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Review Article

Mechanistic Foundation of Diabetic Neuropathy: A Comprehensive Review

Dipamoy Datta[1]*, Dwaipayan Saha[2], Tapan Kumar Biswas[3] and Subhro Prakash Hui[4]*

[1]Department of Cell Biology and Physiology, CSIR-Indian Institute of Chemical Biology (CSIR-IICB), Kolkata 700032, India

[2]Department of Interdisciplinary Health Sciences, University of Texas El Paso, Texas 79968, United States of America

[3]Department of Neurology, Ramkrishna Mission Seva Pratisthan, Kolkata 700026, India

[4]S. N. Pradhan Centre for Neurosciences, University of Calcutta, Kolkata 700019, India

***Corresponding Author:** Dipamoy Datta, Department of Cell Biology and Physiology, CSIR-Indian Institute of Chemical Biology (CSIR-IICB), Kolkata 700032, India and Subhro Prakash Hui, S. N. Pradhan Centre for Neurosciences, University of Calcutta, Kolkata 700019, India.

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Abstract

Diabetic neuropathy (DN) is the highly prevalent devastating diabetic complication that detrimentally affects different parts of the human body in association with nervous system. Although, a sizeable research has been conducted for elucidation of basic pathophysiological mechanisms, biochemical pathways and risk factors in DN, the therapeutic option remains challenging to effectively cure different symptoms of this disease including neuropathic pain. The heterogeneity in DN progression along with specific influence of different risk factors, like diabetes duration, sensory phenotype, sex and genetic background makes it difficult to find a single therapy for efficient clinical management of neuropathic patients. The trends in neuropathy research accompanied by most of the current guidelines strongly emphasize for individualization of diabetic neuropathic treatment according to the nature of neuropathic pain and associated clinical phenotypes. By recognizing this critical need, here we present a mechanistic framework of diabetic neuropathy related complications based on four major DN hallmarks, namely neuronal damage, micro-vascular alterations, metabolic dysregulation and inflammation. We describe the importance of different DN hallmarks and their underlying pathophysiological features in promotion of neuropathy associated complication and disease advancement.

Keywords: Diabetic Neuropathy; Diabetic Neuropathy Hallmark; Neuronal Damage; Micro-Vascular Alterations; Metabolic Dysregulation; Inflammation

Introduction

Diabetic neuropathy is the most frequently observed long-term diabetes associated chronic complications that nearly affect 50% of the patients with diabetes. Diabetic neuropathy can be defined as the occurrence of peripheral or autonomic nervous system dysfunction accompanied by specific sign and symptoms, after elimination of other most possible routes of neuronal damage [1,2]. Although, the clinical sign and symptoms of diabetic neuropathy vary considerably between patients, but general symptoms include numbness or reduction in the ability to recognize pain or temperature fluctuation, tingling or burning sensation, induction of neuropathic pain and muscular weakness appearing in the lower extremities [2-4]. The ultimate clinical outcome of diabetic neuropathy can be disastrous, as it adversely affects diabetic patients' health related qualities of life by producing sharp neuropathic pain, foot ulceration, limb amputation, nerve dysfunction and sensory impairment [1-5]. In order to prevent serious complications of diabetic neuropathy, like cardiac arrhythmias or lower limb amputation, an urgent timely diagnosis is essentially required. But, the heterogeneity of overall disease mechanisms in diabetic neuropathy in association with unpredictability's of pain generation in neuropathic patients predominantly challenges timely diagnosis and development of effective treatment modalities [5]. Therefore, the majority of current treatment guidelines in diabetic neuropathy strongly recommends for development of personalized treatment approach based on a minimal dose start which can be individualized to highest possible clinical response accompanied by the minimization of adverse side-effects [1,6,7].

A mechanistic overview of diabetic neuropathy

On account of high levels of complexity and heterogeneity in diabetic neuropathy progression, the overall pathophysiology of the disease process remains incompletely known [1,5,6]. As a consequence, the mechanisms of diabetic neuropathy associated complications, like neuropathic pain in many situations cannot be fully identified, which is mainly responsible for underassessment during its diagnosis and under treatment [1,6]. The current state of knowledge in diabetic neuropathy research empirically suggests for the role of multiple underlying factors for promotion of disease process, like nerve fiber damage, vascular changes, enhancement in free-radical production, metabolic irregularities and many more [1,5-9]. To specifically address this central-most issues in neuropathic research, here we attempts to define a pathophysiological framework of diabetic neuropathy development and advancement, which is mainly composed of major pathophysiological hallmarks and their underlying features (Figure 1, Table-1). The proposed pathophysiological features of diabetic neuropathy are- neuronal damage, micro-vascular alterations, metabolic dysregulation and inflammation.

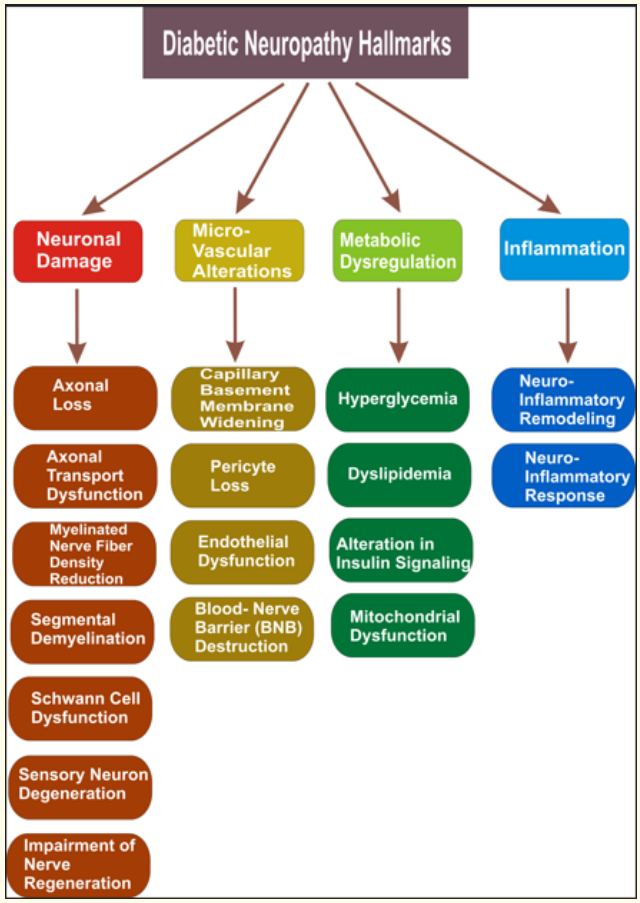

Figure 1: The pathophysiological hallmarks of diabetic neuropath.

Depending on decade long clinical research and knowledge of biochemical pathways, the figure schematically represents four different hallmarks of diabetic neuropathy development. The hallmarks are neuronal damage, micro-vascular alteration, metabolic dysregulation and inflammation. The figure also represents the underlying features of different hallmarks, which are explained in each of the corresponding sections.

