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Diabetic Neuropathy: A Review

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Abstract
The present review is to avail the comprehensive information on the pathgenesis and treatment of diabetic neuropathy. Diabetic neuropathy is the most common form of neuropathy in the developed countries. Diabetic neuropathy has been defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes which may range from hereditary, traumatic, compressive, metabolic, toxic, nutritional, infectious, immune mediated, neoplastic, and secondary to other systemic illness. Both metabolic alternations in the cellular components (mainly neurons and Schwann cells) and microvascular abnormalities are though to play major roles in the development of diabetic neuropathy Several possible mechanisms have been proposed in the pathogenesis of diabetic neuropathy including altered metabolism of polyol, lipids, or amino acids, vascular insufficiency, increased superoxide – induced free radial formation etc. Pain in diabetic neuropathy has found to be multifactorial.

Keywords: diabetes, neuropathy, hyperglycemia, nerve defects

Introduction
Diabetic neuropathies are the complex, heterogenous disorders that encompass a wide range of abnormalities affecting both peripheral and autonomic nervous system causing considerable morbidity and mortality [1]. Diabetic neuropathy is one of the most common disease of nervous system, usually more than 50% the patients with duration of diabetes of 25 years or more develop diabetic neuropathy [2]. Diabetic neuropathy has been defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes [3], which may range from hereditary, traumatic, compressive, metabolic, toxic, nutritional, infectious, immune mediated, neoplastic, and secondary to other systemic illness. Since the manifestations of diabetic neuropathy closely mimic chronic inflammatory demyelinating polyneuropathy, alcoholic neuropathy, and other endocrine neuropathies, hence, before labeling diabetic neuropathy it is mandatory to exclude all other causes of peripheral nerve dysfunction [4].

Epidemiology
Diabetic neuropathy is the most common form of neuropathy in the developed countries of the world., accounts for more hospitalizations [5] than all the other diabetic complications combined and is responsible for 50% to 75% of non-traumatic amputations [6]. Approximately 50% of patients who have had diabetes for >25 years are expected to develop neuropathy [7]. Approximately 50% present with pain as a symptom of neuropathy [8].

Hyperglycemia has been reported to be highly correlated with the development and progression of all neuropathies [9]. The Diabetes control and complications Trial (DCCT) has shown that tight glycemic control can reduce the incidence of neuropathy by 60% [10].

Other risk factors found to be associated with diabetic neuropathy are hyperlipidemia, hypertension, cigarette smoking, consumption of alcohol and increased body weight. Although there have been no trials that show a reduction in neuropathy when addressing these modifiable risk factors, these factors are generally addressed in patients with diabetes to prevent other long-term complications, such as coronary artery disease, peripheral vascular disease and stroke [11].

Classification and Clinical characteristics of diabetic neuropathy
a. Distal Symmetrical sensori-motor polyneuropathy
It is the most common type of diabetic neuropathy. It involves predominantly large fibres [12], small fibres are less commonly involved. Hypoaesthesia is often present [13]. The lesions found in peripheral nerves are usually fairly symmetrical, are ofter most extensive in the distal portions, and practiculary affect the sciatic nerves and their branches [14].

It has been described as predominantly sensory neuropathy, with autonomic involvement which is usually subclinical [4]. Symptoms may appear in the sole of one foot a few days or a week before the other but usually the patient describes a graded disturbance that moves finally symmetrically in centripetal fashion [15]. Haemorhelogical changes may play a part in the pathogenesis of DSP [16].

b. Autonomic Neuropathy (AN)
Autonomic neuropathy has been described as a frequent and often disabling complication of diabetes mellitus [17], These may affect any tissues receiving autonomic innervation but fortunately symptoms of AN, which may be severely disabling, are relatively infrequent [18]. The clinical features of diabetic AN have been considered according to system affected which involves cardiovascular system, respiratory system, Urogenital system, sweating abnormalities, alimentary system and pupils [19]. It has been reported that neuroadrenergic bronopulmonary denervation may occur in diabetic patients with AN despite normal clinical and

respiratory function finding. Diabetic AN has been found to be associated with an impaired vasodilator response of coronary resistance vessels to increased sympathetic stimulation, which is related to the degree of sympathetic nerve dysfunction [20]. A greater prevalence of parasympathetic as compared to sympathetic impairment in diabetic autonomic neuropathy has been demonstrated [21]. The prevalence of cardiac autonomic neuropathy in diabetes mellitus is found to be high [22]. AN is reported to be associated with exercise test parameters and a coronary risk factor profile indicating a high risk of future coronary heart disease [23]. Apart from hyperglycaemia, retinopathy [24] and cardiovascular risk factors e.g. hypertension [25], has shown to predict the risk of AN.

