due to a drop in blood pressure after standing or sitting up
- problems with urination
- erectile dysfunction in men or vaginal dryness in women
- Weakness.

In animals

- Diabetic rats display a range of abnormal behavioral responses to nociceptive stimuli suggesting the presence of hyperalgesia. These include, reduced paw withdrawal thresholds to mechanical stimuli, reduced time to tail-flick after thermal stimulation

and increased flinch responses following the injection of formalin into the paw.

- The emerging interest in these models has prompted a growing appreciation of the mechanisms of normal pain perception (nociception) and abnormal persistent pain following anerve injury (neuropathic pain) which in turn has ed o the application of similar tests to animal models of diabetes. Such studies show that diabetic rodents display physiologic ,neurochemical, and behavioral indices suggestive of altered pain perception which may make them useful for investigating etiologic mechanisms linking hyperglycemia with painful neuropathy⁶.

Table 1: Signs and Symptoms in diabetic neuropathy

LARGE FIBER	SMALL FIBRE	MOTOR	AUTONOMIC
ymptom Numbness, pin sand needles, tingling, poor balance	Pain; burning, shock like, stabbing allodynia, prickling, shooting.	Cramp, weak grip, twitching, foot drop	Decreased or increased sweating, dry eyes, mouth, erectile dysfunction, gastro paresi, faintness
Signs Decreased vibration	Decreased pin prick, temperature sensation	Reduced strength reflexes	Orthostasis, unequal pupil size

Molecular mechanism behind diabetic neuropathy -

Advanced glycation products:

Non enzymatic reactions between reducing sugars and proteins result in advanced glycation end products (AGEs). Three main pathways are responsible for the formation of reactive dicarbonyls (AGE precursors)

- Oxidation of glucose to form glyoxal.
- Degradation of Amadori products (fructose-lysine adducts) and
- Aberrant metabolism of glycolytic intermediates to methylglyoxal.

Glycation end products and reactive dicarbonyls are heterogeneous modified extracellular and intracellular bimolecular components. Intracellular protein, both protein and DNA adducts alter function and cellular transport. Methyl glyoxal, a highly reactive dicarbonyl ((AGE precursors)), is exhibited to induce sensitivity to vascular damage in endothelial cells. Outside cell (extracellular) protein AGEs include plasma and matrix proteins that disrupt cellular adhesion and activate the receptor for AGEs (RAGE). AGE–RAGE receptor interaction activates the transcription factor nuclear factor kappa B (NF-κB). This transcript nuclear factor NF-κB regulates a number of intracellular activities including inflammation and apoptosis. This events activate of neuronal RAGE induces oxidative stress through NADPH oxidase activity. Diabetic RAGE knockout mice (transgenic animals) showed significant development in DPN and diminished expression of NF-κB and PKC compared to wild type diabetic model. The biochemical damage induced by AGEs results in impaired nerve blood flow and diminished neurotrophic support⁷.