DN Hallmarks	Pathophysiological Features	Comment	Reference
Neuronal Damage	Axonal Loss	Axonal loss or axonopathies are archetypic feature of diabetic neuropathy development and mainly involves epidermal nerve fiber loss .	[5,10,11]
	Axonal Transport Dysfunction	Diabetes induced axonal transport dysfunction is significantly associated with dying back neuronal degeneration in diabetic neuropathy.	[12,13]
	Myelinated Nerve Fiber Density Reduction	Reduction in myelinated nerve fiber densities are linked with sensory losses during diabetic neuropathy advancement.	[14,15]
	Segmental Demyelination	Diabetes driven segmental demyelination of nerve fibers are considered as the late phase characteristic feature of DN advancement.	[2,10,13,14]
	Schwann Cell Dysfunction	Dysfunctions in Schwann cells are centrally responsible for both axonal loss and demyelination process in DN development.	[18,20-23]
	Sensory Neuronal Degeneration	Dyeing back neurodegeneration in the distal sensory axon is the major characteristic feature of diabetic peripheral neuropathy (DPN) progression.	[5,8,13,24]
	Impairment of Nerve Regeneration	An impairment of nerve regeneration associated process in various neuronal areas like dorsal root ganglion neurons are closely associated with neuronal dysfunction and diabetic neuropathic pain generation.	[13,24,25]
	Neurotransmitter Imbalance	Diabetes induced abnormalities in neurotransmitters along with an alteration in brain signaling is intrinsically associated with DN related complications development.	[27,28,29]
Microvascular Alterations	Capillary Basement Membrane Widening	An widening of capillary basement membrane in nerve vasculature triggers diabetic neuropathy progression through changes in morphological and functional properties in peripheral nerves.	[8,31,32]
	Pericyte Loss	Diabetes driven pericyte damage along with loss of its functional activities are responsible for generation of endoneurial hypoxia and promotes diabetic neuropathy progression.	[32]
	Endothelial Dysfunction	Endothelial dysfunction is an early stage microvascular alterations associated feature that is involved in DN initiation.	[33-36]
	Blood Nerve Barrier (BNB) Destruction	Destruction of blood-nerve barrier (BNB) based capillary defense system functions in clinical establishment of diabetic neuropathies.	[9,31,32]

Metabolic Dysregulation	Hyperglycemia	Hyperglycemia driven metabolic imbalance actively mediates diabetic neuropathy development through nerve dysfunction, nerve injury and neuronal cell death.	[2,3,5,6,17,30]
	Dyslipidemia	Dyslipidemia or diabetes driven alterations in serum lipid profiles are closely involved in diabetic neuropathy initiation through inflammation, insulin resistance, segmental demyelination and oxidative stress.	[39,40]
	Alteration in Insulin Signaling	A dysfunction in neuronal insulin signaling is involved in diabetic neuropathy progression and associated neuropathy pain generation.	[5,42,43]
	Mitochondrial Dysfunction	Diabetes driven mitochondrial dysfunction and associated oxidative damages in dorsal root ganglion (DRG) neurons, axons and Schwann's cells are closely linked with induction of dyeing back neurodegeneration in diabetic neuropathy.	[44-46]
Inflammation	Neuroinflammatory Response	Diabetes driven neuroinflammatory response plays a crucial role in diabetic neuropathy pathogenesis by mediating neuronal damage, peripheral nerve dysfunction and assisting in neuropathic pain generation.	[47-49]

Table 1: A pathophysiological framework of diabetic neuropathy and related complications.

Neuronal damage

The clinical manifestation of diabetic neuropathy can occur by adopting a variety of different forms, such as sensory, autonomic, motor and focal/multi-focal neuropathies [5,8]. Among this diverse diabetic neuropathy types, distal symmetric polyneuropathy (DSPN) or treatment induced neuropathy covers nearly 75% of diabetic neuropathy cases [8]. Apart from this, there also exist other different diabetic neuropathies, like autonomic neuropathy, mono or focal neuropathy, proximal neuropathy or radiculopathy. Depending on the type of diabetic neuropathy development, the typical neuropathic manifestations are mostly mediated by both diffuse or focal damage of peripheral and autonomic nervous system [7,8]. For an example, the progression of diabetic distal symmetric polyneuropathy occurs mostly by supporting fiber-length responsive manner that generally involves gradual loss of sensory neuronal terminals (distal axonopathy), autonomic dysfunctions, alterations in trophic levels in feet and emergence of neuropathic pain [5,7,8]. The total spectrum of diabetic neuropathy associated neuronal damage most possibly includes axonal loss, axonal transport dysfunction, myelinated nerve fiber density reduction, segmental demyelination, Schwann cell dysfunction, sensory neuronal degeneration, impairment of nerve regeneration and neurotransmitter imbalance.

Axonal loss

Axonal loss along with its degeneration, atrophy or dysfunction is currently considered as one of the prototypic feature of diabetic neuropathy progression. For this reason, the key pathological alteration observed in diabetic polyneuropathies (DPN) and peripheral neuropathies for majorities of its complications are axonopathies, the degeneration of terminal areas of peripheral nerve that causes epidermal nerve fiber loss [5,10]. For an example, distal symmetric polyneuropathy (DSP), the most prevalent subtype of peripheral neuropathy are principally generated by length dependent dyeing back mechanisms, which generally affects the distal nerve areas of the longest sensory axons in the limb [11]. Basically, diabetic neuropathy pathogenesis involves damages of peripheral nervous system by specifically attacking sensory and autonomic axons. As a consequence, gradual loss of sensory functions begins by following a stocking and glove distribution,

including sensation loss to vibration, cold temperature, pinprick and proprioception [5,11]. Due to this stocking and glove distribution pattern of neuropathy progression, diabetic neuropathy is also regarded as length dependent neuropathy with lengthwise progressive loss of axonal functions. In other word, the longest sensory axons are mostly effected and that causes damage of distal leg epidermal axons and subsequently axon loss in further proximal limbs [5,10,11]. For assessment of diabetic neuropathy associated axonal dysfunction, currently sensory nerve excitability testing, nerve conduction (NCV) studies and clinical evaluations are generally used. A number of studies involving those assessment methods have suggested that the sensory axons are much more vulnerable to diabetes induced pathological changes and as a consequence sensory axonal dysfunctions arises much earlier in a different ways in comparison to motor axon [10,11]. At the same time, neuropathy with type 1 diabetes (T1DM) usually exhibits more aggressive axonal loss or atrophy in contrast to type 2 diabetes (T2DM) involvement [10].

Axonal transport dysfunction

It is increasingly hypothesized that axonal transport dysfunction plays an intrinsic role in dying-back neuronal degeneration during the course of diabetic neuropathy development [12]. In normal condition, axonal transport mainly functions to support neuronal development, its survival, post-injury regeneration and preservation of neuronal integrities. This axonal transport process is severely disrupted in the time of diabetes progression that causes major changes in neuronal cytoskeleton proteins, remodeling of neuronal homeostasis, reduction in ATP supply and accumulation of cargoes, which subsequently leads to axonal degeneration [13]. As a result of diabetes induced axonal transport disruption, dysfunctions in peripheral sensory nerves occurs mostly in response of three major factors, including alterations in mitochondrial functions towards diminution of its energy supply, ineptitude of lipids and proteins to arrive in the distal neurons and marked reduction in anterograde transport process [1213]. A dynamic interplays of this inherently linked factors causes sensory loss and an enhancement in neuronal degeneration that triggers diabetic neuropathy progression.

