

DIABETIC NEUROPATHY: OXIDATIVE STRESS AND NEUROINFLAMMATION¹Monalisa Debnath and ²Dr. Shruti Agrawal¹Research Fellow, Sports Authority of India, Netaji Subash Eastern Centre, Salt Lake, Kol-700091.²PhD, Assistant Professor, Department of Food and Nutrition, Bajbaj College, Kolkata.***Correspondence for Author: Monalisa Debnath**

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ABSTRACT

Diabetic neuropathy associated microvascular complications are the most painful, disabling and fatal outcomes with an aetiology of oxidative stress and neuroinflammation; acting as pathophysiological triggers damaging the peripheral nerves and brain cells. It progresses with decreased nerve functionality and nerve blood perfusion that may result in permanent neuronal damage. The clinical manifestations include numbness, burning, tingling sensation and intractable pain. Neuroinflammation initiates pathogenesis resulting in various brain diseases, including not only acute but also neurodegenerative mental disorders. Numerous epidemiological studies have documented an increase in plasma levels of inflammatory markers like CRP, IL-6 and TNF- α along with many other molecules like transforming growth factor- β (TGF- β), MCP1 or LP-PLA2 among patients with metabolic syndromes. Some of the major pathways that play a crucial role in the progression of diabetic neuropathy include polyol pathway, advanced glycation end products, altered activity of (Na⁺-K⁺)ATPase, poly-ADP ribose polymerase (PARP) over-activation and cyclo-oxygenase-2 activation. Nerve cells are prone towards hyperglycaemic injury as neuronal glucose uptake is based on external glucose concentration that is found to be 4-5 folds higher among the diabetic subjects. Drugs like chemical chaperons-trimethylamine oxide and 4- phenyl butyric; peroxynitrite decomposition catalysts, PARP inhibitors; and antioxidants like α -lipoic acid and N-acetyl cysteine have been found to target oxidative stress inflammatory pathways thus improving the sensorimotor and functional deficits associated with diabetic neuropathy. Still, a lot of work is warranted to further elucidate the cross talk of oxidative stress, mitochondrial dysfunction, and inflammation in the pathophysiology of diabetic neuropathy.

KEYWORDS: Diabetic neuropathy, neuroinflammation, neuronal damage, microvascular complications.**1.1 Diabetic neuropathy: prevalence and clinical manifestation**

Diabetes is marked by chronic hyperglycaemia and associated micro-vascular complications that affect the peripheral nerves with a prevalence rate of 50-60%.^[1] Effect of diabetes on brain system is the most painful, disabling and fatal complication with an aetiology of oxidative stress mediated damage in neurons surrounding the glial cells. It progresses with decreased nerve functionality and nerve blood perfusion which may result in permanent nerve damage. The clinical manifestations of Diabetic Neuropathy include numbness, burning, tingling sensation and intractable pain.^[2] Neuroinflammation is an important feature of diabetes that has shown to play an important role in the pathogenesis of various brain diseases, including not only acute but also neurodegenerative and some mental disorders.^[3] Many of the epidemiological studies have noted an increase in plasma levels of inflammatory markers including CRP, IL-6 and TNF- α among patients having metabolic syndromes.^[4,5] along with many other molecules like transforming growth factor- β (TGF- β)^[6],

MCP1^[7, 8] or LP-PLA2.^[9] Some of the major pathways that play a crucial role in development and progression of Diabetic Neuropathy constitutes of polyol pathway^[10], advanced glycation end products^[11], altered activity of (Na⁺-K⁺) ATPase^[12], poly-ADP ribose polymerase (PARP) over-activation^[13] and cyclo oxygenase-2 (COX-2) activation^[14] Nerve glucose cells are prone towards hyperglycaemic injury as neuronal glucose uptake is based on external glucose concentration that is found to be 4-5 folds higher among the diabetic subjects.

1.2. Classical pathways and pathomechanism

Diabetes has shown to affect the peripheral nervous system -both somatic and autonomic divisions. Severe diabetic conditions lead to reduction in nerve conduction velocity by longer nerve fibres with loss of their nerve terminals. It further results in tingling and loss of sensation that ascend to affect other areas.^[11] Reactive Oxygen Species (ROS) is considered as one of the prominent cause of these complications. Several classical hyperglycaemic pathways lead to aggravation of oxidative damage and vascular complications.^[15] During