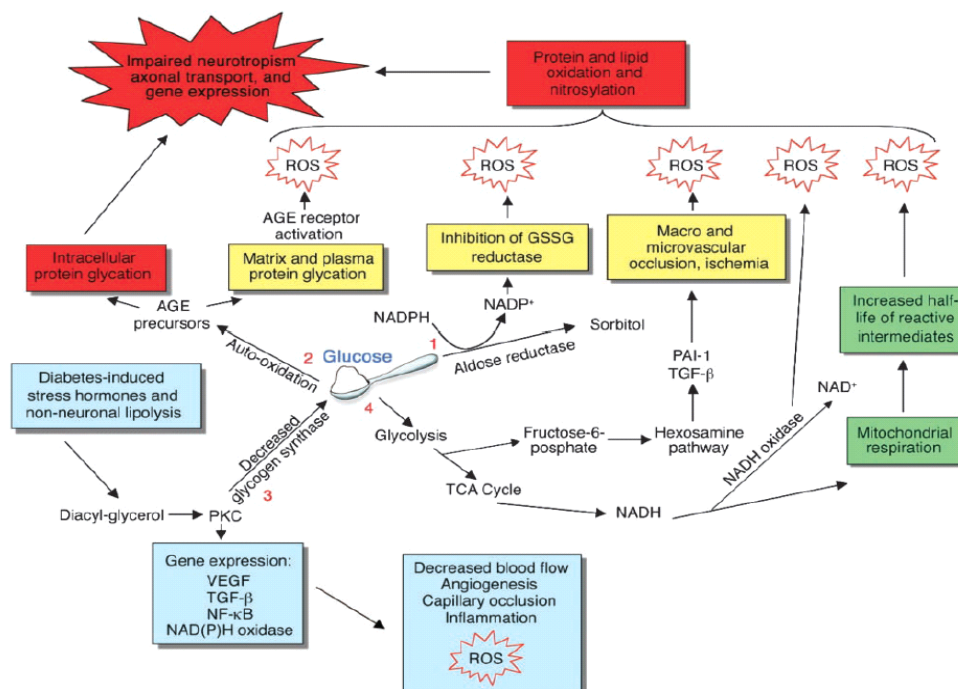


Figure 1 - Pathophysiology of diabetic neuropathy

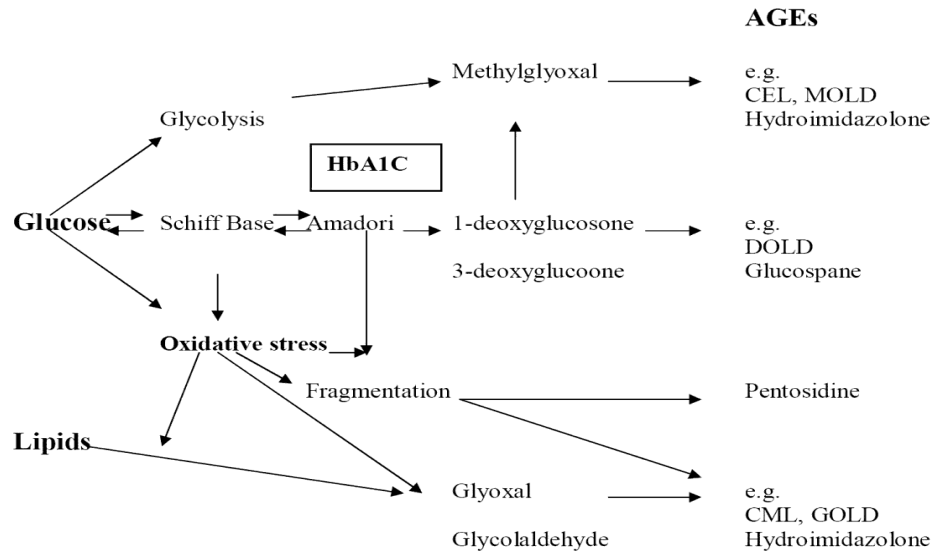


Fig.2. Advanced glycation end products.

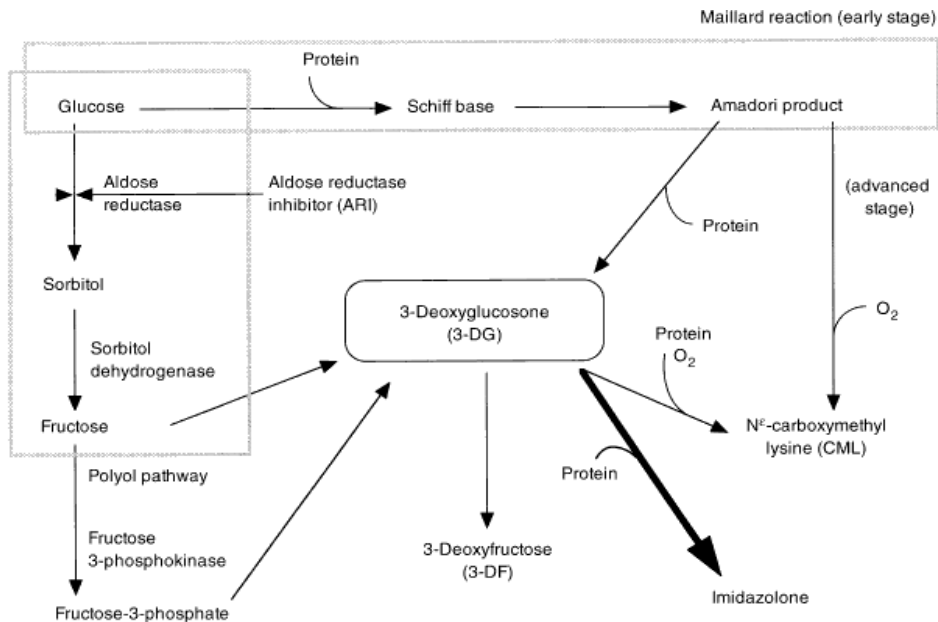


Fig.3. Polyol pathway is one of the major metabolic contenders for the etiology of diabetic neuropathy

