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PATHOGENESIS AND PREVENTION OF DIABETIC NEUROPATHY

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Abstract

Diabetic neuropathy (DN) has been considered as one of the most frequent and troublesome complications of diabetes mellitus. It is the foremost cause of morbidity and mortality among diabetic patients worldwide. In addition, it has been frequently associated with devastating pain. However, the complete knowledge of the history and pathogenesis of the disease remains limited but several mediators have been reported to be involved in the pathogenesis of DN that involve polyol pathway, increased formation of advanced glycation end products (AGEs), enhanced reactive oxygen species (ROS) generation and activation of protein kinase C (PKC). Moreover, management of patients presented with DN has been done by both pharmacological and non-pharmacological strategies. The review critically explains about the pathogenesis and treatment strategies available for the DN.

Keywords: Diabetic neuropathy, Diabetes mellitus, Pathogenesis.

Introduction

Diabetes mellitus (DM) is a metabolic disorders associated with insufficiency of insulin secretion, or insulin action characterized by hyperglycemia [1-2]. It has been comprehensively reported that people presented with diabetes are more prone to nerve damage, blood vessel damage and renal diseases. Diabetic Neuropathy (DN) is regarded as a serious complication of DM which can be defined as the damage of nerve fibres in the body due to hyperglycemia leading to the damage of peripheral nerves such as feet, legs, hands and arms [3-4]. It has been reported that about 20-30 million people are affected by DN worldwide. In India, studies have demonstrated that about 40 million people are suffering from diabetes out of which 10.4 million are suffering from DN. Further, DN has been noted to occur in

both forms of diabetes, i.e. insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) [5]. It has been demonstrated that the chances of development of neuropathy increases with duration of diabetes [6]. DN can be classified into four classes that involve peripheral neuropathy, autonomic neuropathy, proximal neuropathy and focal neuropathy [7-9]. Moreover, various hyperglycemia-induced signaling mechanisms contribute to the pathogenesis of DN that include polyol pathway, increased formation of AGEs, enhanced ROS generation and activation of PKC [10-12]. Various treatment options have been found to be reported for DN that include antidepressants, anticonvulsants, antiarrhythmics, aldose reductase inhibitors and N-methyl-D-aspartate (NMDA) antagonists [13-15]. This review aims to discuss about the classification and pathogenesis of DM. Moreover, treatment strategies in order to prevent and treat DN have been vitally demarcated.

Types of DN

It has been well reported that the signs and symptoms of DN vary depending upon the types of neuropathy and the nerves affected. DN can be classified as peripheral neuropathy, autonomic neuropathy, proximal neuropathy and focal neuropathy [7-9]. Peripheral neuropathy has been considered as the most common type of DN in which the distal parts of the extremities are affected resulting in sensory loss. Moreover, it involves the damage of nerves of feet, legs, hands and arms [16]. The symptoms can be manifested by altered temperature perception, hyperaesthesia, paraesthesia, numbness and deadness in the lower limbs [17]. Autonomic neuropathy is another serious and common type of DN in which the organs connected with the autonomic nerves are affected which ultimately leads to the altered functions of digestive system, heart, sweat glands, sexual organs and urinary system [18]. Studies have shown that about 65% of the type II diabetic patients develop parasympathetic dysfunctions 10 years after diagnosis and 15% patients have both combined sympathetic and parasympathetic neuropathy [19]. Further, the severe form of autonomic neuropathy affects the survival and leads to sudden death. The common symptoms of autonomic neuropathy are gustatory sweating, postural hypertension and diarrhea. The third type of DN is proximal neuropathy which mainly affects the elderly males above 25 years of age with type II diabetes and to females with type I diabetes [20]. It has been noted to cause the damage of nerves resulting in pain and weakness in buttocks, hips and thighs which leads to weakening of legs [21]. In addition, patients presented with this class of DN usually find difficulty in

climbing the stairs due to pain, getting up from squatting position followed by marked weight loss. Focal neuropathy is another type of DN which is observed in patients over 50 years of age and with type II diabetes [8]. It has been noted to cause the damage to a single or specific nerve resulting in pain and weakening of muscle in that part of the body. The specific parts affected with focal neuropathy involve eyes, thighs, abdomen and lower back [22].

