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DIABETIC NEUROPATHY: STILL A CHALLENGE IN PHARMACOLOGY.

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ABSTRACT: Diabetic neuropathy is one of the most serious microvascular complications of diabetes, which appears in about 50% of the patients suffering from diabetes. It is a nerve disorder caused by diabetes, characterized usually by numbness, pain or tingling in the feet or legs, which can lead to serious problems. Patients with diabetic neuropathy suffer from various types of pain. The underlying mechanisms include hyperglycaemia, insulin deficiency, oxidative stress, nitrosative stress, ischaemia, osmolyte accumulation, neurotropic factors deficiency, autoimmune-mediated nerve destruction, alterations in cellular signal pathways and gene expression of proteins. The factors leading to the development of peripheral neuropathy in diabetes are not understood completely, and multiple hypotheses have been advanced which include the polyol pathway, non-enzymatic glycation, oxidative stress, altered neurotropism and apoptosis. At present, there is no clinically proven efficacious drug specifically designated for the treatment of diabetic neuropathy; however, prevention or retardation of the progress of diabetic neuropathy is considered to depend on various antidiabetics, antioxidants, anti-depressants, anticonvulsants, NSAIDs, etc. The new advances in the development of neurotrophic factors and aldose reductase inhibitors herald the host of potentially combined treatments in the field of DN. The use of neurotrophic factors appears to be the most exciting approach because of the potential for the reversibility and regeneration of nerves.

INTRODUCTION:

Diabetes mellitus is a conglomeration of metabolic and chronic inflammatory derangements characterized by hyperglycemia; altered metabolism of carbohydrates, fats and proteins[1, 2].With the availability of new and improved drugs, the life expectancy in diabetes has increased considerably. But progress of the disease is often marred by complications including microvascular, macrovascular, and neuropathic disorders[3]. The macrovascular complications lead to pathological states such as stroke, large vessel ischaemia, etc and the microvascular complications include peripheral and autonomic neuropathies[4].

Diabetic neuropathy is one of the most serious microvascular complications of diabetes, which appears in about 50% of the patients suffering from diabetes from 25 years[5, 6, 7]. It is a nerve disorder caused by diabetes, characterized usually by numbness, pain or tingling in the feet or legs, which can lead to serious problems. Patients with diabetic neuropathy suffer from various types of pain such as hyperalgesia and allodynia[8]. This develops in the early stages of diabetes. The underlying molecular mechanisms for diabetic neuropathy are still debatable but hyperglycaemia has been proposed as the major precipitating factor in various studies[6]. Other mechanisms include insulin deficiency, oxidative stress, nitrosative stress, ischaemia, osmolyte accumulation, neurotropic factors deficiency, autoimmune-mediated nerve destruction, alterations in cellular signal pathways and gene expression of proteins[9]. The cellular mechanism for hyperalgesic and allodynic pain in diabetic neuropathy includes the remodeling of voltage- and ligand-gated Ca^{2+} channels that can increase excitability of the sensory neurons[10]. In the past few decades, several experimental drugs have undergone clinical trials but none has been proved efficacious. This may be due to the fact that diabetic neuropathy is a multifactorial disease and no specific drug has yet been evolved which can herald the progression of the complication by acting on the multiple aetiological targets. Moreover, the biomarkers which can indicate the progression of a disease when it can be reversed is still lacking in case of diabetic neuropathy.