Oxidative stress

- The AGE, polyol, hexosamine, PKC, and PARP pathways all contribute to neuronal damage. It illustrates that the AGE and polyol pathways directly alter the redox capacity of the cell either through direct formation of ROS or by depletion of essential components of glutathione recycling. Hexosamine, PKC, and PARP pathways showed damage through expression of inflammation proteins.
- Axons are susceptible to hyperglycemic damage both due to their direct access to nerve blood supply and their large population of mitochondria

(Mt). Mounting evidence suggests that the hyperglycemic environment coupled with a compromised blood supply overloads the metabolic capacity of the Mt, producing oxidative stress. This oxidative stress leads to Mt damage followed by axonal degeneration and death. Mitochondrial damage occurs due to excess formation of ROS and reactive nitrogen species (RNS).

- ROS, such as superoxide and hydrogen peroxide, are produced under normal conditions through the Mt electron transport chain and are normally removed by cellular detoxification

agents such as superoxide dismutase, catalase, and glutathione. Hyperglycemia leads to increased Mt activity, raising ROS production in the Mt. Peroxynitrite, the primary RNS, is formed by the reaction of superoxide and nitric oxide (NO). RNS induces a number of cytotoxic effects including protein nitrosylation and activation of PARP.

Polyol pathway

- An increase in the activity of the polyol pathway is one of the major metabolic contenders for the etiology of diabetic neuropathy, which include the formation of advanced glycation end product, the alteration of essential fatty acid metabolism and the abnormalities of neurotrophic factors⁸.
- In polyol pathway, glucose is converted into sorbitol by Aldose Reductase (AR) and sorbitol dehydrogenase oxidises, sorbitol to fructose. Nicotinamide Adenosine Dihydrogen Phosphate (NADPH) is consumed by aldose reductase-mediated reduction of glucose to sorbitol (and NADPH is required for regeneration of antioxidant enzyme glutathione (GSH) thus deficient amount of glutathione contributes to oxidative stress (Moreover, conversion of glucose to sorbitol induced osmotic stress and to restore osmotic equilibrium to cell, other osmolytes, particularly taurine and myo-inositol, are effluxes from cells).
- Depletion of taurine and myo-inositol in nerve cells are implicated in PDN and supplementation of taurine and myo-inositol prevented neuropathic deficits. On the other hand, excess formation of fructose in polyol pathway promotes advanced glycation end product as well as depletes NADPH, further augmenting Reactive Oxygen Species (ROS) mediated. Numerous agents have been evaluated over the past 20 years but most have not been licensed because of serious **adverse events** (tolrestat, zenarestat) or a lack of **efficacy** (ponalrestat, zenarestat)⁷⁻⁸.

Hexosamine pathway

- Shunting of excess intracellular glucose into the hexosamine pathway might also cause several manifestations of diabetic complications. In this pathway, fructose-6-phosphate is diverted from glycolysis to provide substrates for reactions that require UDP-N-acetylglucosamine, such as proteoglycan synthesis and the formation of O-linked glycoproteins. Inhibition of the rate-limiting enzyme in the conversion of glucose to glucosamine — glutamine: fructose-6-phosphateamidotransferase (GFAT) — blocks hyperglycaemia-induced increases in the transcription of TGF- α , TGF- β 1 and PAI-1.

Growth factors

- Increasing evidence exists that there is a deficiency of growth factors such as nerve growth factor (NGF) in diabetes, as well as the dependent neuro peptides substance P and calcitonin gene-related peptide, and that this contributes to the clinical perturbations in small fiber function⁹.

Schwann Cell

- Nerve injury resulting from diabetes mellitus is characterized by marked changes in Schwann cells and the axons sheath. The most obvious structural manifestation of diabetic neuropathy is a loss of both large and small nerve fibers, which is a prominent feature of chronic human and long-duration experimental diabetic neuropathy.
- While fiber loss is most prominent distally, particularly in the dorsal roots. Characteristic degenerative changes of unmyelinated fibers include shrinkage of axons, accumulation of enlarged vesicular elements and deterioration of tubular and filamentous elements of the cytoskeleton.
- Both primary segmental demyelination and demyelination secondary to axonal degeneration were documented in the same nerve biopsy. Demyelination has also been observed in long-term experimental diabetes. Myelin defects, such as splitting and ballooning of the sheath, that appear to precede myelination have been documented in the dorsal and ventral roots in rodent models of experimental diabetes and also in nerves of cats with spontaneously occurring diabetes¹⁰.
- Paranodal swelling is thought to precede paranodal demyelination and to be associated with axo-glial dysjunction, the loss of the junctional contacts between paranodal Schwann cell loops and the axolemma on either side of the node of Ranvier. However, the existence of paranodal swelling and axo-glial dysjunction is contentious because, although repeatedly documented by some in experimental and human diabetic neuropathy others (have not detected these abnormalities¹⁰⁻¹¹).

