REVIEW ARTICLE

Painful Diabetic Neuropathy: Mechanisms to Management

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ABSTRACT

Diabetes is one of the major public health concerns the world is facing. Modern lifestyle, obesity and stress are major contributing factors to the increased incidence of diabetes all over the world. The morbidity and mortality of Diabetes is related to the development of many complications which include neuropathy, nephropathy and retinopathy, the most prominent being diabetic neuropathy. The reported prevalence of neuropathy in diabetic patients ranges from 5% to 80%.The combination of peripheral vascular disease and neuropathy leads to the most feared complication i.e. diabetic foot, which is the only leading cause of limb amputation. Diabetic neuropathy is defined as the peripheral, somatic, or autonomic nerve damage attributed to Diabetes Mellitus. Diabetes affects the peripheral nerve at various sites and can lead to mononeuropathy, polyneuropathy, plexopathy, and radiculopathy. Acute or chronic pain occurs in diabetic neuropathic patients seriously affecting the quality of their life. Overall approximately 10% of patients experience persistent pain. The pathogenesis of pain is mainly attributed to alteration in polyol pathway, increased oxidative stress, impaired fatty acid metabolism and release of inflammatory factors. Most of the treatment strategies aim at symptomatic treatment like achieving lesser blood glucose levels and reduction of pain and inflammation.Nowadays a lot of herbal agents have proven to be effective in reducing neuropathic pain and reducing blood glucose levels.These agents include Gamma linolenic acid, Capsaicin, *Withaniasomnifera* (ashwagandha),*Ginkgo biloba* and several other plant species. Also techniques like acupressure and reflexology provide relief from severe neuropathic pain.

Key words: Diabetic Neuropathy, Pain pathogenesis, Gamma linolenic acid

INTRODUCTION

Diabetes is one of the major public health disorders in the modern world. Changes in lifestyle, lack of exercise,improper diet,modernization and stress are the major contributing factors to the multiplied incidence of chronic hyperglycemia all over the world.According to WHO if the current trends prevail, the no. of people affected by Diabetes worldwide is expected to become 438 million by 2030.[1]Diabetes related mortality occurs due to certain microvascular and macrovascular complications.[2]Macrovascular complications are the major cause of death which include stroke,ischemia and other vascular diseases. On the other hand microvascular complications include retinopathy,nephropathy and neuropathy, the most common being Diabetic neuropathy which is prevalent upto 50%. [3]

Neuropathy can be defined as the functional and structural impairment of the nervous system both peripheral and autonomic. Neurological complications can crop up equally in Type I and Type II Diabetes mellitus and in other forms of diabetes. Chronic painful diabetic neuropathy may not contribute to the increased mortality of people with diabetes but it can impair the quality of life of patients to a great extent.An estimated 15% of all the patients with diabetes will develop foot ulcers and neuropathy is the main cause of non-traumatic foot amputation. [4]

Neuropathy can occur as mononeuropathy, polyneuropathy, plexopathy, and radiculopathy. Clinically, it is important to distinguish between symmetric and asymmetric neuropathies because they differ in pathologic mechanisms and require different diagnostic and treatment strategies.

Diabetic polyneuropathy (DPN), a symmetric length-dependent sensorimotor neuropathy is the most common type.Sensory symptoms predominate early in DPN because sensory fibers are longer and more susceptible to metabolic and microvascular damage. Sensory ataxia and motor weakness develops later. Some people experience severe neuropathic pain without much numbness, suggesting involvement of small sensory fibers, whereas others are unaware of

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neuropathy until significant weakness and posture disturbance develops,implicating larger sensory-motor fiber dysfunction. In type 1 and type 2 diabetes mellitus, diabetic polyneuropathy usually develops after many years of hyperglycemia. [3, 5]