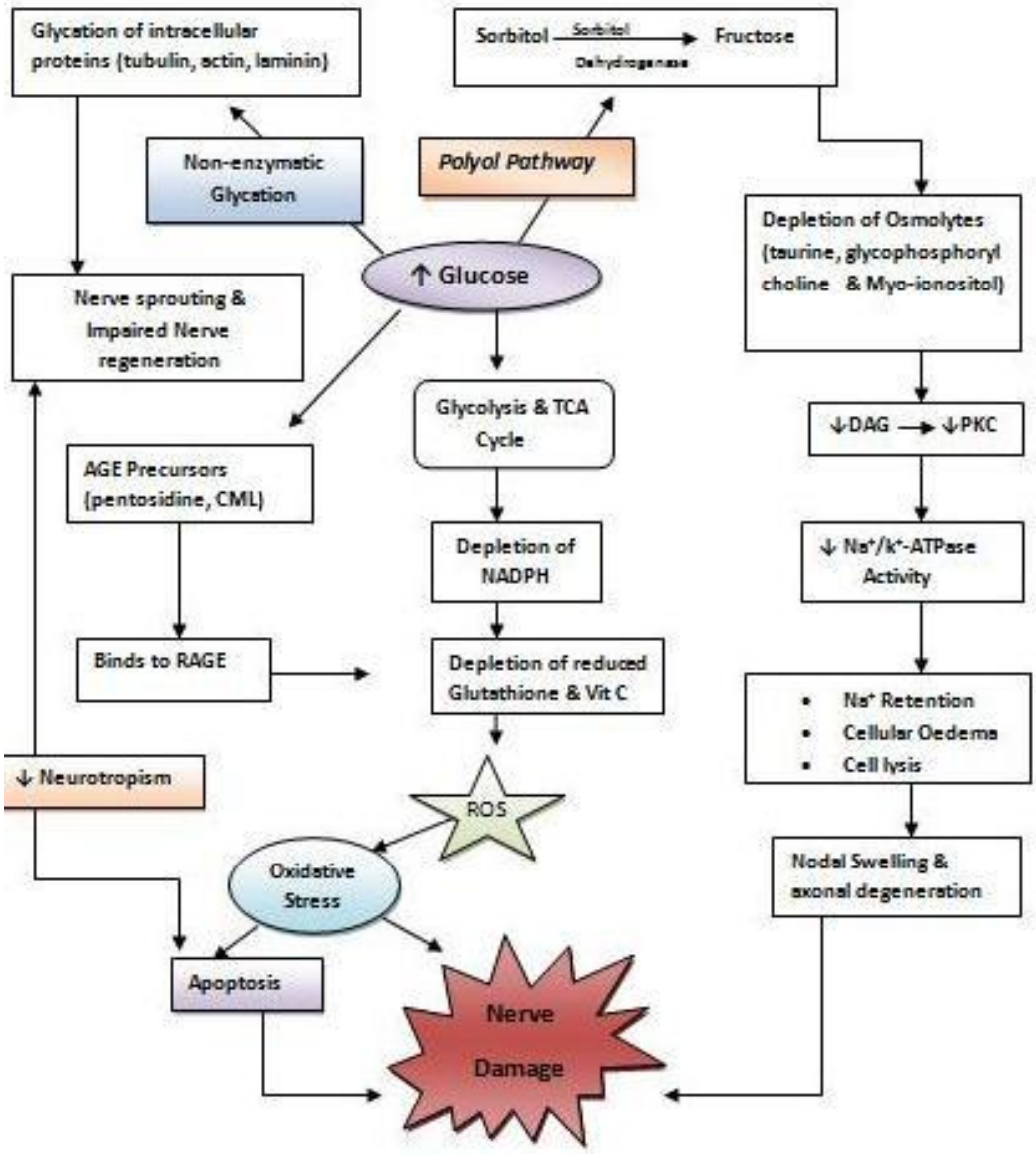
This review focus on (i) the various molecular and pathological basis for diabetic neuropathy (ii) the current therapeutic interventions in diabetic neuropathy (iii) the future prospects for the prevention and treatment of this dreaded complication of diabetes.

Epidemiology & risk factors of diabetic neuropathy: The incidence of diabetic patients affected with neuropathic complications is approximately 45-50%. Around 50% of people who have diabetes for more than 25 years will eventually develop diabetic neuropathy with an average prevalence of approximately 30% of the patients[5, 7, 11]. Pharmacoepidemiologic studies have suggested that 2.5% of the patients with diabetes develop diabetic foot ulcers every year and approximately 15% of the patients develop diabetic foot ulcers during their life time[12].

Potential risk factors for painful diabetic neuropathy include hypertension, hyperglycaemia, smoking, obesity, hyperlipidemia and atherosclerosis[13]. Thus, risk factors apart from hyperglycaemia are probably involved in the evolution of neuropathic complications in diabetic patients.