A common element linking hyperglycemia induced damage

- Although specific inhibitors of aldose reductase activity, AGE formation, PKC activation and the hexosamine pathway each ameliorate various diabetes induced abnormalities in cell culture and animal models, there has been no apparent common element linking the four mechanisms of hyper glycaemia-induced damage. This mechanism concerned that a single hyper glycaemia induced process excessive production of superoxide by the mitochondrial electron-

transport chain. Several studies have proved that diabetes and hyperglycaemia increase oxidative stress but neither the underlying mechanism nor the consequences for other pathways of hyperglycaemic damage was proved⁷.

Diagnosis¹²⁻¹⁶

- Although challenging, DPN can be diagnosed, classified, and managed on the basis of the patient’s history and results of a thorough physical examination.
- Systematic electrophysiological testing is not necessary in diabetic patients with typical peripheral neuropathy. Changes in conduction velocity can be detected in asymptomatic patients, but their presence is not predictive of the onset of symptomatic neuropathy.
- In addition, DPNP does not correlate with nerve conduction velocity, and the diagnosis of DPNP does not require evidence of a large-fiber abnormality. If motor signs are noted on the clinical examination (weakness during muscle testing), referral to a neurologist for electro diagnostic testing is certainly warranted.
- Although the initial recognition of neuropathy may be clinically confirmed by the relative loss of sharp vs light touch discrimination over the distal lower extremities during the physical examination, the use of the 10-g Semmes-Weinstein monofilament permits more careful assessment for pressure perception. The nylon filament is gently pressed against the skin until it just buckles, generating the equivalent of 10 g of force.
- The sensitivity for predicting feet at risk of ulceration ranges from 100% cross sectional studies using the Semmes-Weinstein monofilament.¹⁵ Pressure perception assessments are usually taken at the hallux and metatarsal heads I, III, and V, although there is uncertainty regarding the necessity for multiple measurements.
- No consensus exists on whether 1, 2, or more abnormal measurements constitute a diagnosis of neuropathy.
- The absence of symptoms should not be equated with the absence of neuropathy; up to 50% of patients with DPN may be asymptomatic but are still at risk of foot ulcers. Therefore, monitoring for neuropathy should be a regular part of the clinical care of patients with DM.⁴⁷ Such monitoring should include assessment with a 128-Hz tuning fork to check for vibration sensation, a broken tongue depressor to check for sharp sensation, test tubes that contain warm or cold water to evaluate temperature sensation, the 10 monofilament to check pressure sensation, and cotton wool to check light touch sensation

and the presence of abnormal pain responses from non painful stimuli.

Differential Diagnosis

- Conditions that should be considered and ruled out as sources of neuropathy or pain include malignant disease, toxic causes (eg, alcohol), and infections, particularly human immunodeficiency virus. The patient’s history may suggest other diagnoses as well, such as post herpetic neuralgia.
- Other pain syndromes that may mimic DPNP include tarsal tunnel syndrome, osteoarthritis, idiopathic distal small fiber neuropathy, and erythromelalgia¹¹.

Management

Preventive treatment

- Prevention of diabetic neuropathy and its complications remains the best strategy. Optimum glycaemic control diminishes the risk of developing a disabling peripheral neuropathy, but carries an increased risk of hypoglycemia.
- Patients with diabetes also need advice about foot care and footwear, and about protection of hyposensitive areas and pressure points, to prevent the occurrence of painless ulcers and decrease the risk of bone infection. Prevention and treatment of the 'diabetic foot' are best administered in specialized foot clinics Pancreas transplantation, which might stabilize then Neuropathy, is not yet routinely performed.

Pharmacological therapy

However there is no particular or specific drug available for the diabetic neuropathic condition till date.