Diabetic lumbosacral radiculoplexusneuropathy (DLSRPN) is a type of asymmetric diabetic neuropathy which has a no. of synonyms likefemoral neuropathy, proximal neuropathy, diabetic amyotrophy and diabetic neuropathic cachexia. DLSRPN affects mostly men with type II diabetes and is believed to be associated with angiopathy. Patients experience hip and thigh pain that can last for days and this pain is followed by weakness of hip flexors and adductors,chiefly knee extensors. Recovery in such case is slow and can take 6 to 24 months. It primarily affects the elderly and usually has an abrupt onset. It often co-exists with distal symmetric polyneuropathy. [3], [6]

Table1: Classification of Diabetic Neuropathies [7]

1. Distal symmetrical sensory polyneuropathy
• Small fiber type
• Large fiber type
• Mixed type
2. Autonomic neuropathy
3. Focal and multifocal diabetic neuropathy
• Cranial neuropathy
• Thoracoabdominal neuropathy
• Proximal neuropathy
4. Non diabetic neuropathy
• Chronic inflammatory demyelinating neuropathy
• Entrapment neuropathies
• Neuropathy due to renal failure

Neuropathic pain

Acute or chronic pain occurs in diabetic neuropathic patients seriously affecting the quality of their life. Overall approximately 10% of patients experience persistent pain. Neuropathic pain is defined as the "Pain initiated or caused by the dysfunction of the central and the peripheral nervous system."[8]

The prevalence of neuropathic pain is about 30% high in patients with type 1diabetes mellitus and more than 30% higher in patients with type 2 diabetes mellitus. [7]

The pain can be stimulus-independent or stimulus-evoked.In stimulus independent type of pain patients complain of spontaneous pain with intermittent burning or electric shock like sensations.

Pain related hypersensitivity is evoked in response to stimuli in stimulus dependent type. [8]

Thermal pain thresholds can be determined in animals using behavioral studies that measure the response time to heat by licking or removal of limb from hot plate.

Pain pathogenesis

Pathogenesis of pain associated with diabetic neuropathy is not well understood yet. But it is proposed that the pain mainly involves dysfunction of the Central and Peripheral nervous system with a cascade of biochemical reactions.

Tissue injury activates the peripheral nervous system and releases chemical inflammatory factors like Interleukins. Nerve hypersensitivity occurs in chronic pain and involves mediators of inflammation like PG's and leukotrienes. [9]This in turn causes activation of the peripheral and central nervous system and the pain signals are carried to the brain (Fig. 1).

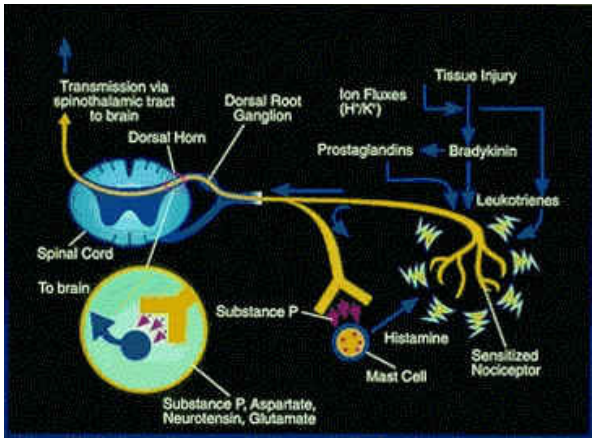

Fig.1: Basic pathway of pain showing involvement of both Central and Peripheral Nervous system

Nerve fibres are of two types:

1) C fibres which are small and unmyelinated. They are responsible for pain transmission

2) Aβ fibres: These are large, myelinated and are responsible for light touch and pressure sensations.

When electrical impulses from C fibres are greater than those transmitted via Aβ fibres, the "pain gate" opens and pain is transmitted. Aβfibres synthesize substance P, a neurotransmitter of pain. This gate is

located in the dorsal horn of the spinal cord and it is closed by encephalin releasing neurons,thereby inhibiting pain impulse. [9]In diabetic neuropathy, the small C fibres have large surface area and lack the myelinated sheath due to which they are more susceptible to damage.[10]

Recently, studies have also shown relationship between peripheral blood flow and pain at times of hyperglycemia. The feet of neuropathic patients are always warm indicating high skin temperatures. Cooling the foot can reduce the neuropathic pain suggesting that the pain may be temperature sensitive.