Myelinated nerve fiber density reduction

The onset of diabetic neuropathy significantly reduces myelinated nerve fiber densities, which is mainly linked with the development of its clinical symptoms, like pain and loss of sensation [14]. In most of the cases, the reduction in myelinated nerve fiber densities for both large and small nerve fibers are significantly associated with diabetic neuropathy associated morphological changes in peripheral nerves [14]. The pathological examination along with morphometric studies of sural nerve biopsies from a substantial number of diabetic neuropathy patients have demonstrated diabetes driven structural alterations in nerve fibers including decrease in myelinated fiber densities, its mean diameters and distribution patterns of fiber diameters [14,15]. In this regard, the changes in myelinated nerve fiber densities are also significantly correlated with reduction in nerve conduction velocities and associated sensory/motor response amplitudes as suggested by electrophysiological studies [14]. In addition, state of aging, levels of endoneurial microangiopathic changes, duration of diabetes and its clinical severity functions as an important regulatory factors towards loss of both myelinated and unmyelinated nerve fiber [14,15]. From a number of clinical studies with diabetic neuropathy patients, it have been suggested that the decrease in myelinated large nerve fibers are mostly involved in muscular weakness, sensory loss and paresthesia. Whereas, small myelinated or unmyelinated nerve fiber loss are mainly associated with the appearances of more severe symptoms of diabetic neuropathy advancement, like regional anesthesia, pain, autonomic symptoms and development of foot ulceration [16]. In this context, it has been found that small fibers covers nearly 70-90% of peripheral nerve fibers and its progressive loss are centrally involved in genesis of diabetic peripheral neuropathies (DPN), which occurs earlier than large fibers engagement. Myelinated and unmyelinated small fibers in diabetic peripheral neuropathies (DPN) are involved in regulation of tissue blood flow, pressure-driven vasodialation, sudomotor function and neuropathic pain perception, which also plays a predominant role in development of diabetic foot ulceration [16].

Segmental demyelination

Apart from axonal loss, segmental demyelination or segmental destruction of myelin sheath in peripheral nerve is another archetypical feature of diabetic neuropathy advancement. The prolonged persistence of pre-diabetes or diabetes causes significant alterations in electrophysiological and neuro-anatomical properties of both myelinated and unmyelinated nerve fiber that often causes segmental demyelination, microangiopathy,

reduction in nerve fiber diameter and axonal loss [10,13,14,17]. This pre-diabetes or diabetes induced segmental demyelination of nerve fiber is strongly associated with several late-stage neuropathological features of diabetic neuropathy including reduction in nerve conduction velocities, stimulation of neuronal degeneration and finally loss of unmyelinated and myelinated nerve fibers [2,13,17]. In comparison to axonal neuropathy (axonal loss by neuronal injuries), the prevalence of demyelinating neuropathy is somehow limited and generally it is mostly found in more advanced cases of diabetic neuropathies [5]. The early pathological events of diabetic neuropathies are primarily linked with structural changes in small nerve fibers, like unmyelinated C fibers and Aδ fibers, which is followed by an initiation of segmental demyelination and remyelination in large nerve fibers. Of note, the occurrence of segmental demyelination during the course of diabetic neuropathy often progress from distal to proximal direction and in many cases it is accompanied by axonal degeneration of myelinated nerve fibers [2]. A detail pathological examination of sural nerve preparations from both diabetic patients and diabetic rodent model usually indicates the presence of cycles of demyelination and remyelination to the establishment of total segmental demyelination in association with preservation of axonal structure. This critical observation somehow suggests, schwannopathy may appear distinctively from the development of axonopathy during diabetic neuropathy progression [18]. In addition, macrophage mediated segmental demyelination also plays a vital role in acquisition of chronic inflammatory demyelinating polyneuropathy (CIDP), a highly heterogeneous immune originated sensory and motor neuropathy. The development of CIDP generally exhibits significant levels of overlap between inflammation, axonal degeneration and macrophage associated segmental demyelination and remyelination in peripheral nerves [19].

Schwann cell dysfunction

Schwann cell dysfunction plays a cardinal role in initiation of diabetic neuropathy pathogenesis and particularly its "stocking and glove" pattern of disease progression [20,21]. Due to its central-most involvement in diabetes associated neuronal damages, Schwann cell dysfunctions are essentially associated with promotion of both axonopathies and demyelinating neuropathis [22]. Basically, Schwann cells (SCs) are glial support cells in peripheral nervous system, which mainly functions to sustain structural stabilities and functions of peripheral nerves by insulation and myelination of its myelinated axons from the adjacent endoneurial milieus and encapsulation of unmyelinated axons. By insulation of axon, Schwann cells (SCs) acts to maintain the homeostasis of peripheral nerves including the regulation of action potential velocities, preservation of the axonal caliber, assisting in nerve regeneration during post-injury period, functional activation of sodium channels and modulation of neuronal microenvironment through secretion of neurotrophic factors [22,23].

During diabetes progression, a number of associated factors, like hyperglycemia, dyslipidemia, oxidative stress, hypoxia, inflammation and mitochondrial abnormalities mediate Schwann cell dysfunction by following a complex mode of interactions [20,23]. Apart from this, diabetes associated microvascular damage also plays a leading role in Schwann cell dysfunction by disrupting the functional interactions between axons and Schwann cells through modulation of hypoxia in endoneurial microenvironment, which largely restricts the supply of glucose, oxygen and trophic factors [18]. The onset of Schwann cell dysfunction eventually triggers diabetic neuropathy initiation through induction of myelin destruction, disruption in myelin conduction velocities, disablement of neuronal regenerations, decrease in anti-oxidative capacities and interruptions of glial-axonal communications [21,23]. With an increase of this diabetes induced neuropathological abnormalities and functional impairment, Schwannopathy related features, like a cycle of lenient segmental demyelination along with remyelination usually begin to appear in normal axon, which is currently recognized as the initial step in diabetic neuropathy pathogenesis [21]. In fact, initiation of Schwannopathy in association with axonal degeneration is considered as the feature of diabetic neuropathy onset, which eventually leads to more severe courses of neurodegeneration, nerve fiber loss and beginning of neuropathic pain [18,21].

Sensory neuron degeneration

Peripheral neuronal degeneration including symmetric degeneration of sensory neurons is the hallmark characteristics of diabetic peripheral neuropathy (DPN). The metabolic consequences of diabetes in many cases are strongly linked with neurodegenerative processes in peripheral nerves, which selectively targets sensory axons and cause its gradual dysfunction [5]. As a result, diabetic peripheral neuropathy patients frequently exhibit sensory symptoms in the early phase of the disease as

compared to motor symptoms. For an example, patients with distal symmetric polyneuropathies (DSPNs) are generally associated with sensory symptoms, like distal foot numbness and paraesthesias, which usually appears in distal areas and in due course progress to further proximal extremities [24]. This very unique mode of disease progression indicates diabetes induced progressive neurodegeneration in the distal sensory axons that mainly follows a retraction and dyeing back mechanism. Diabetes driven metabolic alterations mediates a characteristic pattern of neuronal cell body damage, commonly known as 'stocking and glove' pattern of neuropathy progression that mainly causes retrograde degeneration of terminal sensory axons with an apparent retention of cell bodies or perikaryas [5,8,24]. In this regard, skin biopsies along with estimation of intra-epidermal nerve fiber densities (IENFD) of diabetic patients have explicitly demonstrated that neurodegeneration mediated loss of terminal regions in the sensory axons in distal extremities are more pronounced than that found at further proximal extremities [8].

The clinical manifestations of sensory neuron degeneration during diabetic neuropathy progression is generally accompanied by several characteristic features, such as Wallerian-like degeneration, small fiber degeneration, peripheral nerve fiber loss, axonal atrophy, axonal swelling, reduction in sensory epidermal nerve fiber densities and disruption of axonal transport processes [13,24]. Wallerian degeneration is currently assumed as the typical characteristic attribute of sensory axonal degeneration, which involves self-destruction of axon and myelin in the course of diabetic peripheral neuropathy advancement. This Wallerian degeneration together with other diabetes driven structural alteration associated processes (microangiopathy, segmental demyelination) actively promotes dorsal root ganglia neuronal damage, which subsequently leads to loss of unmyelinated and myelinated nerve fibers [24]. In case of painful diabetic peripheral neuropathy (DPN) that covers nearly one third of diabetic patients, subclinical small sensory nerve fiber degeneration usually occurs during the time of pre-diabetes and before large fiber degeneration. Degeneration of small sensory nerve fibers are crucially linked with loss of sensation and development of intractable pain in DPN, which is aptly responsible for reduction in life qualities in patients [16].