The cardiovascular symptoms and signs, which are thought to be associated with CAN include lack of heart-rate variability, resting tachycardia, limited exercise tolerance and abnormal circadian pattern of blood pressure [26]. To diagnose CAN, QTC interval [27] and ECG [28] could be used with reasonable sensitivity, specificity and positive predictive value.

c. Proximal motor neuropathy

This has been found to be relatively uncommon neuropathy, previously known as 'amyotrophy", has most often seen in older patients with NIDDM particularly males [18]. This has been clinically identified based on proximal muscle weakness and muscle wasting. It may be symmetric or asymmetric in distribution, and is sometimes found to be associated with pain in the lateral aspect of the thighs [12]. Weakness of the proximal muscle makes climbing stair impossible [18].

d. Focal neuropathics or mono-neuropathies

A variety of asymmetric and focal neuropathies may occur independently of peripheral and autonomic neuropathy. It has been described that a minimal degree of background damage in diabetic patients may render them more susceptible [29].

1. Cranial Neuropathy

This mononeuropathy has been found to affect the intraocular nerves (III, IV, VI) and possibly the facial nerve [13]. The third and sixth cranial nerves have been reported tobe affected most often [30]. The occulomotor neuropathy has been described as most frequent. The onset is abrupt and is usually a "medical" third nerve palsy with sparing of the pupils [18].

2. Truncal Neuropathy

It is a less common neuropathy and usually presents with gradual onset of pain and dysthesia in the lower anterior chest or upper abdomen with nocturnal intensification [4]. The distribution of sensory abnormalities in diabetic truncal neuropathy are highly variable [31]. A manifestation of diabetic truncal neuropathy masquerading as abdominal hernia has been described [32]. The potential presence of a diabetic truncal neuropathy should be considered in patients with diabetes who have a painful abdominal mass [33].

3. Entrapment neuropathy

The entrapment neuropathies are described as highly prevalent in the diabetic population. Common entrapments involve the median, ulnar and peroneal nerves, the lateral cutaneous of the thigh, and the tibial nerve in the tarsal canal [34]. The metabolic and phenotypic abnormalities of endoneurium and perineum lie beind the vulnerability of diabetic patients to entrapment neuropathy [35].

Pathogenesis of Diabetic Neuropathy

Despite considerable research the pathogenesis of diabetic neuropathy is still unclear [36]. A variety of hypothesis, including biochemical and vascular factors for the pathogenesis of this complication have been proposed [37]. It is not know whether the primary pathology is metabolic, microvasculaor, or and interaction between the two [36]. Both metabolic alternations in the cellular components (mainly neurons and Schwann cells) and microvascular abnormalities are though to play major roles in the development of diabetic neuropathy [38]. The etiology of diabetic neuropathy is complex and multifactorial [39]. Several possible mechanisms have been proposed including alteed metabolism of polyol, lipids, or amino acids, vascular insufficiency, increased superoxide – induced free radial formation etc. [40]

a. Hyperglycaemia

A number of clinical and epidemiological studies suggest that the magnitude and duration of hyperglycaemia is an essential element for the development of chronic complications of diabetes mellitus including diabetic neuropathy [2]. It is well recognized that the degree and duration of hyperglycaemia correlates with the appearance and severity of the damage to the nervous tissue. Poor glycaemic control has been proposed to be the major determinant of susceptibility and severity of neuropathy [41]. The randomized prospective study by the Diabetes Control and Complications Trial (DCCT) has shown the significant reduction in the development and progression of clinical neuropathy (64%) motor conduction velocity (44%) and autonomic dysfunction (53%) in type-I diabetics with optimal gylcaemic control [42]. The small nerve fibre involvement has been suggested as the earliest detectable sign of neuropathy associated with impaired glucose tolerance [43]. Improving hyperglycaemia by more intensive insulin therapy [42] improves electrophysiology in patients with type I diabetes. The mechanisms that mediate the adverse effects of hyperglycaemia include extracellular monenzymatic glycation processes, sorbitol accumulation through abberant aldose reductase enzymatic activation and alterations of various signal pathways like diacylglycerol (DAG) progein kinase C (pkc) pathway [44].