Table 2: The ABCs of diabetic neuropathy management

A	Antidepressants, anticonvulsants, topical anesthetics are the first-line treatments
B	Blood sugar management
C	Cardiovascular risk factor reduction
D	Diet and exercise for weight management
E	Emerging therapies for diabetes and neuralgia
F	Foot care to reduce infections and amputations

- The traditional analgesic ladder described by the World Health Organization (WHO) is of limited usefulness in the treatment of neuropathic pain. This is because simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are often less effective in neuropathic pain (although, as mentioned above, they may have a role in the treatment of inflammatory ‘flare-ups’)
- In focal neuropathy, including cranial nerve palsy, PDN and truncal neuropathy, the disease course is self-limited, with spontaneous

recovery within a few months in most cases. Control of pain can be difficult both in LDDP and in focal neuropathies. Carbamazepine, phenytoin, clonazepam, or paracetamol in combination with codeine phosphate can be useful.

- Tricyclic antidepressants, such as imipramine or amitriptyline, are often effective; the usual dose varies from 30-150 mg per day. Tricyclic antidepressants might aggravate postural hypotension. The recently introduced drugs duloxetine and pregabalin are also useful.

Table 3-Drugs which are commonly prescribe in neuropathic pain

Category	Drugs	Mechanism of action	Adverse effect
Antiepileptics	Lamotrigine Gabapentin Zonisamide	Blockade of sodium and calcium channel Free radical scavenging property	Blurred vision, ataxia, pruritis, somnolence, peripheral edema, anorexia, agitation & irritability
Antidepressant	Trazodon, Nefazodone, Vaniafaxine	Blockade of serotonin (5-HT) Rupture pump, Down regulation of 5-HT _{1A} auto receptor, Down regulation of postsynaptic 5HT _{2A} receptors	Constipation, ataxia, dry mouth, insomnia, seizures, dizziness, hot flashes, Urinary retention, weight gain, arrhythmia.
Opioids	Morphine, Hydromorphone, Fentanyl, levophanol, Methadone	NMDA receptor antagonist and inhibits the reuptake of NE and 5-HT	Drowsiness, sedation, constipation, dizziness, nausea/vomiting

Non pharmacological devices can be used if a successful therapy could be identified Since there will be no interaction with the devices.

Table. 4- Herbal drug used in the management Diabetic neuropathy

Drug	Mechanism of action
Ginkgo	Blocks induction of inducible nitric oxide synthase (iNOS) and release of nitric oxide (NO)
Panax ginseng	Inhibit the voltage gated Na ⁺ channel
Ocimum sanctum	Decrease the oxidation stress and calcium level
Acorus calamus	Decrease the oxidative stress and calcium level
Emblca officinalis	Inhibit lipid production and release antioxidant enzyme
Combination with psidium guajava, Momoridica charantica and Coccinia indica	Inhibit protein kinase C and act as antioxidant

Physical Therapy

Physical therapy can be beneficial and alternative treatment option for with diabetes patients. This may decrease dependency on pain relieving drug treatments. Some physiotherapy advance techniques can be help for alleviate symptoms brought on from diabetic neuropathy such as deep pain in the feet and legs, tingling or burning sensation in extremities, muscle cramps, muscle weakness and diabetic foot.

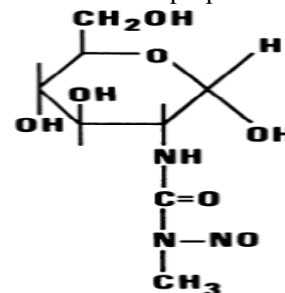
Specific therapy

Antioxidants: Evidence exists to suggest that during hyperglycemia glucose metabolism leads to generation of free radicals which affects endothelial function and vascular activity. In a animal study alpha lipid acid has been showed promising results. Vitamin C is hypothesized to reduce cellular levels of reactive oxygen

species and increase the level of nitrogen oxide similar to that of alpha lipid acid. Vitamin C decreases plasma free radicals and increases levels of reduced glutathione and nitrogen oxide mediated vasodilatation.