Pathophysiological basis of diabetic neuropathy: The exact pathophysiological mechanism of diabetic neuropathy is yet to be understood completely. The various hypotheses proposed include the polyol pathway, non-enzymatic glycation, oxidative Stress, altered neurotropism and apoptosis (fig. 1).

Fig. 1: Pathophysiological mechanisms for Diabetic Neuropathy



Polyol pathway in diabetic neuropathy: Polyhydroxy alcohol pathway involves the conversion of glucose to sorbitol by aldose reductase. This sorbitol is further converted to fructose by sorbitol dehydrogenase which leads to depletion of organic osmolytes like taurine, glycerophosphoryl choline and myo-inositol[14, 15, 16]. Myo-inositol depletion in peripheral nerves results in insufficiency of diacylglycerol necessary to maintain protein kinase C which ultimately resulting in inactivation of Na^+ /K^+ATPase activity, Na^+ retention, cellular oedema and cell lysis[17, 18]. These further results in nodal swelling, axonal degeneration and axonal atrophy[16, 19, 20]. Taurine is not only an osmolyte but also an antioxidant and a neurotrophic factor, depletion of which in peripheral nerves causes nerve degeneration[21].

Non-enzymatic glycation & oxidative stress in diabetic neuropathy: Oxidative stress and oxidative damage to tissues are common end points of chronic diseases, such as atherosclerosis, diabetes, and rheumatoid arthritis. Oxidative stress can occur in diabetes via metabolic changes induced by hyperglycaemia such as activation of aldose reductase and the polyol pathway [20], production of advanced glycation end products and reduced recycling of the antioxidant glutathione by glutathione peroxidase due to depletion of its cofactor NADPH[22]. The increase in glycoxidation and lipidperoxidation products in plasma and tissue suggests that oxidative stress is increased in diabetes. Increased chemical modification of proteins by carbohydrates and lipids in diabetes is the result of overload on metabolic pathways involved in detoxification of reactive carbonyl species[23]. This leads to a general increase in steady-state levels of reactive carbonyl compounds formed by both oxidative and nonoxidative reactions. N epsilon-(carboxymethyl) lysine, N epsilon-(carboxymethyl) hydroxylysine, and the cross-linked pentosidine are formed by sequential glycation and oxidation reactions between reducing sugars and proteins[24]. These glycoxidation products accumulate in tissue collagen with age and at an accelerated rate in diabetes[25].

Oxidative stress is promoted by auto-oxidation of glucose[26] and results in formation of glycoxidation products which generates reactive oxygen species, such as oxygen radicals such as superoxide (O_2^-), alkoxyl ($RO^\cdot$), peroxyl ($ROO^\cdot$), and hydroxyl radicals ($OH^\cdot$), and non-radical derivatives of oxygen, namely, hydrogen peroxide (H_2O_2) and ozone (O_3) that contribute to apoptosis[25]. Reduced sugars like glucose, fructose or galactose react with free amino groups of proteins, lipids or nucleic acids and form reversible Schiff bases and Amadori products that undergo chemical rearrangements to form AGEs, i.e.

Advanced Glycation End Products[24]. The AGE pentosidine is formed by glucose auto-oxidation[27], and Nε-(carboxymethyl) lysine (CML) is an AGE formed by both auto-oxidation and lipid peroxidation[28]. These AGEs binds to RAGE (receptor for AGE) and depletes intracellular reduced glutathione and Vit. C. Due to this, free radicals gets accumulated in nerves and other sites of the body and ultimately results in oxidative stress[29]. The extracellular matrix within a nerve trunk comprises of

the fibrous collagens I and III, basal laminal sheaths and small quantities of connective tissue proteins. All these are required to maintain the normal growth and functioning of nerve cells. If connections between the axon and its end organs are damaged by glycation, it leads to alteration in transport and growth factor changes[24].

The proteins, tubulin and actin that surround the nerve fibre which undergoes glycation and results in axonal atrophy while the protein laminin undergoes glycation resulting in nerve sprouting culminating in nerve fibre regeneration[30, 31, 32, 33]. Myelin components, myelin basic protein and proteolipid proteins are scavenged by macrophages via RAGE, receptor for advanced glycation end products by non-enzymatic glycation resulting in segmental demyelination[34, 35, 36].