Impairment of nerve regeneration

An impairment of nerve regeneration associated processes as regard to neuronal degeneration is regularly found in diabetic neuropathy and it largely contributes in neuronal dysfunctions and associated pathophysiological events [24,25]. Nerve regeneration impairment mediated neuronal dysfunctions may range from an increase in loss of nerve fibers, Schwann cell dysfunction, prevention of reinnervation (final and pivotal step in regeneration) by changing the susceptibilities of peripheral target tissues and modulation of stromal microenvironments in such a manner that impedes axonal regeneration [13,25]. Most importantly, irregularities in nerve regeneration in different neuronal and anatomic locations, such as dorsal root ganglion neurons, nerve trunks and dermis is crucially involved in genesis of neuropathic pain sensation [25]. Studies in diabetic patients and Streptozotocin induced pre-clinical animal models have indicated a substantial decrease in nerve regeneration potential and its involvement in diabetic neuropathy associated complications including severity in neuropathic pain generation [25]. From mechanistic point of view, an impairment in nerve regeneration may arise from several neuropathological features, including reduction in expressions of neurotrophic factors and their receptors, alterations in cell adhesion molecules associated signaling circuitries, abnormalities in macrophage clearance, changes in basement membrane associated regenerative cues, aberrations of growth cones and microangiopathy or ischemia associated remodeling of obstructive microenvironments around peripheral axons [8,13,25]. For personalized treatment of diabetic peripheral neuropathy, currently it is believed that an extensive characterization of different regeneration pathways may provide a new avenue to effectively prevent neuronal degeneration and preservation of axonal integrities [13,24]. In this specific context, a number of patient specific influencing factors have been reported for precise modulation of peripheral nerve regeneration in experimental diabetic model. The influencing factors are patient's age, diabetes duration, endoneurial macrophage infiltration level, patient specific optimal combination of growth factors and nerve conduit, adipose derived stem cells and autologous fat grafting [26].

Neurotransmitter imbalance

A dysregulation in neurotransmitter secretion and function plays a vital role in diabetic neuropathy pathogenesis and associated

neuropathic pain generation. It is growingly presumed that diabetes driven alterations in brain signaling including an interruptions in neurotransmitter signaling systems are actively involved in diabetic neuropathy associated complications development [7,27]. Diabetes driven major pathophysiological alterations, like pancreatic beta cell dysfunction, insulin resistance, oxidative and lipotoxic stress induction along with pre-diabetes to diabetes transition largely dictates the process of neurotransmitter imbalance and changes in brain signaling [27]. The available information reports for the functional impairment of a number of neurotransmitters in the course of diabetic neuropathy development, including glutamate, gamma aminobutyric acid (GABA), serotonin, histamine, acetyl choline, epinephrine, norepinephrine and nitric oxide [27]. At the basic level, the dysregulation of amino acids metabolism in brain critically determines the extent of neurotransmission imbalance and severity of diabetic neuropathy associated pain development. By temporal metabolomic analysis in brain of DNP rat model, it has been suggested that the dysregulation of several amino acids, such as L-Tyrosine, L-Tryptophan, L-Histidine, L-Lysine and D-Proline during diabetic neuropathy progression were significantly linked with the reduction of analgesic neurotransmitters [28].

An imbalance of excitatory Glutamatergic (Glutamate/ Glutamine) and inhibitory Gamma Aminobutyric acid (GABA) levels have been found in particularly the posterior insula of brain regions in diabetic neuropathy patients and supposed to be involved in the diabetic neuropathic pain processing associated signaling pathways within central nervous system [27]. An increase in neuronal release of glutamate along with its neuronal reuptake from synaptic clefts is crucially involved in neuropathic pain generation in diabetic patients. In fact, diabetes induced changes in glutamate and GABA levels often leads to an establishment of concentration gradient around synaptic vesicles or synaptic terminals and subsequently interferes with the neurotransmitters uptake processes [27,28]. Over the course of diabetic neuropathy advancement, serotonergic neurotransmitter serotonin (5-hydroxytryptamine) and peptide neurotransmitter N- acetylaspartylglutamate (NAAG) are mainly involved in modulation of neuropathic pain generation [29]. In addition, severe dysregulation for several other neurotransmitters including epinephrine, norepinephrine and nitric oxide have been reported in context of either autonomic or sensory neuropathy development [28]. But, their exact mode of pathogenesis in diabetic neuropathy along with their precise quantitative estimation in neuropathic patient's brain remains mostly unidentified.

Microvascular alterations

As being a micro-vascular complication, a significant levels of structural and functional alterations in vasa-nervorum are commonly observed in diabetic neuropathy [9]. During the course of diabetes progression, both epineurial and endoneurial micro-vessels exhibits a range of abnormalities, such as notable extent of innervation in epineurial microvessels, an impairment of blood flow in diabetic nerves and massive structural changes in endoneurial micro-vessels along with an upshot of endoneurial hypoxia [9,30]. An extensive ultra-structural analysis of biopsy samples from diabetic neuropathy patients demonstrates salient alterations in nerve microvasculature, like as capillary basement membrane widening, loss of pericyte coverage, endothelial dysfunction and blood nerve barrier (BNB) destruction (Figure-1) [20].

Capillary basement membrane widening

A marked alterations in endoneurial capillary morphology, like capillary basement membrane widening and diabetes associated vascular reactivity is assumed to be involved in the development of diabetic neuropathy [31]. This pathological abnormalities of nerve microvasculature is mostly responsible for generation of occlusive angiopathy, endoneurial ischemia and tissue hypoxia, which together plays a profound influencing role in pathological emergence of diabetic neuropathy. As a consequence of diabetes driven endoneurial micro-vascular alterations, both morphological and functional properties of peripheral nerves are largely compromised in point of reduction in endoneurial oxygen tension, nerve blood flow (NBF) and nerve conduction velocities [8]. A number of pre-clinical model in diabetic distal symmetric polyneuropathy (DPN) and pathological investigations of nerve biopsies derived from diabetic neuropathy patients also supports this major endoneurial capillary dysregulations. In addition, both pre-clinical model and clinical studies in diabetic neuropathy also suggests these capillary abnormalities are linked with diabetes duration and clinical courses of disease severity [8,32].

Pericyte loss

Loss of pericyte function and pericyte damage is linked with endoneurial capillary dysfunction and frequently observed event during the early stage of diabetic neuropathy [31,32]. Nerve biopsies from patients with diabetic polyneuropathy have indicated an ample degeneration of pericytes along with microvessel abnormalities in endoneurial capillaries, which shows increased levels of

correlation with clinical aggressiveness of diabetic polyneuropathy [32]. It is firmly assumed that loss of pericytes is intrinsically linked with the disorganization of endothelial cells, which subsequently leads to reduction in perfusion of peripheral nerves and thereby induces endoneurial hypoxia. The generation of endoneurial hypoxia are strongly associated with different pathophysiological aspects of diabetic neuropathies including microangiopathies or endoneurial capillary dysfunctions, inflammation, oxidative and nitrosative stress generation and blood-nerve barrier (BNB) destruction, which together increases the clinical severity of diabetic neuropathies [31]. From a morphological point of view, pericytes are found in endoneurial capillary associated basement membrane and functions in maintenance of structural integrities of endothelial cells and blood-nerve barriers (BNB) in association with preservation of its permeability barrier properties [31,32]. Of note, endoneurial pericytes also exhibits paracrine activities by secretion of several growth factors that also assists in regulation of blood-nerve barrier (BNB) functions. During the loss of pericytes at the time of diabetes progression, its paracrine activities are mostly reduced that eventually leads to BNB disintegration and development of diabetic neuropathies [31]. But, still the exact mechanistic role of pericyte loss in context of diabetic neuropathy initiation and pathogenesis remains to be identified.