The proposed pathogenesis in Diabetic neuropathy is**:** [3, 4, 9, 11, 12]

- Alteration in polyol pathway
- Increased AGE formation,
- Increased oxidative stress
- Advanced glycation end products
- Cytokine release
- Protein kinase C pathway
- Hexosamine pathway
- Impaired fatty acid metabolism

Hyperglycemia causes perturbation of each of these pathways directly or indirectly and leads to overproduction of superoxides that leads to tissue damage.Chronically elevated blood glucose leads to activation of the polyol pathwaythat leads to sorbitol and fructose accumulation, NADPH-redox imbalance, and increase in PKC activity. Increased protein kinase C activity leads to altered vascular permeability, contractility, basement membrane synthesis, and cellular proliferation, all of which may lead to the development of diabetic microvascular complications.[3, 13]

Hyperglycemia leads to nonenzymaticglycation of different intracellular and extracellular proteins that then cross-link to form advanced glycation end products (AGEs). [9, 14]The cross-linking of these proteins alters their structure and function. This may account for the slowing of axonal transport in Diabetic polyneuropathy. Hyperglycemia also leads to impaired phospholipid and fatty acid metabolism. This results in the altered metabolisms of prostaglandins that in turn leads to nerve dysfunction. Essential fatty acids are required for the structure and function of cell membrane and activity of membrane-bound proteins. The metabolism of essential fatty acids is impaired in diabetes, mainly the conversion of linoleic acid to arachidonic acid. [15, 16]

The confluence of these various metabolic and vascular disturbances leads to impaired neural function and loss of neurotrophic support and, over time, can mediate apoptosis of neurons and schwann cells(Fig.2).

Diagnosis

The diagnosis of diabetic neuropathy rests heavily on a careful history, for which a number of questionnaires have been developed by Young et al, [17]Dyck, [18]Vinik and Mitchell[19], and others. [20]The initial neurologic evaluation shouldbe directed toward the detection of the specific part of the nervous systemaffected by diabetes.

The 1988 San Antonio conference on DN and the 1992 conference of the American Academy of Neurologyrecommended that at least one parameter from each of the following five categories are measured to classify DN:[21]

- Symptom profiles
- Neurologic examination
- QST
- Nerve conduction study
- Autonomic function testing.

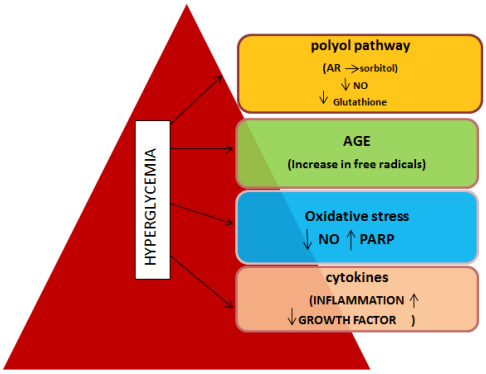

Fig 2: Factors responsible for peripheral diabetic neuropathy

Medical management of Diabetic Neuropathy

Despite the many advances in the treatment of type 1 and type 2 diabetes mellitus, there has been no breakthrough therapy for the treatment of diabetic neuropathy.The main strategy aims at symptomatic treatment.

The conventional treatment strategies include the following:

1. Reduction of blood glucose [4, 22, 23]

Studies have suggested that glycemic control has beneficial effect on progression of diabetic neuropathy. The prevalence rates for clinical or electrophysiological evidence of neuropathy were reduced by approximately 50% in those treated by intensive insulin treatment after 5 years.

Therefore, it is advised to achieve glycemic control as much as possible, particularly in those patients who have evidence of early neuropathy.

2. Reduction of pain and inflammation[3, 4, 21, 23]

Pain is transmitted via A delta and C fibers. These myelinated and unmyelinated nerves transmit painful stimuli to dorsal horn, spinothalamic tracts, thalamus, and sensory cortex. Thus medications aimed at substance P, N-methyl-D-aspartate (NMDA), glutamate, membrane stabilization, mitogenactivatedprotein kinases, and cytokines have been more clinically helpful.

