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Review Article

Biochemistry Section

Tracking the Biochemical Trail of Neuroinflammation in Diabetic Neuropathy: A Narrative Review

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ABSTRACT

Diabetic Neuropathy (DN) is a long-term persistent neuro impairment associated with Type 2 Diabetes Mellitus (T2DM). DN develops when chronic hyperglycaemia damages peripheral and autonomic nerves, giving rise to a broad spectrum of clinical symptoms. The mechanism of DN is elaborate and multicomponent, mediated by persistent hyperglycaemia, lipid metabolic dysfunction, oxidative imbalance, impaired mitochondrial activity, and neuroinflammation, together giving rise to progressive peripheral nerve injury. Persistently raised glucose levels promote the accumulation of glycotoxins, leading to alteration in protein synthesis and function. Inflammatory mediators such as Interleukin-6 (IL-6), C-Reactive Protein (CRP), IL-18, IL-8, and Tumour Necrosis Factor alpha (TNF-α) further amplify nerve damage by activating Nuclear Factor kappa B (NF-κB) and Mitogen-Activated Protein Kinase (MAPK) signaling pathways. Modern strategies for managing DN focus on glycaemic control, lifestyle modifications, and emerging treatments namely Sodium-Glucose Cotransporter 2 (SGLT2) targeting drugs and Glucagon-Like Peptide-1 (GLP-1) mimetic. Further the identification of biochemical markers and molecular targets may facilitate early diagnosis and enable more personalised interventions. Continued collaboration between basic science scientists and clinicians will be essential in translating biochemical insights into tangible benefits for individuals. Despite our growing knowledge of the complexity of DN has sustainably improved in prior years, yet such knowledge of biochemical aspects and earlier predictor of neuropathy associated with diabetes are not entirely clear. Hence, the present review tends to describe the present comprehension about biochemical aspects, mechanism of neurological progression, and interconnected pathways involved in DN.

Keywords: Biochemical aspects, Diabetes mellitus, Hyperglycaemia, Neurological complication, Oxidative stress

INTRODUCTION

The DN is a degenerative pathology characterised by the impairment and deterioration of sensory and motor nerves. Based on the classification system of the National Diabetes Authority, DN encompasses three main groups: 1) diffuse symmetric forms, 2) mononeuropathies, and 3) radiculopathies. DN is a chronic neurological consequence of DM and harms nearly half of the individuals affected by DM over time [1,2]. It is commonly associated with distal symmetric polyneuropathy, results in sensory deficits, nerve-derived pain, and impaired limb motor activity. Diabetes linked peripheral neuropathy is also a leading contributor to foot ulceration and lower-limb amputation in diabetic patients [3]. Recent advances in biomedical research have provided major insights into the interplay of metabolic, oxidative, inflammatory, and vascular factors contributing to nerve injury in diabetes. The key pathways include hyperglycaemia-mediated oxidative burden, biosynthesis of AGEs, stimulation of polyol pathway, and mitochondrial dysfunction. Further, emerging evidence points to significance of lipid metabolism and neuroinflammation in modulating the onset and progression of neuropathic changes [4]. This review aims to decode DN from a biochemical perspective, synthesising current knowledge on the molecular and cellular alterations that plays a part in the initiation and evolution of diabetic neuropathies.

Pathological Mechanisms of Diabetic Neuropathy (DN)

Diabetic Peripheral Neuropathy (DPN): It constitutes small fibre neuropathic disorder, large fibre neuropathic disorder, and mixed fibre neuropathic disorder.

a. **Small fibre neuropathic disorder:** This involves pathological changes in fine unsheathed fibres and myelinated Aδ fibres, disrupts normal pain and temperature detection. Painful DN linked to SFN is seen in roughly 25% of people with diabetes and greatly affects daily functioning due to persistent pain and sensory issues [5]. Early signs involve burning sensation, sharp shooting pains, and an exaggerated response to painful stimuli [6].

b. **Large fibre neuropathic disorder:** The condition involve damage to the large insulated Aβ s, which leads to both sensory and motor impairments. Sensory problems oftens include reduced vibration perception and impaired proprioception, contributing to balance issues and numbness [7].

c. **Mixed fibre neuropathic disorder:** They lead to sensory abnormalities and neuropathic pain with the involvement of both types of nerve related fibres. Symptoms commonly begin as symmetrical loss of sensation in the toes which gradually extends upward in a “glove and stocking” distribution. When autonomic fibres are involved, patients experience irregular sweating and low blood pressure upon standing [8].

Autonomic neuropathy: Autonomic neuropathy is a common as well as severe diabetes-related disorder in which high glucose damages autonomic nerves. About 20-40% of people with diabetes develop dysfunction in systems regulated by these nerves, including heart, digestive tract, and urogenital organs [9]. Autonomic neuropathy includes several forms such as cardiovascular neuropathy, gastrointestinal neuropathy, sweating abnormalities in volving various organs [10].