Pathogenesis of DR

Ample of studies have comprehensively reported that various hyperglycemia-induced signaling mechanisms including polyol pathway, enhanced formation of AGEs, enhanced generation of ROS and PKC activation contribute to the pathogenesis of DN [10-12]. In addition, other factors like insulin like growth factor (IGF) and C-peptide also finds their role in development and progression of DN. In chronic hyperglycemia, the increased intracellular glucose level has to be metabolized by the polyol pathway, also called as sorbitol/aldose reductase pathway. The excess glucose is converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase respectively [23]. The sorbitol and fructose accumulate within the nerve due to their inability to permeate into the nerve cells [24]. The increased level of both glucose and sorbitol compete for the uptake of myoinositol in the cells and tissues leading to the decreased level of myoinositol [3]. The reduced NADPH acts as a cofactor for nitric oxide synthase (eNOS) which reduces NO formation ultimately leading to decreased vasodilation resulting in impaired blood supply to the nerves [25]. It has been reported that due to the presence of hyperglycemia in the blood, glucose can be incorporated into proteins non-enzymatically by the unregulated glycation reaction. Moreover, other body proteins like hemoglobin, collagen, glycoprotein, lipoprotein and plasma albumin also undergo non-enzymatic glycation which leads to the altered functions of the proteins [26]. These non-enzymatically glycated proteins slowly form the fluorescent cross linked products, referred to as AGEs. It has been suggested that high glucose concentration leads to the increased formation of AGEs which is evident by the fact that long standing diabetic patients possess levels of AGEs twice to those of normal subjects [27]. Furthermore, it has been noted that the presence of AGEs in peripheral nerves interfere with the axonal transport that is believed to damage the tissues due to their ability of protein cross linking ultimately leading to the development and progression of DN [27-28].

PKC belongs to the family of serine-threonine kinases which are multifunctional isoenzymes acting as an intracellular signal transduction system for many hormones and cytokines [29]. The PKC superfamily is Ca^{2+} dependent and activated by the second messenger i.e. di-acyl glycerol (DAG) [30]. In DN, the PKCs have been noted to be activated by increased DAG levels either by the inhibition of DAG kinase or by the denovo synthesis. Moreover, it has been observed that the PKC activation causes abnormalities in the blood flow and promotes the activation of nuclear factor kappa-B (NF-κB). The complications in blood flow result in the interrupted blood supply to nerves ultimately causing neuronal damage [31]. Further, ROS have been noted to play crucial role in the pathogenesis of DN. ROS are the small molecules which are highly reactive molecules that include free radicals, peroxides and oxygen ions, formed by cellular energy metabolism as their natural byproducts [32]. The ROS have been found to be increased in diabetic patients, the sources of which are advanced glycation, abnormal or inefficient mitochondrial function and auto-oxidation of glucose and its metabolites [33]. Moreover, studies have shown that ROS can directly damage neuronal cells, i.e., schwann cells. ROS have been noted to produce perfusion of peripheral nerve which produces the earliest defects in nerve function and further increases in nerve damage by causing ROS-dependent effects [34]. Furthermore, it has been shown that ROS inhibition helps in restoration of both vascular and metabolic imbalances which may lead to the blockage of initiation and progression of complications in DN [35].

In addition, some other factors like IGF and C-peptide have also been found to possess crucial role in the pathogenesis of DN. The IGFs are produced in the skeletal muscle, spinal cord, kidney and peripheral glia, which perform various functions like neutrite outgrowth and regeneration, expression of gene encoding axonal cytoskeletal proteins and control of neuronal survival [36]. IGFs have been noted to act on specific receptors which are present 100 times more as compared to insulin in the circulation. The IGF receptors are present in sensory neurons and Schwann cells [37]. The role of IGF in the pathogenesis of DN has been confirmed by various clinical and preclinical studies which showed that the abnormal levels of circulating IGF and changes in receptor's expression was observed in diabetic human subjects, in streptozotocin (STZ) rats and in type II diabetes zucker diabetic fatty (ZDF) rat model [38-39]. Consequently, the insufficiency of IGFs may lead to the pathogenesis of regenerative capacity, neurodegeneration and irreversible stages of DN [40]. Furthermore, C-peptide is a segment of proinsulin molecule

which is used to form insulin. The C-peptides produces multiple insulin and IGF-like effects by acting on its own receptors and by modulating the activity of insulin receptors [41]. It has been demonstrated that the autophosphorylation of insulin receptors and the effects of insulin are increased by C-peptide [42]. Moreover, the insufficiency of C-peptide has an important role in the pathogenesis of DN. The C-peptide treatment regulates skin microcirculation in the diabetic patients, thermal hyperalgesia, atrophy and endoneurial blood flow confirming the role of C-peptide in the progression and development of DN [43-44].