Endothelial dysfunction

Endothelial dysfunction can be accounted as the initial pathological event towards the onset of micro-vascular alterations during diabetic neuropathy initiation [33,34]. At the same time, it is also known as the most primitive change in arteriosclerosis in the development of diabetic autonomic neuropathy (DAN), the least recognized serious complications of diabetes and pre-diabetes [35]. The common vascular abnormality with endothelial dysfunction includes endothelial cell hyperplasia and hypertrophy, which significantly correlates with nerve pathologies from diabetic neuropathy patients [9,30,34]. As suggested by pre-clinical animal model and sural nerve based *in vivo* studies from distal symmetric polyneuropathy (DSP), the characteristic features of endothelial dysfunction includes endoneurial hypoxia, reduction in nerve blood flow and an enhancement in endoneurial vascular resistance [9,34].

Recently a cross-sectional, retrospective study on 112 diabetic patients in Japan have indicated that type 2 diabetes (T2DM) mediated impairment of endothelial dysfunction plays a leading role in pathogenesis of small fiber neuropathy (SFN) by an intensification of autonomic nerve damage. This vital clinical relationship was established by finding a strong association between reactive hyperemia peripheral arterial tonometry (RH-PAT), a non-invasive endothelial marker with parameters of Corneal confocal microscopy (CCM), a diagnostic modality for assessment of autonomic nerve damage in diabetic polyneuropathy (DPN) [33]. Moreover, a reduced expression of endothelial constitutive nitric oxide synthase (ecNOS) in the skin of diabetic neuropathy patients is also involved in the endothelial dysfunction. The occurrences of endothelial dysfunction in diabetic neuropathy are crucially associated with the development of diabetic foot ulceration (DFU), a severe complication of uncontrolled diabetes that generally affects the planter areas of the foot [36]. Although, a number of factors are linked with the progression of diabetic foot ulceration (DFU), but endothelial dysfunction is primly responsible for reduction of vasodilatory response in diabetic foot that eventually leads to ischemia and impairment of wound healing [33,36].

Blood-nerve barrier (BNB) destruction

An increasing number of clinical reports indicate that destruction of blood-nerve barrier (BNB) plays a predominant role in onset and pathophysiological expansions of diabetic neuropathies and related immune-driven complications like multifocal motor neuropathies (MMN) and chronic inflammatory demyelinating polyrediculoneuropathies (CIDP) [37]. Actually, blood-nerve barrier (BNB) functions as a peripheral nerve based capillary defense system that regulate the interactions between endoneurial micro-capillaries with central most layer of the multilayered perineurium in one hand and in other hand strictly restricts the passage of pathogenic leukocytes and undesirable soluble mediators, like cytokine, chemokine etc. from blood circulation to peripheral nerve parenchyma [37,38]. Diabetes induced morphological alterations in endoneurial micro vasculatures like micro-vascular occlusion, endothelial cell hyperplasia, disorganization of endothelial cell associated tight junctions, widening of micro-vascular basement membrane and degeneration of micro-vessel associated pericytes are typical indicators of BNB disintegration during the course of diabetic peripheral neuropathies (DPN) [38].

Although, the exact mechanistic basis of BNB destruction is not properly known due to limitations of in-vitro studies and challenges in establishment of human cell lines from pericytes and endothelial cells derived from BNB [37,38]. As per existing

information, the key steps of BNB destruction generally include an increase in BNB permeability, inflammation, endonureal hypoxia and pericyte degeneration. A local or systemic enhancement in BNB permeability's by different types of neuronal damage, such as peripheral nerve injury plays a pivotal role in induction of nerve edema, disruption of BNB and subsequent genesis of diabetic neuropathies [31,37,38]. The characteristic feature of pathological destruction of BNB mainly includes para-cellular secretion of toxic molecules into nerve tissues and an increased expression of cell adhesion molecules on BNB surface, which stimulates activation of local inflammatory signaling by an enhancement of trans-cellular migration of immune cells into the endoneurium [31]. The initiation of BNB disruption is largely linked with an exacerbation of diabetic neuropathies and associated pains through simultaneous activation of different pathological events, including peripheral nerve specific homeostasis disruption, local inflammation induction, impairment in capillary barrier function, obstruction in microcirculation, stimulation of axonal degeneration and Schwann cell damage [37,38].

Metabolic dysregulation

Metabolic abnormalities are recurrently responsible for outset of diabetic neuropathy and their aggressive clinical manifestation. A growing number of clinical studies have indicated the most possible involvement of metabolic syndrome and pre-diabetes in the genesis of neuropathy related complications [10,17,21]. Diabetes associated metabolic imbalances, namely hyperglycemia, dyslipidemia and mitochondrial dysfunction, accompanied by alterations in insulin signaling functions in a coordinated manner that together with other risk factors activates several metabolic as well as cell signaling pathways and mainly induces metabolic nerve injury. This metabolic dysregulation plays a central most role towards promotion of major pathophysiological alterations, such as segmental degeneration, Schwann cell dysfunction, peripheral nerve degeneration, microvascular changes and DRG neuronal apoptosis, which are intrinsically involved in establishment of diabetic neuropathy [2,3,15,17,21].

Hyperglycemia

Chronic hyperglycemia is one of the crucial diabetic risk factor that particularly plays a vital role in diabetic neuropathy initiation and progression (Figure 2). Chronic hyperglycemia driven neurotoxic mechanisms are predominantly involved in progressive damage of parasympathetic and sympathetic nervous systems in both peripheral and autonomic diabetic neuropathy [5,15,17,30]. The duration of hyperglycemic state along with other metabolic determinant actively drives nerve dysfunctions by mediating oxidative stress, inflammation and alterations in gene expressions in several cell types, including neuronal, glial and vascular cells. Depending on patients age, duration of diabetes, overall disease profile and cell types, the hyperglycemic state triggers dysregulation of several metabolic pathways, such as glycolysis, hexosamine and polyol pathways that eventually causes neuronal cell apoptosis, mitochondrial dysfunction, oxidative stress induction and DNA damage and ultimately leads to diabetic neuropathy development [2,3,5,17,30]. Apart from this, long term hyperglycemia are also significantly linked with acquisition of diabetic neuropathy associated critical features, such as autonomous dysfunction, epineurial metabolic shunting, hypoxic microenvironment and peripheral nerve damage [30].

Persistence of hyperglycemia for a long period of time in diabetic patients often causes metabolic imbalance, which in due course mediates nerve injury, neuronal dysfunction and apoptotic cell death [2,3,5,17,30]. This hyperglycemia associated metabolic imbalance is mainly modulated by alterations in insulin resistance and decrease in insulin signaling, that essentially fuels several metabolic aspects of diabetic neuropathy progression. The hyperglycemia modulated metabolic aspects are advanced glycation end-products (AGEs) formation, reduction in cellular anti-oxidants levels, increase in lipid peroxidation mediated peripheral nerve injury, loss of neurotrophic signaling, stimulation of pro-inflammatory transcription factors and induction of endoplasmic reticulum stress [2,5,39]. Long term hyperglycemia in association with dyslipidemia and insulin resistance mediates an activation of AGE, polyol, PKC and poly (ADP-ribose) polymerase (PARP) signaling pathways in peripheral nerves that together subsequently leads to amplification of downstream events, like endoplasmic reticulum stress, cellular edema, inflammation