Mononeuropathy: Mononeuropathy occur when a single nerve or a small cluster of nerves is damaged, producing localised pain, muscle weakness, or sensory changes in the specific area supplied by the affected nerve. Although it appears in fewer than 1% of diabetic patients, it often affects cranial and peripheral nerves, such as oculomotor or facial nerves [11]. The underlying process involves reduced blood flow due to blockage of the vasa nervorum, metabolic disturbances from persistent hyperglycaemia, oxidative stress, and neuronal damage [12].

Radiculoplexus nerve disorder: Radiculoplexus nerve disorder is rare, affecting less than 1% of cases, and mainly involves lumbar plexus [13].

Clinical Manifestation and Progression of DPN

The DPN typically presents as symmetrical numbness in the distal limbs with reduced sensation, and approximately one-fifth of diabetic patients develop neuropathic pain [14]. Pain symptoms include sudden, piercing neuropathic pain, itching, and heightened sensitivity [14]. Chronic hyperglycaemia and metabolic abnormalities also weaken immune defenses, increasing the risk of infections and serious limb damage. Diabetes-related peripheral neuropathy represents the atraumatic lower-extremity amputation [15]. A range of biochemical disturbances driven by high blood glucose, abnormal lipid levels and insulin resistance—along with their downstream effects—disrupts mitochondrial activity promote inflammation, generate oxidative stress, and ultimately results in neuronal damage [16]. Certain medications, such as proton pump inhibitors, may aggravate DPN by reducing vitamin B12 levels [16].

Hyperglycaemia and metabolic imbalance: High blood glucose is the primary driver of DN due to its harmful impact on nerve tissue. Multiple metabolic disturbances amplify this injury, including increased oxidative stress and mitochondrial dysfunction caused by heighted transmembrane voltage [17]. Activation of polyol pathway, from excess glucose leads to sorbitol and fructose build up, triggers osmotic strain, impairs neuronal function, and increases oxidative stress through myoinositol loss and high NADPH consumption. Persistent hyperglycaemia also promote the formation of AGEs compounds which results in protein integrity and activate inflammatory immune signaling in Schwann cells, further amplifying oxidative stress [18].

Oxidative stress and mitochondrial dysfunction: Oxidative stress is a major contributor to DN. High glucose level increases ROS generation through various pathways such as accelerated glucose metabolism and mitochondrial impairment. Elevated ROS levels damages biomolecules which results in neural injury and dysfunction [19]. Elevated blood glucose levels interfere with mitochondrial energy pathways, lowering ATP output and driving excess ROS formation. The resulting energy shortage, combined with the build-up of mitochondria, abnormalities adds to neuron damage and nerve fibre depletion. Disruption of mitochondrial production and maintenance creates small, dysfunctional mitochondria that hinder the function of nerve-supporting glial cells [20]. Lipoic acid helps reduce nerve related symptoms and enhance nerve conduction velocity in individual with diabetic-related peripheral neuropathy [21].

Polyol pathway activation: When glucose levels rise, some of it is shunted into a secondary metabolic route where aldose converts glucose into sorbitol. Sorbitol buildup disturbs osmotic pressure and causing the cell to lose important molecules such as inositol and taurine. Ongoing activation of this pathway results in nerve malfunction, while the corresponding rise in ROS heighten oxidative damage [22]. Treatment strategies, involve Aldose Reductase Inhibitors (ARIs), which lowers sorbitol buildup and help relieves neuropathic symptoms in clinical evaluations [23].

Advanced Glycation End Products (AGEs) and Rage Signaling: Chronic high glucose drives the non enzymatic attachment of sugars to biomolecules, generation of AGEs. These compounds increase within peripheral nerves and bind to RAGE receptors on cell surfaces, activate intracellular signaling cascades involving NF-κB. This leads to increased production of inflammation related cytokines and cell adhesion protein resulting in oxidative damage and vascular injury [24].

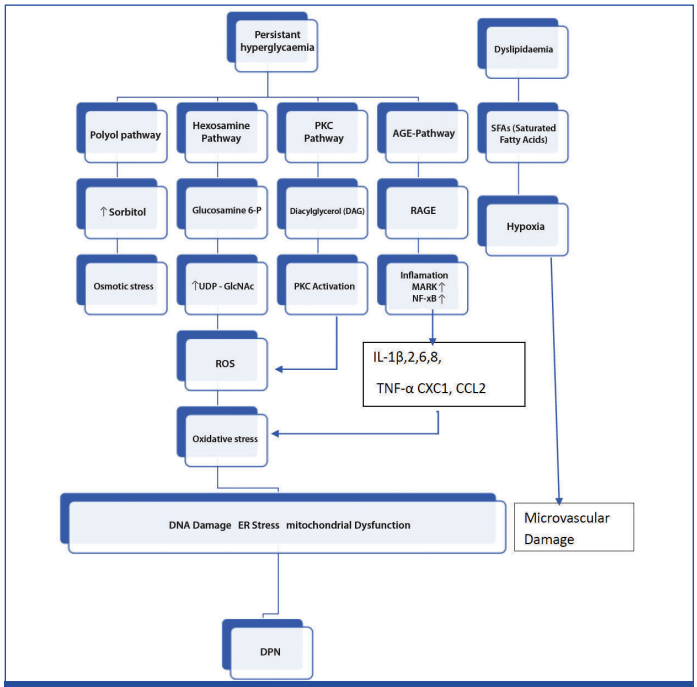
Protein Kinase C (PKC) pathway and vascular dysfunction: The PKC functions as an important regulator of intracellular signaling pathways. Elevated blood glucose levels increase intermediates such as diacylglycerol, which stimulates PKC pathway. Glucose-6-phosphate also fuels the Krebs cycle, generating cofactors that further enhance PKC activity. Once activated, PKC phosphorylates key enzymes and disrupts vascular regulatory factors, resulting in vasoconstriction and disrupted metabolic activity [25].