Altered neurotropism in diabetic neuropathy: Altered neurotropism is associated with diabetic neuronal dysfunction[19, 20]. Nerve growth factor (NGF) which is selectively trophic to small-fiber sensory and sympathetic ganglion neurons is reduced due to oxidative stress and this leads to neuronal damage[37, 38, 39, 40]. NGF, normally blocks induction of ROS and thus stabilizes mitochondrial membrane potentia[41]. Administration of NGF administration has been documented to prevent the reduction of neuropeptides such as substance P and Calcitonin gene-related peptide in dorsal root ganglion (DRG) and sciatic nerve of diabetic rats[42, 43]. These neuropeptides mediate nociceptive and thermoreceptive sensations and are vasodilators. NGF binds to high- and low- affinity NGF receptors. The high affinity NGF receptor is a tyrosine kinase transmembrane protein called TrkA and the low affinity receptor is a 75-kD glycoprotein known as p75. Both the receptors are located on small, unmyelinated fibres of sensory neurons in ANS, CNS and PNS.

In diabetes, the expression of TrkA is reduced while p75 is increased, which results in decreased NGF in DRG neurons[44]. IGF-I and II promotes nerve regeneration, astrocyte functions and also co-ordinates with glial cell neurotropic factor changes[45]. IGFs have neurotrophic actions on sensory, sympathetic and motor neurons. Reduction in IGF-1 levels and increased IGF-1 binding protein levels contributes to impaired IGF-1 activity and causes peripheral nerve damage [46].

Neurotropins (NT) promote development, survival and differentiation of neurons[47]. Tropomyosin related kinases (A, B, C) modulate nerve functions45. Reduced expression of TrkA in the respective neurons and decreased synthesis of the neurotrophin-3 contribute to nerve dysfunction in DPN[39].

Role of apoptosis in diabetic neuropathy: Apoptosis is a cell suicide mechanism that enables tissues to control cell number. Certain cells have unique sensors, termed death receptors, on their surface. Death receptors detect the presence of extracellular death signals and, in response; they rapidly ignite the cell's intrinsic apoptosis machinery[48].These caspases thenactivate death receptors, mitochondrial dysfunction, leading to

endoplasmic reticulum (ER) abnormalities and alterations in calcium homeostasis and ultimately neuronal cell death[20].

Therapeutic interventions in diabetic neuropathy: The exact pathophysiology of diabetic neuropathy is not clearly understood. Treating neuropathy is a difficult task for the physician and most of the conventional pain medications primarily mask symptoms.The most effective strategy currently available to prevent diabetic neuropathy is the strict glycaemic control[11]. Various other therapeutic strategies used in the management of neuropathic pain include non-pharmacological measures like monochromatic near-infrared treatment[49, 50, 51], electrical nerve stimulators[50], acupuncture therapy[51] and application of Opsite which is a thin adhesive film[50].

Surgical Management include pancreatic transplantation in patients with diabetic and end-stage renal disease can stabilize neuropathy and in some instances improve motor, sensory and autonomic function for as long as 48 months after uremia plateaus[52]. The pharmacological management of neuropathic pain includes antidepressants, anticonvulsants, NSAIDS, etc. Although these drugs provide symptomatic relief to the patients but are associated with a number of side-effects (Table 1).

The pharmacological treatment has been reported using antidepressants[53]. Tricyclic antidepressants are primarily considered as first line agents in the management of neuropathic pain which include duloxetine[54], amitryptyline[55] and now venlafaxine [56]. Amitryptyline was the first drug that went under clinical trials for diabetic pain and is widely used but it carries a high incidence of anticholinergic side effects[55]. Venlafaxine has a combination of both norepinepherine and serotonin reuptake inhibiting effects without having anticholinergic side effects but it include other side effects like increased blood pressure, irritability, insomnia, constipation, vomiting [56]. Selective Serotonin Reuptake Inhibitors (SSRIs) such as fluoxetine have been reported to reduce pain in depressed patients[57]. These agents increase the concentration of serotonin at the receptor site.