In both humans and laboratory animals, the progressive nerve fibre damage and loss associated with the distal symmetric sensorimotor polyneuropathy, the most common form of neuropathy associated with diabetes mellitus, parallels the degree and duration of hyperglycaemia [45].

b. Polyol Pathway

There is ample evidence to implicate the involvement of the involvement of sorbitol or polyol pathway in the pathogenesis of diabetic neuropathy [46]. Chronic hyperglycaemia of diabetes results in elevated intracellular glucose levels which has to be metabolized in alternative pathway [2]. The rate limiting enzyme aldose reductase for polyol pathway has been found to be expressed in Schwann Cells [38]. The polyol pathway consists of two enzymes. The first enzyme, aldose reductase, reduces glucose to sorbitol with the aid of its co-factor NADPH, and the second enzyme, sorbitol dehydrogenase, with its co-factor NAD+., converts sorbitol to fructose. Fructose and sorbitol both being osmotically active compounds lead to increase in the water content in the nerves [45]. Accumulation of sorbitol in the cell leads to a cascade of metabolic abnormalities like hypoxia, pseudohypoxia and tissue is ischaemia [41]. Further the oxidation/ reduction state of the cell is altered with loss of reduced nicotinamide-adenine dinucleotide phosphate (NADPH) and glutathione stores. It leads to a cascade of events like reduced membrane Na^+ - K^+- ATPase activity, intra axonal sodium accumulation which reduces nerve

conduction velocity and brings abut structural breakdown of the nerve [45]. Enzyme aldose reductase is the major contributor to hyperglycaemia induced oxidative stress in the nerve [47]. Various scientific data implicate sorbitol and glucose induce myoinositol depletion [46] and altered phosphoinositide metabolism [48] in a series of biochemical and functional abnormalities in peripheral nervous system in diabetes. This in combination with glycolysis, is able to alter intracellular redox balance [2]. Other available evidences suggest that the polyol pathway hyperactivity results in lowering protein kinase C activity [49] and CAMP reduction in sciatic nerves which may be closely related to the pathogenesis of diabetic neuropathy [50]. Recently increasing evidence suggests that glycation and oxidative stress [47] have a cross link with polyol pathway. Furthermore, a close relationship between increased polyol pathway activity and carnitine deficiency in the pathogenesis of diabetic neuropathy as been suggested [37]. Qates supported the hypothesis that the metabolic flux through the polyol pathway, rather than concentration of corbitol in the nerve is the predominant pathogenetic factor in diabetic peripheral nerve [51]. Collectively, the polyol osmotic theory, alterations in myo-inositol and sodium metabolism, intermediatory metabolites, abnormal changes of the redox state ($NADH/NAD^+$ ratio) and an abnormality of kinase C dependent protein phosphorylation have been proposed as the pathogenetic factor in diabetic neuropathy.

c. Advanced glycation and products (AGEs)

Formation of advanced glycation end product (AGE) is another important factor for the development of peripheral neuropathy. The levels of AGEs have been found to be increased in the serium and also in peripheral nerves obtained from diabetic patients. Structural and functional proteins of these nerves are also glycated, which results in impaired nerve function and characteristic pathologic alterations [52]. A series of spontaneous and non-enzymatic reactions between glucose and proteins have been found to occur in both intra and extra cellular compartments. This non-enzymatic glycation of proteins by reducing sugars which occur in a cascade of complex reactions has been reported to result in beterogenous class of components which have been classified as AGEs [53]. This has been demonstrated that these reactions are favoured by hyperglycaemia [54]. AGEs in humans have been predominantly chemically characterized by the detection of pentosidine and N-carboxy-methyl lysine [55]. AGEs have been found to act directly to induce cross-linking of long-lived proteins such as collagen to promote vascular stiffness and alter vascular structure and function [56] and secondly, they have been reported to act on specific receptors for AGEs (RAGE). AGEs with RAGE alter intracellular signaling, gene expression, release of pro-inflammatory molecules and free radicals [57].

RAGEs have also been reported to induce phosphatidylinositol-3 kinase activity which is found to be associated with formation of reactive oxygen species, caspase – 3 activation, and nuclear DNA degradation [58]. Recently one evidence has been provided by experiental diabetic neuropathy models that RAGE and RAGE-dependent sustained activation of the protein transcription factor nuclear factor kappa B might significantly contribute of reduced nociception to support the molecular mechanisms underlying loss of pain perception in diabetic neuropathy [59].

d. Miscellaneous

1. Free radical and oxidative stress

It has been demonstrated that free radicals and oxidative stress could damage nerve by direct toxic effects or with different biochemical changes that lead to endothelial dysfunction, the most important is the inactivation of nitric oxide, which is key to maintaining vascular tonus [60]. The nerve blood flow is reducted due to an increased ratio of free NADH/ NAD^+. which has been found to be caused by increased oxidation of substrate, coupled to reduction of the co-factor NAD to NADH [2]. Proteins that are damaged by oxidative stress have shown decreased biological activity which lead to loss of energy metabolism cell signaling, transport and, ultimately to cell death [61]. A clinical evidence demonstrates the role of free radicals in diabetes-induced congenital malformations [62]. In diabetic tissues, free radical generation has reported to be enhanced by the process of non-enzymatic glycation [58] and polyol pathway [47]. Additionally, other mechanisms have also been implicated in the development of oxidative stress which include overproduction of superoxide by the mitochondrial electron transport chain [63] and ischemia reperfusion injury [64].