Hexosamine pathway O-GlcNAc: Excess glucose that is not routed through glycolysis is diverted into the hexosamine biosynthesis pathway, increasing the formation of UDP-N-acetylglucosamine. Such alterations refined gene activity and protein behaviour, inflammatory responses, and oxidative injury. Together, these disturbances play a significant role in development of DPN [26].

Inflammatory and immune mediators: Inflammatory mediators such as IL-8, IL-18, IL-6, CRP, COX-2, and IL-1β increase oxidative stress and disrupt vascular function by activating signaling pathways like NF-κB and MAPK. Oxidative stress and stimuli such as calcium influx further enhances MAPK phosphorylation, strengthening this inflammatory signaling. NF-κB becomes the major cell internal targets during glucose overload and redox imbalance. IL-6 intensifies nerve damage and pain, and other inflammatory cytokines intensify Schwann cell dysfunction by weakening axonal support and promoting demyelination. Activation of Toll-Like Receptors (TLRs) amplify the inflammatory environment, that maintains peripheral nerve damage [27]. High glucose levels and elevated oxidative damage reduce myelin quality, slowing nerve impulse flow. Hyperglycaemia also suppresses the PI3K/Akt pathway, increase DNA methyltransferases and decreases autophagy, all of which aggravate Schwann cell stress. Mitochondrial malfunction in these cells alter lipid metabolism, contributing to nerve fibre damage and myelin disruption [28].

Lipid metabolism and dyslipidaemia: Abnormal lipid profiles significantly influence diabetes-associated nerve dysfunction, irrespective of high blood sugar. Increased circulating triglycerides accelerate the progression of neuropathy and contribute to myelin sheath disruption. Saturated Fatty Acids (SFAs) induce lipotoxicity, mitochondrial dysfunction, and apoptosis. Hydrogenated fat triggers lipotoxicity and neuronal damage, impairing mitochondrial function producing less quantity and speed of mitochondria than sensory gangliaon. Dyslipidaemia further worsens nerve damage by amplifying metabolic stress within peripheral nerves [29]. Gene expression assessment show that nerves affected by DN nerve disorder present altered lipid handling pathways, implying that faulty lipid metabolism participates in neuropathy progression [Table/Fig-1] [30-33].

Mitochondrial dysfunction and energy imbalance: Elevated glucose disrupt normal mitochondrial energy production, lowering



[Table/Fig-1]: Showing the biochemical mechanisms in the initiation of Diabetic Neuropathy (DN) due to persistence hyperglycaemia and dyslipidaemia in Type 2 Diabetes Mellitus (T2DM) [30-33].

ATP generation. The resulting shortfall in cellular energy, along with the buildup of damaged mitochondria, related neuronal damage. This related Schwann cell function, and neuronal damage [20].

Molecular and genetic insights: MicroRNAs, long regulatory RNAs, closed loop RNAs act as key modulators of gene activity, shaping inflammatory responses, oxidative balance, and nerve repair [34]. Genetic differences affecting inflammation, oxidative damage and pathways can heighten vulnerability to DN. Environmental factors, particularly chronic high glucose can drive epigenetics changes and modify gene expression and contribute to DN [35].

Therapeutic implications and future directions: Modern therapeutic approach namely SGLT2 targeting drugs and GLP-1 mimetic are increasingly used to manage DN. Addition option includes agents targeting sodium and calcium channels, and NMDA receptors, to reduce neuropathic pain. Emerging biomarkers, including non coding RNAs and indicators of nerve injury, may improve diagnosis and prognosis [36]. Drugs like Ranirestat limit sorbitol accumulation, while benfotiamine blocks multiple metabolic pathways that drive neuropathic progression [37].

CONCLUSION(S)

DN results from a complex interplay of biochemical disturbances triggered by high blood glucose. The neuronal malfunction in diabetes is multitasking like interaction of polyol pathway, heightened synthesis of Advanced Glycation End products (AGEs) oxidative damage, mitochondrial malfunction and inflammatory signaling. These modes not only disrupt nerve function but also compromises vascular supply, exacerbating neuronal degeneration. Therapeutic approaches targeting these pathways offer promising avenues to complement current symptomatic treatments. Further the identification of biochemical markers and molecular targets will help in early diagnosis and enable precision-based interventions. Continued collaboration between basic scientists and clinicians is essential for translating biochemical insights into tangible benefits for patients.

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