Table 2: Examples of analgesics used in reducing neuropathic pain

Acetaminophen (650-1300 mg)	Anti-arrythmic agents • Lidocaine • Mexiletine
Diphenhydramine (25-50 mg)	Topical agents • Capsaicin • Lidocaine
Melatonin (1-3 mg)	
Zolpidem (5-10 mg)	
Benzodiazepines	
Amantadine	
Opioid analgesics • Oxycodone • Hydrocodone • Tramadol	
Antidepressants • Amitryptaline • Imipramine • Venlafaxine	

3. Antioxidant therapy

Various antioxidant agents have proven to be effective in cases of diabetic neuropathy. Four categories of agents are commonly used:[24]

- Lipophilic scavengers
- Hydrophilic scavengers
- Transition metal chelators
- Drugs withindirect antioxidant action.

Table 3: Commonly used antioxidants in neuropathic treatment[4, 21, 22, 23, 24]

Glutathion Alpha lipoic acid Taurine (amino acid)	Co-enzyme Q10 Nicotinamide Eugenol U83836E Oleuropein Melatonin Apocynin Rutin Dimethylthiourea Nitecapone N-acetylcysteine
Nutritional treatment • Vitamin B,C & E • Minerals (Zn, Se,etc.) Lipid lowering agents • Rosuvastatin	
Metal chelating agents • Deferoxamine • Trientine	

4. Aldose reductaseinhibitors[4, 21, 22, 23, 24]

Inhibition of aldose reductase is an effective strategy for the treatment of diabetic neuropathy because increased aldose reductase activity causes many negative effects. ARIs reduce the flux of glucose through the polyol pathway, inhibiting tissue accumulation of sorbitol and fructose and preventing reduction of redox potentials.

5. Regulation of fatty acid metabolism [24]

Alteration in fatty acid metabolism pathway has shown to be effective in neuropathy by using substances like linoleic acid, acetyl-l-carnitine and COX-2 inhibitors.

6. Gene therapy[25]

Recently, studies have shown that various neurotrophins such as recombinant human nerve growth factor, neurotrophin-3, and IGF canbe used effectively to reverse the symptoms of diabetic neuropathy.Gene transfer represents a novel means to express identified transgenes in targetedlocations in the nervous system.

7. Immunotherapy[25]

Both multifocal axonal neuropathies werefound to be responsive to immunotherapy consisting of

immunoglobulin and steroids. Intravenous immunoglobulin (IVIg) treatment was also found to be successful in the treatment of diabetic amyotrophy.

Alternative Treatment Strategies

Alternative treatment options include a lot of herbal agents which have proven to be effective in reducing neuropathic pain and reducing blood glucose levels. There is a mention of several herbal agents in our ayurvedic texts.Herbal drugs have been in use since ancient times and are considered to be safe and non-toxic.

Here's a list of herbal agents on which lot of research has been done and have shown promising results in treatment of neuropathy:

1. Gamma linolenic acid

Essential Fatty Acids (EFA) like Omega-3-fatty acids and Omega-6-fatty acids play a major role in generating anti-inflammatory compounds in the body. They are essential for proper neuronal, visual, reproductive and tissue function.[26,27]Gamma Linolenic Acid (GLA) is an Omega-6-Polyunsaturated fatty acid (PUFA) made in the body from the essential Omega-6-fatty acid: Linoleic acid(LA).[28]Secondary messengers derived from GLA such as prostaglandins or diacyl glycerol are required for normal neuronal function and nerve microcirculation which help in reduction of peripheral neuropathic pain. While young, healthy individuals can synthesize GLA from Linoleic Acid (LA), a large percent of population is unable to produce GLA due to dietary deficiency, alcohol, smoking and disease state. In Diabetes the first step in metabolism of LA to GLA is impaired. [29]

The fatty acid molecule is comprised of 18 carbon atoms with three double bonds. GLA is found naturally in the fatty acid fractions of some plant seed oils. Sources of GLA include evening primrose oil (7-14%), borage oil (20-27%), black currant seed oil(15-20%), and hemp seed oil. GLA is found in some fungal sourcesis also present naturally in the form of triglycerides.[30]

Linoleic acid is converted first to GLA then to arachidonic acid by an alternating sequence of delta-6-desaturation, chain elongation, and delta-5-desaturation, in which hydrogen atoms are selectively removed to create new double bonds. GLA formation is dependent on the activity of the delta-6-desaturase enzyme, which is hindered by numerous factors, including aging,nutrient deficiency,trans-fatty acids, hydrogenated oils,smoking, and excessive alcohol consumption.