hyperglycaemic condition, excess of glucose in the blood is converted into sorbitol by aldose reductase enzyme, which is later oxidised to fructose by sorbitol dehydrogenase with NAD^+ as a cofactor in polyol pathway. This eventually results in increased flux and oxidative stress^[16] as a consequence of which, the $(\text{Na}^+-\text{K}^+)\text{ATPase}$ activity is reduced that further activates PKC pathway.^[12] Activated Protein Kinase C (PKC) increases cytosolic phospholipase A2 activity that leads to the production of archedonate and prostaglandin E2 (PGE_2) which further inhibits cellular $(\text{Na}^+-\text{K}^+)\text{ATPase}$.^[17] Hence, number of PKC isoform may initiate tissue injury by diabetes induced ROS^[18], which leads to enhanced de-novo synthesis of DAG from glucose via triose phosphate. Elevated triose phosphate concentration increases the formation of both methyl glyoxal and diacylglycerol (DAG) which are activators of PKC.^[19] It has been documented by various researchers that enhanced activity of PKC isoforms initiates signalling mechanisms like mitogen activated protein kinases (MAPK), nuclear factor kappa light chain enhancers of B cells (NFkB) which further leads to initiation of inflammatory processes.

1.3. Diabetes leading to neuroinflammation

Prolonged hyperglycaemia results in neuroinflammation and nerve damage which occurs when there is a persistent release of proinflammatory mediators that include $\text{TNF-}\alpha$, IL-6, IL-1 β , COX-2 and iNOS as well as several chemokines; and the pathways are activated through the corresponding cytokines in neuronal cells.^[20] Antibodies or chemical agents against these cytokines and chemokines could alleviate the proinflammatory episode associated with diabetic neuropathy.^[8,9] These agents are known to inhibit the consequences of inflammatory changes associated with neuroglial activation. The classical pathways constituting the polyol pathway, PKC pathway, MAPK pathway and; excess accumulation of AGE products of proteins and lipids stimulate the production of inflammatory mediators.^[21] and activation of transcription factor NF-kB which are inducers of inflammatory process.^[22] Various receptors present on the micro-ganglia and macrophages are acted upon by the AGEs that stimulate the production of cytokines-IL-1, IL-6, IL-17, $\text{TNF-}\alpha$, C-reactive protein and chemokines like CCL-2, CXCL-1 etc.^[23,24] IL-6 is produced by many cell types including fibroblasts, endothelial cells, and monocytes-macrophages.^[25,26] A link between IL-6 levels and inflammation has been suggested in the pathogenesis of diabetes mellitus^[27] and it can be considered as a biomarker for early risk detection. CRP is a member of the pentraxin family of oligomeric proteins involved in PRRs activation. It enhances leukocyte reactivity, complement fixation, modulation of platelet activation and clearance of cellular debris from sites of active inflammation.^[28,29] Hence, CRP is considered as a common marker for inflammation.^[30] Tumor necrosis factor alpha ($\text{TNF}\alpha$) is one of the central mediators of neuroinflammation.^[31]

1.4. Diabetes alters the neuronal structure

The structural features of neuron is affected by prolonged hyperglycemia induced inflammatory cascade as the glycosylation of myelin protein alters its antigenicity causing infiltration of monocytes, macrophages and neutrophils from the blood circulation that in turn secrete inflammatory cytokines, result in damaged myelin sheath, activated glial cells of the nervous system and neuropathic pain^[32-34] Thus, the nerve excitability increases leading to oedema and neuro-inflammation that further aggravates nerve damage due to apoptosis induced by MPAK signalling.^[35] Hypoxic condition and ischemia occurring during diabetes predisposes the inflammatory condition through induction of inducible nitric oxide synthase (iNOS) which releases NO_2 acting as the physiological mediator of neuroinflammation.^[36]

2.1. Management strategies for Diabetic Neuropathy

2.1.1. Diagnostic method for diabetic neuropathy

Identifying the pathomechanisms responsible for disease pathogenesis is crucial to devise new treatment strategies as well as to discover new disease biomarkers. Assessment of vibration perception threshold (VPT) and calculation of neuropathy disability score (NDS) based on ankle reflexes and perception changes to variety of stimulus are considered as the currently available diagnostic method for diabetic neuropathy.^[37]

Newer techniques with minimal invasion or non-invasive operation include corneal confocal microscopy (CCM) and skin biopsy techniques. CCM allows the identification of corneal nerve fibre length and nerve density and thus can be used as diagnostic aid to quantify peripheral neuropathy.^[38] To quantify the number of nerve fibres per unit area, skin biopsy and consequent immuno-histochemistry are followed.^[39] To accurately monitor the disease progression and response to treatment, the diagnostic procedures can be combined with examination of biochemical changes. In accordance to the compelling evidence forwarded by many research groups, it is clearly depicted that oxidative stress mediated neurodegeneration and the accompanied inflammatory reactions play a pivotal role in the pathogenesis of diabetic neuropathy.^[21] Modulating these pathways using pharmacological agents may prevent the functional and pathophysiological disturbances that have significant associations with peripheral neuropathy which can further accelerate the discovery of new treatment strategies.