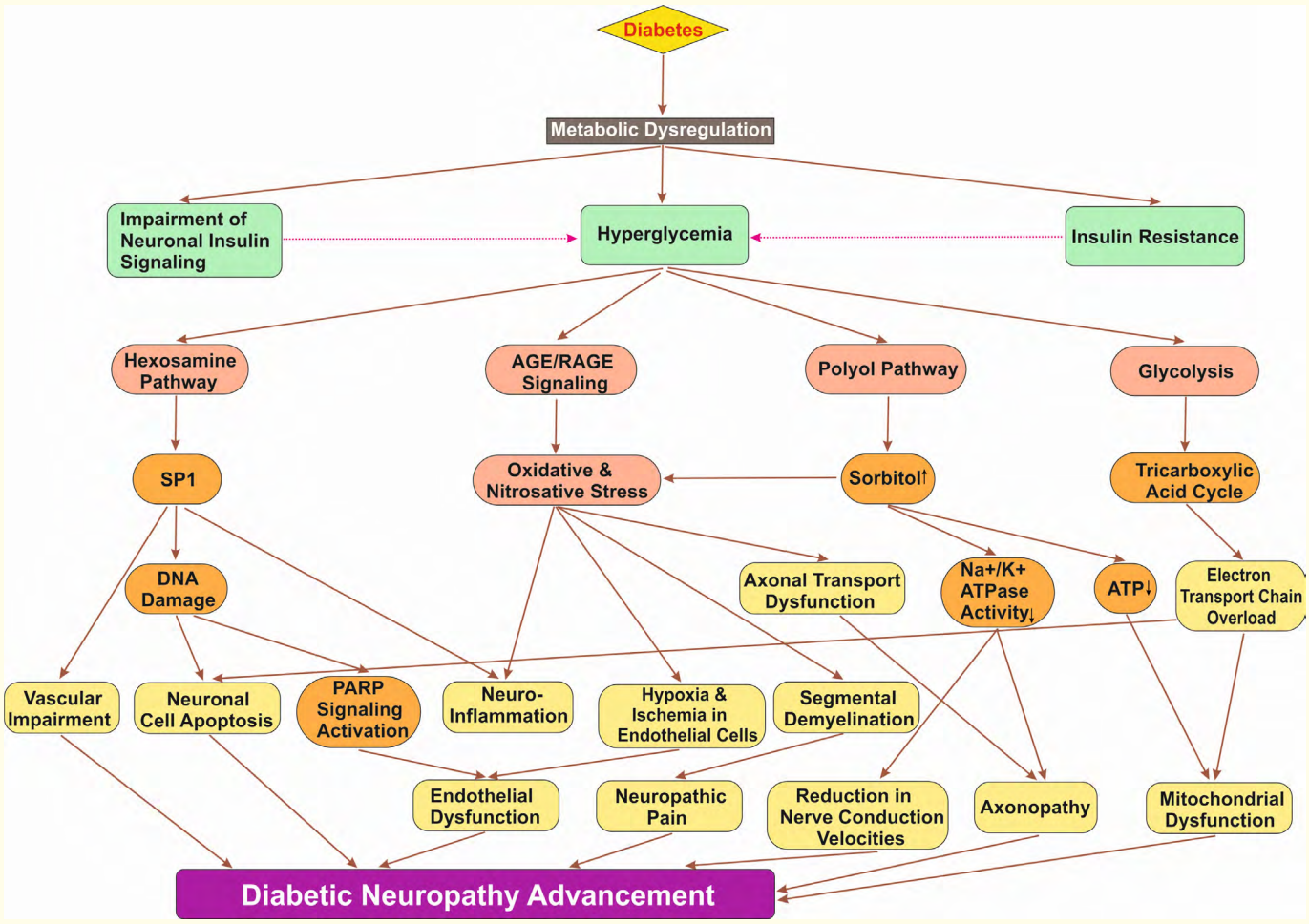

Figure 2: The role of hyperglycemia in diabetic neuropathy pathogenesis.

Diabetes induced metabolic dysregulation strongly modulates hyperglycemia associated neurototxic mechanisms through impairment of neuronal insulin signaling and alterations in insulin resistance. The duration of hyperglycemic state triggers activation of several metabolic pathways, like glycolysis, hexosamine, AGE/RAGE and polyol pathways, which collectively drives pathological alterations in neurons and vascular cells. Hyperglycemia induced pathological alterations are neuronal cell apoptosis, mitochondrial dysfunction, DNA damage, neuroinflammation, segmental demyelination and endothelial dysfunction. These factors together with other major neurophysiological alterations like axonopathy, neuropathic pain generation and reduction in nerve conduction velocities are involved in the promotion of diabetic neuropathy advancement. The role of hyperglycemia in development of diabetic neuropathy depends on a number of factors including duration of diabetes, patient's age, cell types (neuronal, vascular) and disease profiles.

and mitochondrial dysfunction (Figure 2). Hyperglycemia in Schwann cell plays a major role in increased activation of late-stage metabolic events accompanied by an accumulation of toxic metabolic intermediates that promotes axonal degeneration and diabetic peripheral neuropathy advancement [5,6].

Dyslipidemia

Lipids are basic structural components of the nervous system and their metabolic dysregulation are increasingly believed to be implicated in diabetic neuropathy development (Figure 3). Dyslipidemia or changes in serum lipid profiles, such as free fatty acids, triglycerides, medium-chain acyl carnitines, phosphatidyl cholines and lysophosphatidyl cholines are intrinsically involved in diabetic neuropathy pathogenesis [3,17,39]. According to a recently conducted meta-analysis covering 32,668 patients including diabetic neuropathy, it has been indicated that an alterations in serum lipid profile can be accounted as one of the pathobiological characteristics in diabetic neuropathy. In the corresponding meta-analysis of 39 different clinical trials, it has been suggested that an increase in serum levels of triglyceride and low-density lipoproteins (LDL) enhances the risks for diabetic neuropathy predisposition [40]. In addition, in several cases it has been found that diabetic patients with an up to standard glycemic control (HbA1c) can also develop diabetic neuropathy, which essentially suggests for the presence of an independent driving factor other than hyperglycemia [39-41]. Patients with type 2 diabetes (T2DM) generally exhibit an abnormal serum lipid profile during early phase of the disease, which significantly correlates with clinical progression of diabetic neuropathy [40].

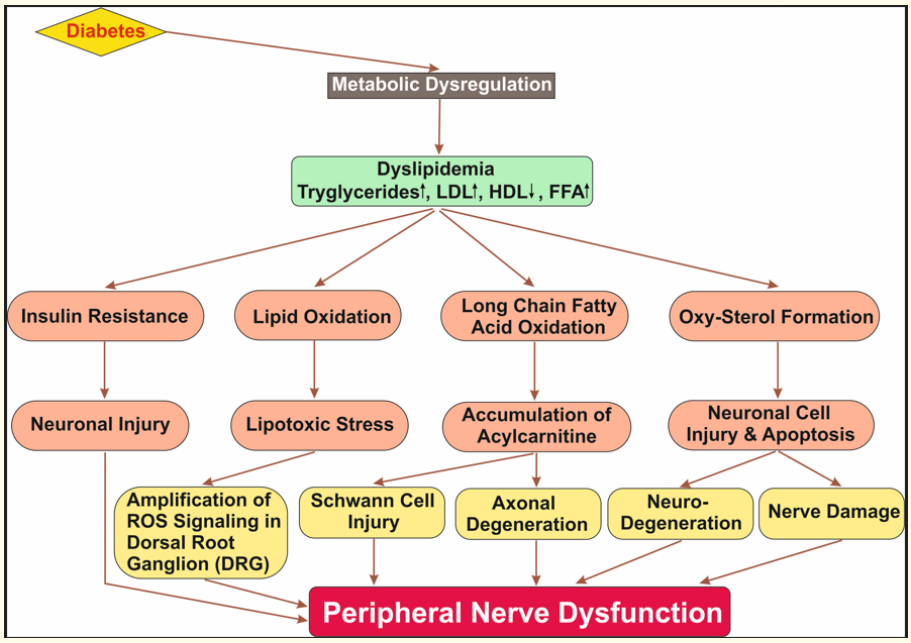

Figure 3: The role of dyslipidemia in diabetic neuropathy advancement.