Treatment of DN

Although, there have been none of viable available treatments which can restore the nerve function. However, the management of DN relies on the pharmacological treatment of the symptoms of DN alongwith non-pharmacological therapy including nerve stimulation therapies like acupuncture and electrical nerve stimulation to improve the quality of life of the patients presented with DN. In the pharmacological treatment, various drugs have been reported for the treatment of DN that includes antidepressants, anticonvulsants, antiarrhythmics, aldose reductase inhibitors and NMDA antagonists [13-15]. The tricyclic antidepressants (TCAs) have been considered as the first line drugs in treatment of pain in diabetic peripheral neuropathy [45]. It has been found that these agents prove helpful in promoting analgesia to mechanical, thermal and electrical stimuli in diabetic patients [46]. The mechanism of analgesic action of TCAs involves the inhibition of the reuptake of amines like norepinephrine and serotonin alongwith modulation of voltage gated sodium channel [47]. Further, the TCAs have been found to be effective in both diabetic and non diabetic forms of painful neuropathy. Studies have reported that TCAs with mixed serotonergic and noradrenergic reuptake inhibition are more effective than the selective noradrenergic effects [48]. Some side effects have been associated with TCAs that include blurred vision, dry mouth, sedation, cardiac arrhythmias and hypertension. Another class of drugs that have been well reported for the treatment of DN involves anticonvulsants**.** Gabapentin is a first line anticonvulsant agent used in the treatment of neuropathic pain [49]. The drug produces the analgesic action by inhibiting voltage activated sodium and calcium channels at spinal cord level [50]. However, various side effects have been linked with anticonvulsants like dizziness, headache, confusion and diarrhea. Another anticonvulsant agent used in the treatment of DN is carbamazepine, which has limited use in painful DN [51].

Phenytoin has been shown to possess various beneficial effects in DN at a high dose of 600mg/day. Moreover, another potent anticonvulsant used in the treatment of DN is lamotrigine which possesses beneficial properties for pain relief in the patients presented with DN [52]. Topiramate, another anticonvulsant, showed multiple mechanisms of action like ability to block sodium channels and potentiation of gamma-amino butyric acid (GABA) activity by interacting with $GABA_A$ receptors.

Further, antiarrhythmic agents like lignocaine and lidocaine have been reported in producing beneficial effects in painful DN [53]. Lignocaine has been used for patients exhibiting neuropathic pain, which showed amelioration of pain in patients presented with DN [54]. Maxiletine, class IB antiarrhythmic agent, has also been demonstrated to play beneficial role in the treatment of diabetic neuropathic pain. Capsaicin, a natural colloid extracted from the red chilli peppers, helps in the depletion of substance P from afferent nerves suggesting significant effects in DN [55]. Moreover, Capsaicin has shown beneficial effects in reducing pain and improving daily activities in patients with DN. In addition, aldose reductase inhibitors like zopolrestat, alreastat, tolerestat, sorbinil and epalrestat inhibit the conversion of glucose to sorbitol in the presence of hyperglycemia thereby preventing the polyol pathway cascade [56]. Moreover, the aldose reductase inhibitors have been suggested to act by activation of Na^+-K^+ ATPase and reduced glutathione levels ultimately improving the blood flow to the nerves [57]. Furthermore, NMDA antagonists like dextromethorphan has been demonstrated to show satisfactory results in relieving pain in patients presented with DN [58].

In addition, non pharmacological therapy involving nerve stimulation therapies and electrical spinal cord stimulation have also been reported to improve the quality of lives of DN patients. The nerve stimulation therapies include acupuncture, transcutaneous electrical nerve stimulation (TENS) and percutaneous electrical nerve stimulation (PENS). These therapies show their action by stimulation of endogenous opioids at spinal cord level [59-60]. Acupuncture, a therapy of nerve stimulation, involves application of fine needles into the skin to relieve from pain. The safety and efficacy of acupuncture has been shown by a study in which 67% of patients have stopped or reduced their medications over 18-52 weeks [61-62]. The beneficial effects of nerve stimulation therapies for the treatment of DN has been proved by the results obtained in a trial conducted for evaluation of TENS that showed

results of reduced pain in 53% of patients with peripheral nerve damage. Moreover, PENS is an electroanalgesic therapy consisting of both TENS and acupuncture, which showed short term relief in various acute and chronic pain syndromes associated with DN [63]. Another non-pharmacological therapy for the relief of DN symptoms is electrical spinal cord stimulation which can be performed in patients with chronic neuropathic pain [64]. In this therapy, an electrode is implanted into the thoracic or lumbar disc space of the diabetic patient. This therapy causes the stimulation of endogenous opiate production in a similar manner to TENS [65]. The beneficial role of the therapy has been further confirmed by the fact that significant reductions in pain in 8 diabetic patients having chronic neuropathic pain at 3 and 14 months was noted that evidenced the role of the therapy in the prevention and treatment of painful DN. Furthermore, counseling and psychological treatment has also been reported for the prevention of DN which emphasizes on the objective to train the patients to recognize the influence of thought and perception over pain responses [66-67].

Conclusion

DN represents one of the major health concerns today which is characterized by pain and nerve damage in feet, legs, hands and arms. Various treatments are available for DN including antidepressants, anticonvulsants antiarrhythmics, capsaicin, aldose reductase inhibitors and NMDA antagonists. Moreover, therapies like nerve stimulation and electrical spinal cord stimulation also pave the way in the treatment of DN. However, the treatments have not been well reported to completely diminish the progression of DN. Hence, new studies are demanded in order to afford complete treatment and prevention from this very complication of diabetes.

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