2. Nitrosative Stress

The role of reactive nitrogen species in pathogenesis of peripheral diabetic neuropathy has been demonstrated in two experimental models of Type – I diabetes mellitus. Nitrosative stress is a major contributor to energy failure in experimental diabetic neuropathy [65] Nitrosative stress has been reported to have a important role in functional abnormalities associated with large motor, large scnsory, and small sensory fiber neuropathy [66].

3. Biochemical Abnormalities

The activity of dopaminergic system in the nigrostristal pathway and the synthesis of norepinephrine and epinephrine have been reported to be reduced in diabetic neuropathy due to a reduced release from terminal vescicles [67]. Further, nerve blood flow and nerve oxygen tension have also found to be reduced in experimental diabetic neuropathy [68]. The axo-glial dysfunction in diabetic neuropathy has been implicated as fundamental interactive biochemical abnormalities which cause impairement of nerve conduction. These metabolic alternations were found to be initiated by insulin deficiency [69]. A study on electrophyscological and biochemical effects of exposure to 2,5 – hexanedione on peripheral nerve in experimental diabetic rats have given the hypothesis that workers with hyperglycemia could suffer from neuropathy due to exposure to n-hexane earlier than those without hyperglycemia [70]. Moreover, depletion of carnitine has been found in diabetic nerves which could impair ATP production and peripheral nerve function. Carnitine deficiency has bee found to be closely relayed to polyol pathway hyperactivity [57]. Activication of P38 MAP Kinase, is also known to be activated in sensory neurons in both diabetic rats and humans [71].

4. Vascular and haemorrheological Abnormalities

Major structural and functional changes occur in diabetic neuropathy like thickening of endothelial in the endothelial basement which are reported to be involved in resulting nerve damage [72]. The cellular mechanisms for the development of diabetic endothelial dysfunction are reported to be non-enzymatic glycation and hyperglycaemia [60, 73]. At supraphysiological levels of plasma glucose, endothelium has found to loose its properties of anticoagulant [60]. Hypoxia has been reported to govern the expression of key response genes such as vascular endothelial growth factor and erythroprotein [74].

Defects in nerve regeration

Nerve growth factors (NGF) are responsible for regeneration of nerves. In experimental models of diabetes, a reduction in the availability of NGF, its high affinity neceptor, trk A has been found which leads to decreased support of NGF dependent sensory neurons [5]. Expression of their neuropeptides Substance P and calcitonin gene related peptide are also reduced that may contribute to the clinical symptoms resulting from small fiber dysfunction [5, 75]. Similarly, neurotrophin-3 (NT-3) has found to be important for large fiber and insulin like growth factors (IGFs) for autonomic neuropathy [5]. The insufficiency of IGF's may add to the pathogenesis of regenerative capacity, neurodegeneration and irreversible stages of distal peripheral neuropathy [76].

1. Pro-inflamatory mechanisms of diabetic neuropathy

Hyperglycaemia and dyslipidemia have been reported to give rise to oxidative stress [47, 60, 61] and formation of AGEs [56, 57]. Oxydative stress and AGEs have found to stimulate inflammatory processes with nuclear factor kappa-B (NF-kB) activation being of central importance [39]. The production of tumor necrosis factor-a (TNF-a) also found to be increased [77]. TNF-a impairs blood. It has cytotoxic effect on endothelial cell [15]. Under, chronic hyperglycemia, endogenous TNF-a production has reported to be accelaerated in microvascular and neuronal tissues, which may undergo an increased microvascular permeability, hypercoagubility, and nerve damage, thus initialting and promoting the development of characteristic lesions of microangiopathy and polyneuropathy [77].

Conclusion

Regardless of the exact pathogenesis of diabetic neuropathy, it is now clear that chronic hyperglycaemia has a pivotal role in the pathogensis of diabetic neuropathy. The earliest effects of hyperglycaemia are generally metabolic while electrophysiologic and morphologic changes are considered to be of late occurrence.

Pain in diabetic neuropathy has found to be multifactorial and could occur at different levels starting at the parasympathetic nervous system in the skin (C-Fibres) and migrating to involve A-beta and A-delta fibers. A predominant dageneration of small fibre has been implicated in the pathogenesis of pain in diabetic neuropathy by the finding that blood flow in the foot is sustainly increased in patients with diabetic neuropathy. The damaged sensory fibres have shown a higher concentration of sodium channels, an alternation that would increase spontaneous firing. Both, TTX-S and TTX-R sodium channels have been demonstrated to play important roles and that differential phosphorylation of sodium channels involving both serine/ threonine and tyrosine sites and contributes to painful diabetic neuropathy.

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