Dyslipidemia is a major contributor in diabetes induced metabolic dysregulation and plays a vital role in shaping the advancement of diabetic neuropathy. Dyslipidemia is typically characterized by an alteration in lipid metabolism, including an increase in serum levels of free fatty acids (FFA), triglycerides, low-density lipoproteins (LDL) and concomitant decrease in high-density lipoproteins (HDL). An abnormality in lipid profile significantly influences the onset of diabetic neuropathy and its associated symptoms by an increase in oxidative environment, like lipid oxidation, long chain fatty acid oxidation, oxy-sterol formation and insulin resistance. The progressive rise in lipotoxic stress subsequently triggers an acquisition of late stage pathological events in neurons, such as Schwann cell injury, neurodegeneration, axonal degeneration and dorsal root ganglia neuronal damage. The ultimate consequence of this nerve damaging pathophysiological alterations mainly drives peripheral nerve dysfunction and diabetic neuropathy advancement.

An acquirement of dyslipidemia during diabetes progression significantly influences several pathophysiological features, like insulin resistance, inflammation, oxidative stress and segmental demyelination, which in a complex mode of interactions subsequently triggers neuropathy onset and its advancement [17,39-41]. Diabetes induced increase in oxidation of low-density lipoproteins (LDL) cholesterol markedly triggers production of reactive oxygen species (ROS), which is mechanistically linked with diabetic neuropathy pathogenesis by mediating a variety of downstream events, namely modulation of oxidative microenvironment, induction of pro-inflammation, changes in neuronal electrical properties and mitochondrial dysfunction [39]. Dyslipidemia promotes diabetic neuropathy advancement by two different ways- first, by an amplification of ROS mediated stress signaling in dorsal root ganglion, which largely stimulates peripheral nerve injury [39,40]. Second, by enhancing Schwann cell injury and axonal degeneration through an accumulation of neurotoxic acylcarnitines by activation of long chain fatty acid associated beta-oxidations [3,5].

Alteration in insulin signaling

A dysregulation of insulin signaling is supposed to be involved in peripheral nervous system dysfunction and development of diabetic neuropathy associated symptoms [5]. Impairment in neuronal insulin signaling can be regarded as the core pathogenic mechanisms of diabetic neuropathy that can function independent of hyperglycemia. In actual fact, a reduction in insulin signaling is mainly responsible for intensification of hyperglycemia driven neuronal damages due to its inability to repair corresponding damaging sites in peripheral nerve as a consequence of loss in insulin responsive trophic support [42]. Numerous studies have indicated the role of insulin signaling for maturation and physiological functioning of peripheral nerves, which is drastically impaired during the onset of diabetic neuropathy. Even though, the exact mechanism of neuronal insulin signaling dysfunction in context of diabetic neuropathy remains unidentified, existing reports suggests for the involvement of core insulin signaling machineries, including insulin, IGF1 and PI3K/AKT/MTOR signaling in this event [43]. More specifically, insulin associated metabolic dysfunction in Schwann cells are also crucially involved in axonal dysfunction, sensory neuronal impairment and impairment of developmental myelination, which concomitantly fuels diabetic neuropathy progression [43]. Several pre-clinical experimental rodent models, such as Streptozotocin (STZ) induced rat model, $IGF1^{-/-}$ rodents and normoglycemic pre-diabetes model have demonstrated the potential role of insulin insufficiency in diabetic neuropathy pathogenesis and neuropathic pain generation [42,43].

Mitochondrial dysfunction

Mitochondrial dysfunction along with its involvement in stress generation plays a paramount role in diabetic neuropathy advancement. Mitochondria generated oxidative damage in axons, Schwann cells and dorsal root ganglion (DRG) neurons are centrally involved in the development of dying back neurodegeneration during diabetic neuropathy progression [44,45]. The presence of hyperglycemic stress during attainment of diabetic state causes major damage of mitochondrial structural units and associated functions, including destruction of mitochondrial electron carriers, reductions in respiratory chain activities, depletion of mitochondrial DNA contents in DRG neurons and depolarization of inner mitochondrial membrane potentials [17,46]. Furthermore, diabetes associated metabolic dysregulation, like dyslipidemia mediates an extensive amplification of mitochondrial dysfunctions in sensory nerves and DRG neurons [17,45]. As a consequence, diabetes induced mitochondrial alterations, such as an enhancement in ROS signaling, decrease in ATP generation, impairment in axonal transport, impairment in intra-mitochondrial calcium regulation and an induction in neuronal apoptosis in conjunction with other risk factors collectively drives axonal degeneration in peripheral nervous system [44-46]. Studies with a variety of pre-clinical diabetic neuropathy models have exhibited the possible role of mitochondrial dysfunction in diabetic neuropathy pathogenesis, such as significant alterations in mitochondrial ultra structure, oxidative stress related adaptations in mitochondrial functions and disruption of axonal transport processes that somehow increase the overall clinical complexities and severities of diabetic neuropathy progression [44]. Most essentially, these pre-clinical animal models also suggests for the potential role of NAD^+ responsive SIRT1-PGC1alpha-TFAM signaling axis in emergence of diabetic neuropathy associated characteristic metabolic phenotypes, inclusive of repression in mitochondrial oxidative metabolism and overreliance over anaerobic glycolysis [44,46].

Inflammation

Chronic subclinical inflammation that functions as a vital link between diabetes and obesity plays an important role in genesis

and clinical establishment of diabetic neuropathy (Figure 4) [47]. During the initial phase of diabetes development, several risk factors like insulin resistance and an increase in adiposity triggers endothelial dysfunction along with inflammatory responses that progressively mediates dysfunction of peripheral nerves by damaging both large and small nerve fibers [48]. Numerous pre-clinical studies have indicated the crucial role of pro-inflammatory cytokines (IL-1, IL-6, IL-8, MCP-1, TNF-A, IFN-G, CRP) and chemokines (CXCL1, CXCL5, CXCL9, CXCL12) in the amplification of inflammatory responses towards neuronal damage and initiation of diabetic neuropathic pain [47,48]. The current state of diabetic neuropathy research emphasizes for the role of diabetes induced dysregulation of neuro-inflammatory systems that eventually increases the aggressiveness and clinical severity of diabetic neuropathy (Figure 4). This neuro-inflammatory remodeling is closely linked with the development of diabetic neuropathies by several ways, like stimulation of pro-inflammatory mediators production by supporting activation of vicious feedback loop between different infiltrated immune cells, myelin sheath damage associated increase in nerve excitabilities and induction of nerve damage through an increase in MAPK signaling mediated neuronal cell apoptosis [49].