Several anticonvulsants like carbamazapine[53], pregabalin[58, 59, 60], gabapentin[61, 62, 63], topiramate[64], valproate[65, 66, 67] and lamotrigine[68, 69] are usually considered as second-line therapy in neuropathies but are mostly associated with anticholinergic side effects**.** Sodium channels blocking activity on the nerve fibres by these agents is the proposed mechanism for treating neuropathic pain[53]. Pregabalin has also been approved by the FDA for diabetic neuropathy[58, 59, 60].It acts peripherally at the GABA receptor to block the perception of pain. Pregabalin is well tolerated in patients and causes less sedation than gabapentin. However, it is associated with other serious adverse effects, including rhabodmyolysis, acute renal failure, central nervous system effects, hyperthermia, and secondary acute-angle glaucoma[54]. Topiramate is another agent used in the treatment of diabetic neuropathy that is associated with weight loss[64].

Table 1: Current Therapeutic Drugs for Diabetic Neuropathy

Medication	Drugs	Adverse Events
Tricyclic antidepressants	Amitriptyline Nortriptyline Imipramine Desipramine	Dry mouth, sedation, dizziness, confusion, orthostatic hypotension, constipation, urinary retention, blurred vision, weight gain, arrhythmias
Other Antidepressants	Venlafaxine Duloxetine	Headache, nausea, sedation, constipation, sexual MAO inhibitors dysfunction, somnolence, hypertension, seizures, SIADH (syndrome of inappropriate antidiuretic hormone secretion),hyponatremia
Antiepileptics	Carbamazepine Lamotrigine Valproate Topiramate Gabapentin Pregabalin	Agitation, dry mouth, sedation, ataxia, nausea, vomiting, blurred vision, confusion, fatigue, nystagmus, aplastic anemia, rhinitis, toxic epidermal necrolysis, Peripheral edema, diplopia, rhabdomyolysis, acute renal failure, thrombocytopenia
Analgesics		
	NSAIDs like ibuprofen and Sulindac	Renal dysfunction
	Opioids	Tolerance & dependence
Other Agents		
	Capsaicin cream	Localized burning and itching, cough, sneezing
	Tramadol	Nausea, sedation, constipation, headache, dry mouth, urinary retention, confusion, tremor, seizures
	Mexilitine	Dyspepsia, dizziness, tremor, ataxia, insomnia, diarrhea, constipation, headache, nervousness, hepatotoxicity, arrhythmia, agranulocytosis, toxic epidermal necrolysis

Lamotrigine acts peripherally to treat neuropathic pain but is found to be less efficacious than carbamazepine and is associated with aplastic anemia and toxic epidermal necrosis[68, 69].

NSAIDS like ibuprofen and Sulindac offer some pain relief in diabetic neuropathy[70]. These agents are limited in use because they cause renal dysfunction[54]. Opioids and topical agents like capsaicin have been used for symptomatic relief of pain in diabetic neuropathy[54, 71].

Other agents like tramadol which acts through both monoaminergic and opioidergic mechanisms to block the pain[72] and mixeletine which is a class IB antiarrhythmic drug and acts peripherally as an ion channel blocker to prevent the perception of pain[73, 74, 75] are also being used in the neuropathic therapy[76].

Future Prospects for therapy: The study of neurotrophic factors and C-peptide growth factors on several animal models appears to be the most exciting approach because of the potential for the reversibility of nerve abnormalities associated with diabetes. These neurotrophic factors and C-peptide growth factors are still under clinical trials and may prove efficacious for the treatment of diabetic neuropathy (Table 2).

Nerve Growth Factor: This protein promotes survival of sympathetic and small-fiber neural crest–derived elements in the peripheral nervous system[77]. In animals with diabetes, both production and transport of NGF are impaired. Antioxidants have been used to enhance the effects of NGF. This includes combinations of growth factors like Brain Derived Neurotrophic factor (BDNF) so that large fibre neuropathy can also be targeted. NGF has indicated beneficial effects in treating dysfunction of small sensory fibres[78].