Unopposed omega-6 supplementation may cause an increase in arachidonic acid and the undesirable pro-inflammatory 2-series prostaglandins.A combination of alpha-linolenic acid or eicosapentaenoic acid (EPA) and docosahexaenoic (DHA) with GLA may antagonize conversion to arachidonic acid.[31]

The result will be more favorable, with an increase in anti-inflammatory and antithrombotic effects. GLA has shown promising results in the treatment of diabetic complications in several human and animal studies.[32,33]In a double-blind, placebo-controlled, parallel trial of 111 patients with mild diabetic neuropathy,patients were given either 480 mg GLA or placebo daily.

After one year, GLA-treated patients showed favorable improvement in all parameters, including hot and cold threshold, sensation, tendon reflexes, and muscle strength compared to placebo.

In a smaller, double-blind, placebo-controlled trial of 22 patients with distal diabetic neuropathy,similar results were achieved at a dose of 360 mg GLA daily for six months.[32,34]

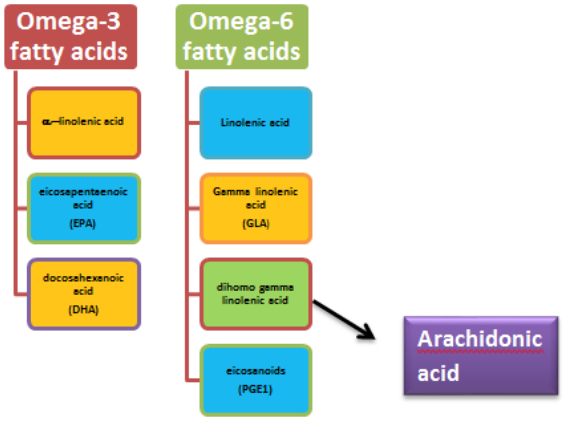

Fig.3. Metabolism of Essential Fatty Acids (EFA's)

2. *Withaniasomnifera* (ashwagandha)

Withaniasomnifera (L.)Dunal is a valued herb, upto 1.5m high shrub with ovate leaves and greenish-yellow flowers can be found in western India, and is locally known as Ashwagandha.

Fig. 4: Fresh leaves and roots of *Withaniasomnifera* (Ashwagandha)

It has several activities such as anti-inflammatory, muscle weakness and tension, adaptogenic and anti-diabetic properties. The biologically active chemical constituents are alkaloids (ashwagandhine, cuscohygrine, anahygrine, tropine etc.), steroidal compounds, including ergostane type steroidal lactones,withaferin A, withanolides ,withasomniferols A-C, withanone etc.[35]Studies have found that ashwagandha could attenuate nociceptive score in an experimental model of diabetes mellitus and this may be considered as a potential treatment for painfuldiabetic neuropathy.[36]A typical dose ashwagandha is 3-6 grams daily of the dried root.[37]

3. *Cynodondactylon* (durva)

Fig.5: Leaves of *Cynodondactylon* (durva) grass

Cynodondactylon (durva) is a sacred herb which is used since ancient times for treatment of various ailments.The major chemical constituents are ß-sitosterol, ß- carotene, vitexin, synergin and ferulic acid. [38]Literature shows that durva leaves have shown potent anti-inflammatory and antidiabetic properties.