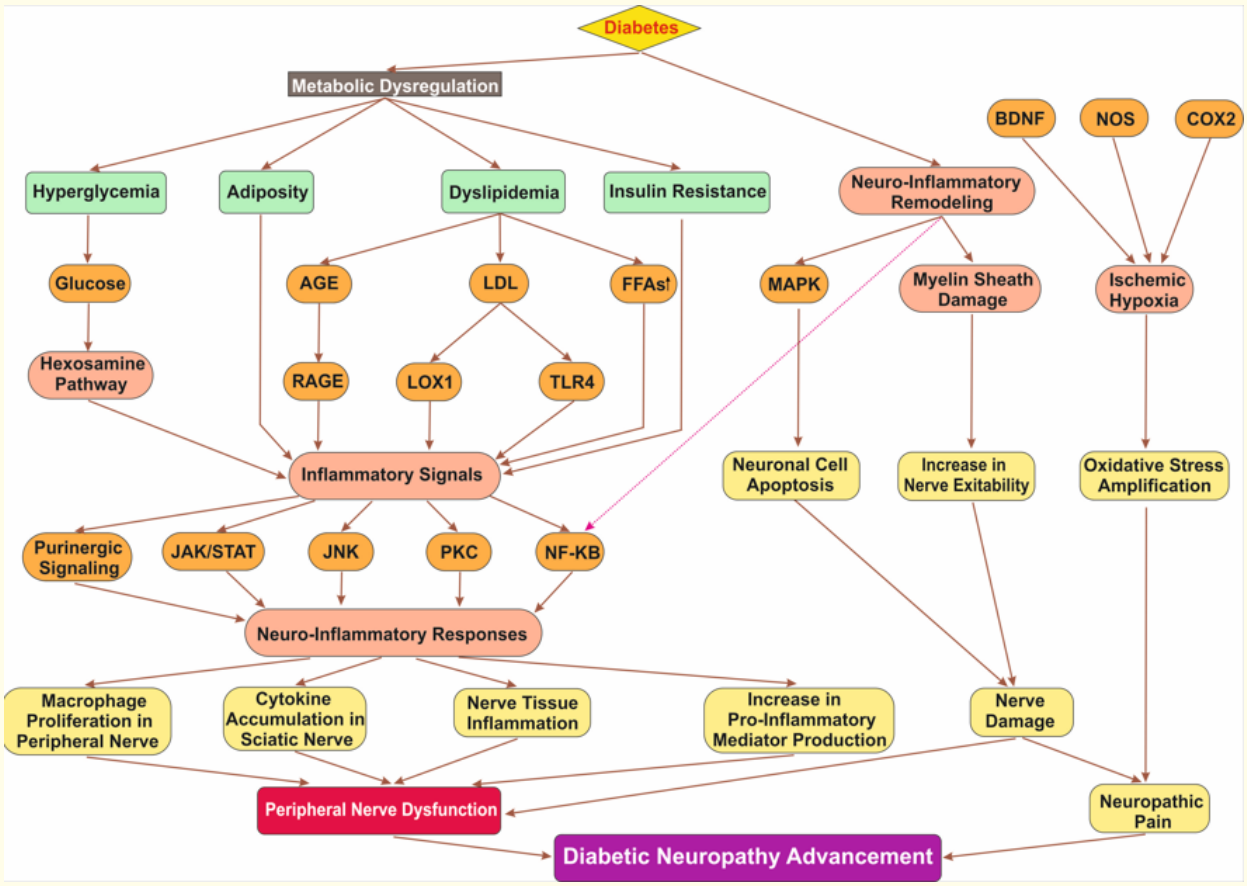

Figure 4: The role of inflammation in diabetic neuropathy pathogenesis.

Diabetes associated metabolic dysregulation critically induces inflammatory signal generation through stimulation of different metabolic pathways and risk factors, such as hyperglycemia, dyslipidemia, adiposity and insulin resistance. These inflammatory signals, on the other hand drives development of neuro-inflammatory responses through activation of diverse cell signaling pathways, like JAK/STAT, NF-KB, JNK, PKC and purinergic signaling. Diabetes induced neuro-inflammatory responses principally drives peripheral nerve dysfunction through a variety of means, including nerve tissue inflammation, increase in pro-inflammatory mediator production, cytokine accumulation in sciatic nerve and macrophage proliferation in peripheral nerve.

Glial cells including microglia and astrocytes from the central nervous system (CNS) and peripheral nervous system (PNS) plays a modulatory role in amplification of neuro-inflammatory responses with regards to the development of painful diabetic neuropathies. The nerve damaging effects of glial cells are mainly accomplished by secretion of cytokines and chemokines through activation of multiple signaling pathways, like JAK/STAT, NF-KB/TLR, and purinergic signaling. In addition of these pathways, other signaling axis including MAPK, protein kinase C (PKC) and jun N-terminal kinase (JNK) also essentially participates in inflammatory processes in response of hyperglycemia and dyslipidemia associated oxidative/nitrosative stresses. All of this stress associated signaling pathways are ultimately involved in production of pro-inflammatory cytokines and chemokines, which eventually leads to neuronal damage by enhancement of inflammatory responses and further activation of vicious cycles of oxidative/nitrosative stresses [48,49]. Moreover, induction of neurotrophic factors, like BDNF from microglia and activation of enzymeslike nitric oxide synthase and COX2 also participates in neuronal damage and exacerbation of diabetic neuropathy associated pains through promotion of ischemic hypoxia and amplification of oxidative/nitrosative stresses. In this major context, redox-sensitive transcription factor NF-KB functions as the master regulator in manifestations of inflammatory responses in relation to diverse range of stimuli, such as pro-inflammatory mediators, oxidative stress and hyperglycemic stress. From mechanistic point of view, NF-KB regulates majorities of diabetic neuropathy associated inflammatory gene expressions, including lipoxygenase, NO-synthase, endothelin-1 and COX-2 [48].

Concluding Remarks

The current therapeutic modalities including pharmacological manipulation and combinatorial treatment approaches are mostly unable to effectively prevent either diabetic neuropathy associated alterations or alleviation of its total pain symptoms. At the same instant, disease modifying treatments for diabetic neuropathy that have the potential to crucially impacts the natural history of neuropathy progression are mainly lacking. At this present situation, our currently proposed mechanistic framework may provide an unique opportunity to intensely characterize the pathophysiological basis of diabetic neuropathy advancement. Most especially, a patient centric assessment of diverse pathophysiological features across different neuropathy clinical sub-types may represent a real world foundation for both mechanisms based pharmacological treatment in diabetic neuropathy and its phenotype-based patient stratification. In this regard, a detail further characterization of mechanistic basis of peripheral nerve damage including its morphological alterations, changes in myelinated nerve fiber densities, mode of axonal dysfunction, degeneration of small sensory nerve fibers, appearances of Schwannopathy like features, identification of nerve regeneration associated pathways and profiling of sensory phenotypes will essentially support in fine classification of diabetes associated neuropathic pain symptoms along with tailoring of diabetic neuropathy treatment. At the same time, the proposed framework can also effectually assist for development of multi-target therapeutic approach in diabetic neuropathy by attainment of patient specific metabolic control. Because, achievement of metabolic control in diabetic neuropathy is a difficult task as an intensive glycemic control cannot properly prevent neuropathy progression in patients with type 2 diabetes. In this major context, a precise evaluation of patient specific metabolic dysregulation pattern or diabetes induced metabolic reprogramming in peripheral nerves, such as hyperglycemia, dyslipidemia, insulin signaling, insulin resistance and mitochondrial dysfunction may offer an exclusive means to individualize multi-target therapeutic strategies in diabetic neuropathies. And finally, for application of currently offered mechanistic framework in diabetic neuropathy precision medicine, an urgent initiative is required for identification, clinical validation and paneling of prospective and predictive biomarkers of different categories, such as oxidative biomarker, inflammatory biomarker and enzymatic biomarkers for increasing the accuracies in precision diagnosis and prognosis.

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Declaration of Competing Interest

The authors declare no potential conflict of interest.

Author's Contribution

DD and SPH are mainly involved in study conceptualization, DD searched the literature, all authors contributed in formal analysis and validation, DD has written the original manuscript, all authors equally contributed in manuscript review and editing, SPH supervised the overall study. All authors provided their final approval for manuscript submission.

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