2.1.2. Treatment therapy

Oxidative stress is also known to enhance the endoplasmic stress through accumulation of misfolded proteins. Endoplasmic reticulum (ER) is responsible for the proper folding and processing of proteins. Oxidative damage to the ER results in dysfunctional protein processing system that initiates the accumulation of non-functional proteins.^[40] Administration of chemical chaperons which are the ER proteins, such as

trimethylamine oxide and 4- phenyl butyric acid are found to inhibit diabetes associated oxidative stress in the spinal cord and dorsal horn by processing newly synthesized proteins, reducing intra-epidermal nerve fibre loss and ameliorating peripheral nerve damage. Hence, it can be used efficiently as a therapeutic strategy for diabetic neuropathy.^[41] Nitrosative stress, primarily constituting peroxynitrite as the toxicant has also shown to contribute in the pathogenesis of diabetic neuropathy^[42] by causing biomolecular damage and PARP activation that further depletes cellular energy pool and causes necrotic cell death.^[43] Neuronal damage associated with diabetic neuropathy can be prevented by the use of peroxynitrite decomposition catalysts and PARP inhibitors as these agents have been found to alleviate the biochemical and functional impairment.^[44,45] Ample of antioxidants are being used among patients with diabetic neuropathy because of massive involvement of oxidative stress in the pathogenesis. Alpha-lipoic acid, vitamin E and acetyl-L-carnitine are the common components being used in several controlled prospective clinical trials^[46-48], among which alpha-lipoic

acid has shown to relieve sensory and functional deficits during diabetes neuropathy and is also approved by FDA for therapeutic use.^[49] Antibodies and chemical agents against the cytokines and chemokines have seemed to alleviate the pro-inflammatory episodes of diabetic neuropathy^[33,50] by inhibiting the consequences of inflammatory changes associated with neuroglial activation. Antioxidants like α -lipoic acid and N-acetyl cysteine have remarkable therapeutic efficacies.^[49,51]

Oxidative stress and neuroinflammation are the pathophysiological triggers occurring in diabetes neuropathy associated microvascular complications. The use of drugs targeting oxidative stress inflammatory pathways was found to improve the sensorimotor and functional deficits associated with diabetic neuropathy. Still, a lot of work is warranted to further elucidate the cross talk of oxidative stress, mitochondrial dysfunction, and inflammation in the pathophysiology of diabetic neuropathy.

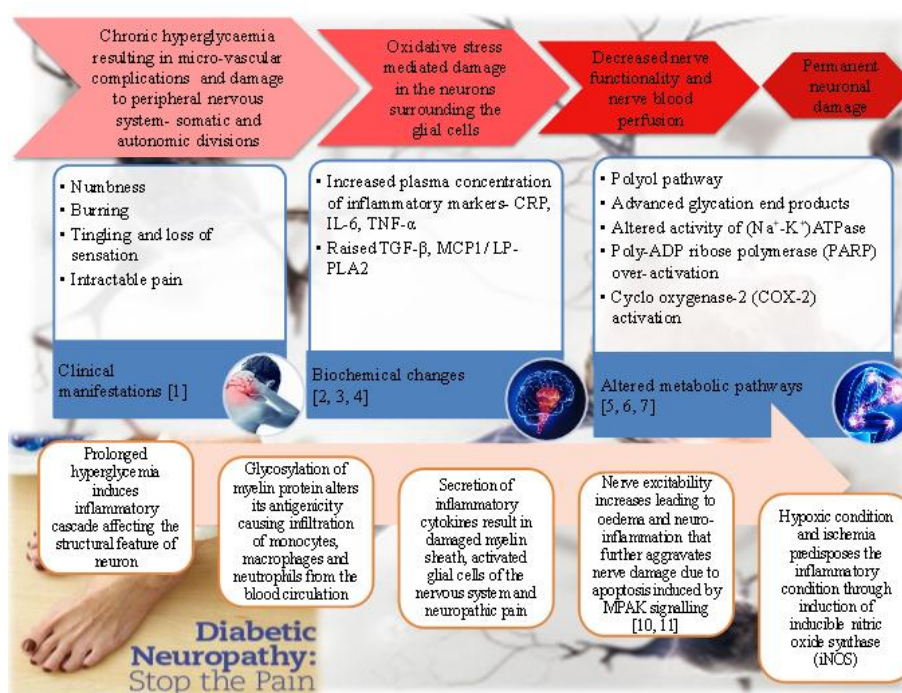


Figure 1. Progression and pathophysiology of diabetic neuropathy

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