4. Capsaicin

The fresh or dried fruits of different capsicum species are also used medicinally for modulation of pain. Capsaicin is the major capsaicinoid in chilli peppers, followed by dihydrocapsaicin.it exhibits various activities like anti-inflammatory, antimicrobial, antineoplastic, etc. Capsaicin is currently used in topical ointments to relieve the pain of peripheral neuropathy in the concentration of 0.025%-0.075%.[39]It is also widely used in the form of transdermal patches.[40]

Fig 6: Fruits of *Capsicum annum*

Capsaicin directly affects C-fibers. Initial application of capsaicin stimulates these fibers and depletes endogenous neurotransmitters associated with pain transmission, such as substance P, vasoactive intestinal peptide, cholecystokinin, and somatostatin. Application of capsaicin initially produces a burning sensation. Successiveapplication results in a dose-dependent degeneration and desensitization of afferent fibers, blocking further action potential conduction.[41]Thus it effectively modulates the conductionand transmission of pain.

5. *Ginkgo biloba* [42,43]

Extracts of Ginkgo leaves contain flavonoid glycosides (myricetin and quercetin) and terpenoids (ginkgolides, bilobalides) and have been used pharmaceutically. These extracts are shown to exhibit reversible, nonselective monoamine oxidase inhibition, as well as inhibition of reuptake at the serotonin, dopamine, and norepinephrine

transporters. *Ginkgo* supplements are usually taken in the range of 40–200 mg per day.

Ginkgo biloba increases metabolism, regulates neurotransmitters and boosts oxygen levels in the brain. This action may be beneficial in diabetic foot ulcers healing. In fact, *Ginkgo biloba* can be combined with any diabetes medication and it is used as a diabetes herbal remedy. *Ginkgo biloba* also acts as a powerful antioxidant and is effective in the management of diabetic neuropathy.Studies have shown that *Ginkgo biloba* extract attenuates mechanical and cold stimuli evoked pain in neuropathic rat model. It is also suggested that treatment with *Ginkgo biloba* extract may protect disturbed axonal transport and alteration of peripheral nerves.

6. Botanical oils[44]

Some studies have shown that applying botanical oils such as geranium oil can reduce the pain of postherpetic neuralgia. Case study results showed the use of peppermint oil, black pepper oil and rosemary oil effective in increasing circulation and decreasing pain from peripheral neuropathy.

Apart from these agents there are several methods which can provide relief from pain and inflammation

- **Acupressure**

A 2009 study published in the "Journal for Complementary and Alternative Medicine" tracked the effects of acupressure therapy for complications of type 2 diabetes, including neuropathy. After three years, nerve conduction improved in the patients receiving acupressure, suggesting that acupressure mitigates neuropathy complications in diabetics.[45]Acupressure may reduce the severity of neuropathy, though more research is necessary to fully understand the benefits of acupressure.

- **Reflexology**

Reflexology, or zone therapy, is an alternative medicine involving theact of applying pressure to the feet, hands, or ears. It is based on what reflexologists claim to be a system of zones and reflex areas that they say reflect an image of the body on the feet and hands, with the premise that such work effects a physical change to the body.[46]Reduction of pain is a significant result of reflexology work.

There is no consensus among reflexologists on how reflexology is supposed to work; a unifying theme is the idea that areas on the foot correspond to areas of the body, and that by manipulating these one can improve health through one's qi. Reflexologists divide the body into ten equal vertical zones, five on the right and five on the left.[47, 48]

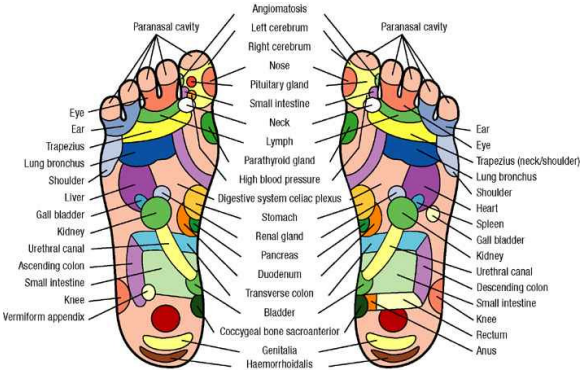

Fig.7: Reflexology chart demonstrating the areas of the feet that practitioners believe correspond with organs of the body

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