Aldose Reductase Inhibitors: Drugs like alrestatin have been shown to improve sensory impairment by inhibiting the aldose reductase in polyol pathway[79]. Sorbinil, another aldose reductase inhibitor has been shown to improve both motor and sensory conduction velocities compared to placebo[80]. Tolrestat, an aldose reductase inhibitor improves the autonomic function tests as well as vibration perception in diabetic patients[81]. A large number of aldose reductase inhibitors are still under trials and may come out as a novel target approach for diabetic neuropathy.

Insulin or C-peptide Growth Factors: Insulin and C-peptide growth factors have been shown to improve nerve regeneration[20]. Administration of C-peptide improves autonomic nerve function. C-peptide stimulates nerve Na^+ K^+ ATPase activity, resulting in improved electrolyte and enzyme state. This improves endoneural blood flow, stimulates endothelial nitric oxide synthase with release of nitric oxide[19]. Proinsulin C-peptide is known to enhance the effects of insulin[82].

Other Agents: Alpha lipoic acid is a strong anti-oxidant, acts as a coenzyme of hydrogen transfer in oxidative stress[20]. Acetyl- L- carnitine and gamma-linolenic acid have been useful in endothelial dysfunction[83, 84].

Table 2: Future Prospects for Diabetic Neuropathy

Novel Therapeutic Implications	Examples
Neurotrophins(NT)	Nerve growth factor Brain- derived neurotrophic factor NT - 3 NT-4/5 NT - 6
Insulin - like growth factors (IGF)	Insulin IGF - I IGF - II
Epidermal growth factor (EGF)	EGF Transforming growth factor (TGF) - α
Haematopoietic cytokines	Ciliary neurotrophic factor Granulocyte colony- stimulating factor LIF Oncogene M Interleukin (IL) - 1 IL - 3 IL - 6 IL - 7 IL - 9 IL - 11
Heparin – binding Factors	Acdic fibroblast growth factor (FGF) Basic FGF int - 2 onc hst/k-fgf onc Keratinocyte growth factor FGF - 4 FGF - 5 FGF - 6
TGF – β Factors	TGF - β1 TGF - β2 TGF - β3 Glial - derived neurotrophic factor Persephin Neurturin Activin A BMP_S
Tyrosine kinase - associated cytokines	Platelet - derived growth factor Colony - stimulating factor - 1 Stem cell factor
Antioxidants	Natural herbs Alpha-lipoic acid
Miscellaneous	Acetyl-L-carnitine gamma-linolenic acid Myoionositol supplements Gangliosides Human Intravenous Immunoglobin (IVg) Laminin

Aminoguanidine which is an inhibitor of the formation of AGEs has been reported to improve the nerve conduction velocity[85, 86]. Gangliosides have been shown to improve nerve cell membranes[87, 88, 89, 90]. Myoionositol supplements in normal diets have been reported to improve neuropathy by Na^+ K^+ ATPase activity which improves the nerve growth[91]. Human Intravenous Immunoglobin (IVg) treatment potentially ameliorates neurologic disturbances in diabetic patients[92]. Recombinant nerve growth factor administration has been demonstrated to restore the neuropeptide levels towards normal and prevent the manifestations of sensory neuropathy in animals[93].

Laminin has been shown to promote neurite extension by cultured neurons[94]. Laminin is a large, heteromeric, cruciform glycoprotein composed of a large A chain and two smaller B chains, B1 and B2[95]. It has been reported that recombinant human erythropoietin (rhEPO) has efficacy in preventing and reversing nerve dysfunction in streptozotocin-induced diabetes in rats[96].

CONCLUSION:

Diabetic neuropathy accounts for the most serious microvascular complications in the diabetic patients. Although there are many useful therapeutical drugs to treat painful diabetic neuropathy, a growing body of evidence suggests that these drugs are effective only in early stages of diabetic neuropathy and are incapable to control the late stage symptoms of diabetic neuropathy. We are still lacking in the disease-modifying treatment strategies including the biomarkers for indicating the progression & reversal of the disease. It may be possible in future to depict the possible biomarkers not only to detect the manifestations of progression but also to predict the progression of the disease so that it can be reversed. Understanding the complete patho-physiological background of the disease will enable us to design appropriate therapeutic strategies to herald the progression of this devastating complication of diabetes in near future.

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