Mechanism of streptozotocin causing diabetic neuropathy¹⁷⁻¹⁹

- Streptozotocin is approved by the U.S. Food and Drug Administration (FDA) for treating metastatic cancer of the pancreatic islet cells. Since it carries a substantial risk of toxicity and rarely cures the cancer, its use is generally limited to patients whose cancer cannot be removed by surgery.
- The molecular weight of STZ is 265g/mol and the structure is composed of nitrosourea moiety with a methyl group attached at one end and a glucose molecule at the other end .Streptozotocin (STZ) (2-deoxy-2-([methyl (nitroso)amino]carbonyl)amino)-β-D-glucopyranose) is a naturally occurring compound, produced by the bacterium Streptomyces achromogenes, that exhibits broad spectrum antibacterial properties



Structure of streptozotocin

Beta cell selectivity of streptozotocin

- The toxic action of streptozotocin and chemically related alkylating compounds

requires their uptake into the cells. Nitrosoureas are usually lipophilic and tissue uptake through the plasma membrane is rapid; however, as a

result of the hexose substitution, streptozotocin is less lipophilic. Streptozotocin is selectively accumulated in pancreatic beta cells via the low-affinity GLUT2 glucose transporter in the plasma membrane.

- Thus, insulin-producing cells that do not express this glucose transporter are resistant to streptozotocin. This diminishes cellular NAD^+ , and subsequently ATP, stores.
- The depletion of the cellular energy stores ultimately results in beta cell necrosis. Although streptozotocin also methylates proteins, DNA methylation is ultimately responsible for beta cell death, but it is likely that protein methylation contributes to the functional defects of the Beta cells after exposure to streptozotocin. Inhibitors of poly ADP-ribosylation suppress the process of DNA methylation.

Mechanism of beta cell death²⁰⁻²²

- Mode of Beta cell death result Chemical diabetes cells than MNU and methyl methanesulphonate has been taken as support for the notion that in insulin producing cells, as in other cell types, the mechanism of toxic action is due to alkylation, with methylation of DNAbases being more toxic than ethylation.
- Nitric oxide (NO) donor. Both streptozotocin and MNU contain a nitroso group and can liberate NO. In fact; streptozotocin has been shown to increase the activity of guanylyl cyclase and the formation of cGMP, which are characteristic effects of NO.
- In addition to STZ-induced cytotoxicity through DNA alkylation, reactive oxygen species, including superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (HO^\cdot), and nitric oxide (NO^\cdot), play a critical role in the mechanism of DNA damage and cytotoxicity of STZ. Streptozotocin is cytotoxic to pancreatic β -cells and effects can be seen within one hour after administration.
- Types of DNA lesions formed by STZ include mono adducts, single and double stranded breaks, and alkali-labile sites. Severe DNA damage by STZ results in cell death by apoptosis or necrosis. Diabetic individuals and experimental animals exhibit high oxidative stress due to persistent and chronic hyperglycemia, thereby depleting the activity of oxidative defense system, and thus promoting deNovo free radical generation. Oxidative stress has recently been shown to be responsible, at least in part, for pancreatic β -cell dysfunction caused by glucose toxicity.
- Under hyperglycemia production of various reducing sugars, such as glucose-6-phosphate and fructose, increases through glycolysis and polyol pathways. During this process, reactive

oxygen species (ROS) are produced and cause tissue damage.

- So, STZ is widely employed to induce experimental diabetes in animals. Administration of a single dose of STZ (40 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg and 65 mg/kg i.p. or i.v.) in rats results in hyperglycaemia within 72 hours. STZ treatment causes significant increases in lipid peroxidation (MDA) and nitric oxide (NO) generation, and decreases antioxidant enzymes such as catalase, Glutathione peroxidase, and superoxide dismutase activities as well as pancreatic insulin contents when compared with the control animals in experiments. Decreases in antioxidant activities, and simultaneous increases in MDA and NO Activities, reflect susceptibility of pancreas to STZ's significant oxidative stress.

Animal Model of Diabetic Neuropathy²³⁻²⁴

In Vivo Animal Models

In vivo animal models for diabetic neuropathy studies can be subdivided into two groups: induced models and genetic models that mimic either type 1 (insulin dependent) or type 2 (insulin resistant) diabetes. In addition, other tissue-specific transgenic models can be rendered diabetic to study a specific pathway that might be involved in the pathogenesis.

- Diabetic neuropathy in type 1 diabetic models
- Diabetic neuropathy in type 2 diabetic models (Zucker diabetic fatty (ZDF) rat
- The NOD mouse
- Otsuka Long-Evans Tokushima fatty (OLETF) rat
- Goto Kakizaki (GK) rat
- ob/ob mouse
- db/db mouse
- Transgenic mice expressing fluorescent sensory/motor neurons (thy-YFP)
- Transgenic and knockout models in other pathways regulating insulin action
- Transgenic mice lacking peripheral axonal neuro filaments (Nf-H-lacZ).

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